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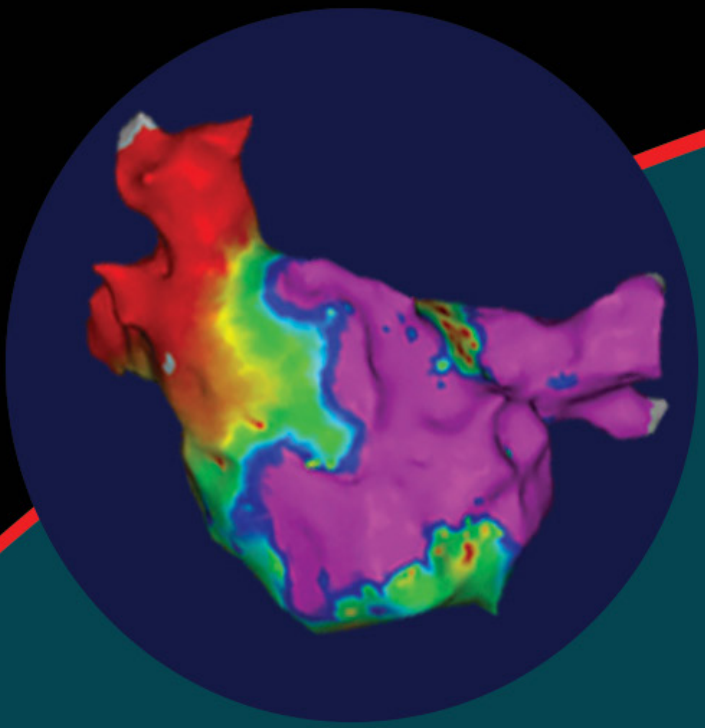

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Editorial

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Welcome To 2016

Dhanunjaya (DJ) Lakkireddy, Andrea Natale

Dear Colleagues

On behalf of JAFIB we welcome you to 2016. Hope you had a productive and fruitful 2015 on the personal and professional fronts.

We want to thank all the contributors whose efforts enhanced the value of JAFIB in its mission of quality education for healthcare professionals and patients alike. Several exciting inventions, discoveries, theories and hypothesis have marked 2015 in the AF world. Clearly the focus shifted from target specific therapies to a comprehensive systemic approach. The importance of risk factor modification in arresting the evolution of the disease processes is the evolving mantra.

Earlier this month, the 20th Annual AF Symposium (Formerly Boston AF Symposium) concluded in Orlando over an exciting 3 day academic retreat. Special thanks to Dr. Jeremy Ruskin and co-directors for putting together a very important educational meeting that became synonymous with the progress we made in AF management. The 4rd International Symposium on Left Atrial Appendage (ISLAA 2015) is coming up next week in New York. JAFIB is proud to be the official journal of the meeting. With the recent approval of an LAA occlusion device by FDA with pending coverage decision from the CMS, this meeting reflects the collective interest in the field. Those of you who are still thinking it's time to spring to action and join us in NYC in spring!

This edition of JAFIB has some exceptionally good original articles and reviews that we are sure you will enjoy.

We wish you a happy New Year and a blessed 2016 in all your endeavors.

Best regards
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Safety and Feasibility of Contrast Injection During Pulmonary Vein Isolation with the nMARQ™ Multi-Electrode Catheter

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Abstract

Introduction: Pulmonary vein isolation (PVI) using the irrigated multi-electrode ablation system (nMARQ™) remains challenging in complex atrial anatomy cases and when CARTOMERGE™ technology is not available, due to absence of a leading guide-wire.

Objectives: Our objective was to assess feasibility and safety of PVI using nMARQ™ catheter with intra-procedural contrast injections through the deflectable sheath compared to nMARQ™ alone.

Methods: This is a prospective non-randomized observational study of 78 consecutive patients who underwent PVI only with nMARQ™. The first group (n=37, 64±10.5 years, 62% male, 13.5% persistent AF) underwent the procedure with the guidance of signal mapping, fluoroscopy, and electro-anatomical mapping (EAM) alone. Since 12/2013 an automatic closed-loop contrast media injector was added to improve catheter location (n=41, 62.5±11 years, 71% male, 34% persistent AF).

Results: Total procedure time was 78±19 and 85.5±18.5 minutes, and mean fluoroscopy time was 30±9 and 29.5±8.7 minutes for the first and second groups, respectively (NS); acute success rate was 97% and 97.5%, with a mean of 14.7±5 and 17.6±5.4 RF applications, respectively (p=0.02); and mean total burning time of 10.3±3.6 and 12±4 minutes, respectively (p=0.08). Mean contrast used was 60±18 mL versus 203±65 mL, with no effect on renal function or major complications. One year freedom from AF was 77% and 83%, respectively (p=0.5).

Conclusions: Addition of contrast injections to standard nMARQ™ procedure is feasible and safe. It has no benefit in routine use but further studies may confirm its potential added value to EAM in catheter localization by newly trained operators and in selective cases of large/common PV anatomy.

Introduction

The irrigated multi-electrode electro-anatomically guided nMARQ™ catheter (Biosense Webster Inc., Diamond Barr, CA, USA) for atrial fibrillation (AF) ablation was recently launched in the market.[1]

The first generation nMARQ™ consists of an 8.4F decapolar irrigated-based catheter with an adjustable circular array 20–35 mm in diameter. The catheter can be recognized by the CARTO 3 system (Biosense Webster Inc., Diamond Bar, CA, USA), which allows 3D electro anatomical mapping (EAM) of the left atrium (LA) and pulmonary veins (PVs). The RF energy is delivered in either unipolar or bipolar mode, and atrial and pulmonary vein PV signals can be recorded during ablation.

Yet, this catheter's relatively large diameter and lack of a leading guide wire (which is used in another circular ablation method)[2,3] frequently causes technical difficulties and some uncertainty regarding the exact location of the catheter relative to the PV ostia, especially during the training of new operators and in cases of patients who have large PVs or common PVs, where the EAM does not provide adequate guidance and the impedances are not accurate in reflecting PV boundaries. Also in small and medium sized PVs, the large size of the nMARQ™ catheter prevents operators from mapping inside the PVs, and the addition of intra-cardiac echocardiography for antral localization increases the procedural costs. Cartomerge™ technology may assist in catheter localization, but this option is not available in every center and is of lesser accuracy for guiding nMARQ™ procedure.

In order to overcome this difficulty, we introduced a tool for pulmonary vein isolation (PVI) when using the nMARQ™ system: we connected the steerable long sheath to a closed-loop automatic injector contrast delivery system: ACIST CVi System (ACIST Medical Systems Inc., Eden Prairie, MN, USA). Selective intra-procedural contrast media injections in cases of large/common PVs helped us in localizing the catheter at the PV antrum (Figure 1).

Key Words:

Atrial Fibrillation, Catheter Ablation; Multi-Electrode Ablation Catheter, nMARQ, Contrast Injection.Agnisciet quamus, simus si

Disclosures:
None.

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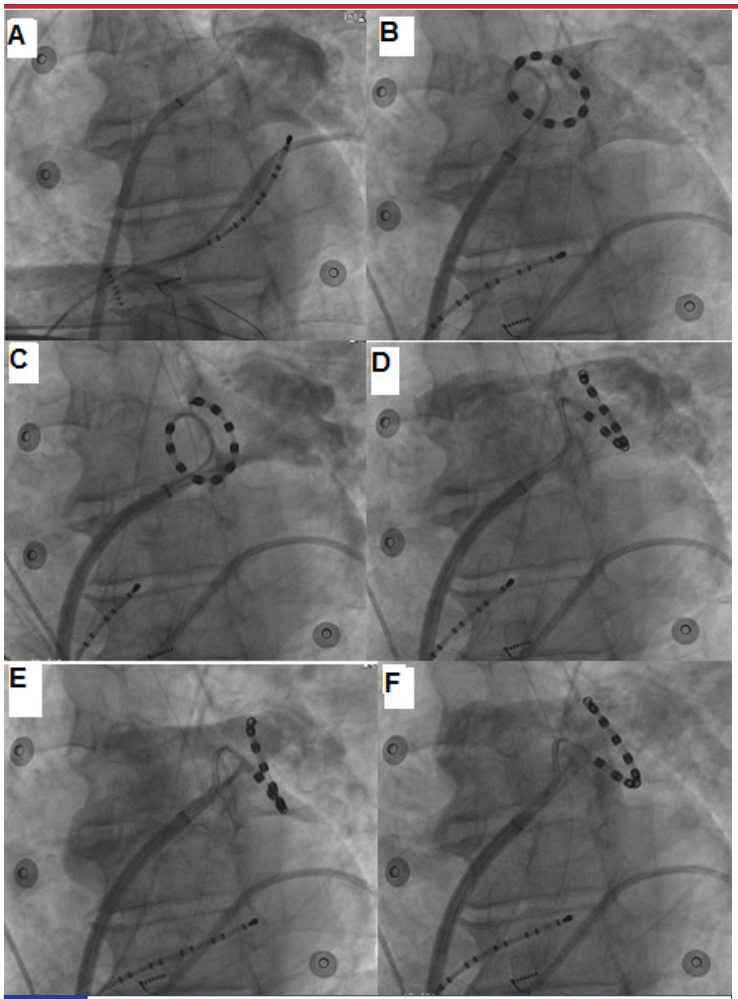

Figure:1 An example of a patient in group II with a large left common pulmonary vein. A. A selective angiogram through the deflectable sheath before introducing the nMARQ™ catheter. B-F. There was difficulty in isolating the vein, so injection through the ACIST CVi System was applied. Different positions of the catheter thought to be appropriate according to signal recordings and electro-anatomical mapping and impedances are demonstrated – but according to contrast injections by the ACIST CVi System – not in optimal areas of the vein. Finally an optimal target for ablation was found and the vein was eventually isolated.

The purpose of this study was to compare our preliminary experience of PVI using an nMARQ™ catheter with the aid of this closed-loop contrast injector versus nMARQ™ alone regarding feasibility, safety, as well as procedure and application times and one-year follow up, as reflected by our non-randomized single center registry. The study was not designed to prove superiority of the contrast injection method but to demonstrate its applicability in selective cases during training or complex PV anatomy.

Material and Methods

Patient Population

We studied all consecutive patients with symptomatic drug-refractory documented AF who underwent AF ablation using the irrigated multi-electrode circular ablation catheter in our center. Only paroxysmal and persistent AF patients who underwent PVI without additional lines of ablations were included in this study. They were included in a prospective non-randomized observational registry and were followed up in our institution.

Overall, out of 111 patients who underwent PVI with nMARQ™ ablation system in our center, 78 were included in this study. The others were excluded due to the addition of ablation lines beyond PVI. Cartomerge™ technology was unavailable. All patients provided an informed consent prior to the procedure; the study protocol was approved by our institution review board and was not influenced by Biosense Webster Company.

Table 1: Patient characteristics

	Group I nMARQ™ (n=37)	Group II nMARQ™ with contrast (n=41)	p-value
Age (y)	64±10.5	62.5±11	0.5
Gender (%male)	23 (62%)	29 (71%)	0.4
CHA2DS2 VASC score	2.3±1.5	2.1±1.3	0.6
Anti-arrhythmic drugs AADs (mean N ± STD)	1.3±0.7	1.45±0.71	0.5
Left atrial size (AP, mm)	38.7±5.5	39.8±6.7	0.47
LV EF (%)			
Good/mild dysfunction	32 (86%)	37 (90%)	0.05
Moderate dysfunction	1 (3%)	4 (10%)	
Severe dysfunction	4 (11%)	0 (0%)	
H/O CVA/TIA	1 (3%)	1 (2.4%)	0.9
H/O CAD	7 (19%)	7 (17%)	0.8
cal GFR prior to procedure (ml/min/1.73):			
>90	8 (22%)	11 (27%)	0.6
60-89	26 (70%)	25 (61%)	0.4
30-59	2 (5%)	5 (12%)	0.3
15-29	1 (3%)	0	0.3
<15	0	0	
>60	34 (92%)	36 (88%)	0.5
Persistent AF (%)	5 (13.5)	14 (34)	0.03

AAD = anti arrhythmic drugs; AF = atrial fibrillation; CAD = coronary artery disease; cal GFR = calculated GFR according to the equation: GFR (mL/min/1.73 m2) = 175 × (Scr)-1.154 × (Age)-0.203 × (0.742 if female); CVA = cerebrovascular event; EF = ejection fraction; H/O = history of; LA = left atrium; LV=left ventricle; STD = standard deviation; TIA = transient ischemic attack

Group I (n = 37) underwent the procedure using nMARQ™ ablation system. Group II (n = 41) underwent AF ablation using the nMARQ™ ablation system with the aid of contrast injections through the deflectable sheath while the catheter was inside the LA to help localize the catheter in large/common PV ostia. This tool was introduced in December 2013.

Mapping and Ablation Procedure

The nMARQ™ ablation system was previously described.[1,4-6] All patients underwent trans-esophageal echo (TEE) up to 48 hours prior to the procedure. An interrupted anti-coagulation approach was used. All patients underwent the ablation under conscious sedation with midazolam, propofol, and pethidine hydrochloride, without the presence of an anesthesiologist. We introduced a naso-gastric tube for marking the proximity of the esophagus to the ablation sites. Vascular access was obtained through a femoral vein with continuous hemodynamic monitoring through the radial or femoral artery. A decapolar catheter was positioned in the coronary sinus. Trans-septal puncture was performed using a long sheath (SL0, SJM, Minnetonka, MN, USA), a SafeSept™ J-shaped guide wire, and a Brockenbrough needle (BRK, SJM, Minnetonka, MN, USA) under fluoroscopic and contrast guidance. After accessing the left atrium LA, heparin was given intravenously with a target active clotting time (ACT) of 300–350 seconds. By placing a wire in the left superior PV (LSPV), the fixed sheath was exchanged for a steerable guided sheath (Channel 9.5F, Bard, Lowell, MA, USA; or FlexCath, 10F or 12F, Medtronic

Cryo Cath LP, Canada; or Oscor 10F, Oscor® Inc., FL, USA). Selective angiograms of all PVs were then performed through the deflectable sheath and before introducing the nMARQ™ catheter in all patients in order to demonstrate LA anatomy and PV size. The ablation catheter was then introduced into the deflectable sheath under continuous flushing of the deflectable catheter with heparinized saline and under continuous flushing of the nMARQ™ catheter by the Cool Flow Pump at 60 mL/min and at 4 mL/min inside the LA.

For both groups we started mapping and ablating at the right inferior pulmonary vein (RIPV), which was the last vein to be demonstrated by the selective angiogram. We used the selective pre-catheter-insertion angiograms, fluoroscopy, EAM, impedances, and intracardiac signals from the nMARQ™ catheter for targeting the ablation zone in all patients.

In Group II patients we connected a contrast delivery system to the deflectable sheath: ACIST CVi System. We used it for short injections of contrast media (8 mL each) through the deflectable sheath whenever there was a doubt regarding catheter localization in relation to PV orifice (Figure 1). Those patients were treated with intravenous saline (1000 mL/24h) during the procedure or until the day after, and routine renal function tests were taken the day post-procedure.

Before ablating the right superior PV (RSPV), a high energy pacing (10 mV/2 ms at CL 500 ms) was performed from each electrode of the circular catheter to rule out phrenic nerve stimulation, in which case this electrode was shut down.

We applied unipolar RF energy with power settings of 20 Watts for the non-posterior zones and 15 Watts for the posterior areas. Each application lasted until the PV signals disappeared, between 15–60 seconds each. In case of lack of atrial signals on some of the multi-electrodes, those displaying no signal were shut off during subsequent energy delivery.

PV isolation was proved by entrance and exit block technique for very large PVs, in which the whole catheter could enter. In smaller veins, RF delivery was continued until no PV signals were observed at the antrum (along the inner aspect of the circumferential ablation line) and atrial loss of capture could be proven (the pace-and-ablate technique)[7] or dissociated PV activity could be shown.

Our approach for patients with persistent AF was as follows: in patients who entered the procedure in AF rhythm, ablation of right PVs was performed, then DC cardioversion and completing PVI in sinus rhythm was applied – for better signal recording and proving isolation.

Table 2: Procedural data (mean±SD)

	Group I nMARQ™ (n=37)	Group II nMARQ™ with contrast (n=41)	p-value
Procedure time – overall (min)	78±19	85.5±18.5	0.1
Fluoroscopy time - overall (min)	30±9	29.5±8.7	0.8
Applications (mean ± STD)	14.7±5	17.6±5.4	0.02
Total burning time (min)	10.3±3.6	12±4	0.08
Overall amount of contrast media used during the procedure (cc)	60±18	203±65	<0.0001
Charring of catheter	0	0	

Min= minutes

Post-Ablation

All patients were monitored overnight and underwent echocardiography the day post-procedure to rule out pericardial effusion. Oral anticoagulation was continued for three months for all patients and for lifetime for those with CHA2DS2-VASC score above 1. Antiarrhythmic drugs were continued for two to three months post-procedure and all patients were treated with proton pump inhibitors for one month post-procedure.

Statistics

Patient characteristics for comparing the two groups were described by percentage and mean±SD. Continuous variables were compared using independent Student t-test; categorical variables were compared using chi-square test or Fisher's exact test. A p-value < .05 was considered statistically significant. Analyses were carried out using SPSS version 21.0 statistical package (SPSS IBM Inc.).

Results

Patient Characteristics

We studied prospectively 37 consecutive patients in our center who underwent AF ablation using nMARQ™ ablation with contrast injection for demonstrating selective PV angiography through the deflectable sheath while the nMARQ™ catheter was not yet applied to LA (64±10.5 years; 62% male; 13.5% persistent AF) – group I. We compared them to 41 consecutive patients who underwent AF ablation using nMARQ™ ablation with contrast injection as in group I but with additional contrast injections through a closed loop automatic injector connected to the deflectable sheath while the nMARQ™ catheter was introduced in PV ostia (62.5±11 years; 71% male; 34% persistent AF) – group II.

There was no statistical difference between the groups regarding baseline characteristics, except for the ratio of patients with persistent AF and baseline ejection fraction (EF) (Table 1). All patients had symptomatic documented AF that was refractory to at least one antiarrhythmic drug AAD. There was no significant difference between the two groups regarding percentage of patients with good left ventricular function, left atrial LA size, history of stroke, history of coronary artery disease, CHA2DVASC2 score, number of anti-arrhythmic drugs AADs used, and baseline kidney function (Table 1).

Procedural Data

Table 2 shows intra-procedural data for both groups.

Overall mean procedure times (from cleaning the groin to pulling back all catheters) were 78±19 minutes for group I and 85.5±18.5 minutes for group II (p = 0.1). Overall mean fluoroscopy times were 30±9 minutes for group I and 29.5±8.7 minutes for group II (p = 0.8).

The number of applications was 14.7±5 for group I and 17.6±5.4 for group II (p = 0.02); the total burning times were 10.3±3.6 and 12±4 minutes, respectively (p = 0.08).

During the procedure overall 60±18 mL of contrast media were injected intravenously in group I patients (selective angiograms before introducing the catheter) versus 203±65 mL in group II (both selective angiograms and injection through the ACIST CVi System while catheter in LA) (p < .0001).

No charring of the catheter was noted in both groups.

Safety Issues

Table 3 describes the complications during the procedures in the two groups. There was one tamponade that occurred in group II during manipulation of the catheter from the left PVs to the

Table 3: Safety and follow-up

	Group I nMARQ™ (n=37)	Group II nMARQ™ with contrast (n=41)	p-value
Acute complications (N)			
Pericardial tamponade	0	1	0.3
TIA/CVA	0	0	
Clinical PV stenosis	0	0	
A-E fistula	0	0	
Phrenic nerve palsy	0	0	
Access site	4 (10.8%)	0	0.03
Transient STE (inferior leads)	3 (8%)	0	0.06
Acute success (%)	36 (97%)	40 (97.5%)	0.9
Worsening of renal function tests (%)	1 (2.7%)	0	0.3
1year freedom from AF (available f/u) after one PVI	27/35 (77%) 6/27 (22%) with AAD	20/24 (83%) 10/20 (50%) with AAD	0.56 0.13
1year freedom from AF (available f/u) after two PVIs	29/35 (83%) 6/29 (21%) with AAD	22/24 (92%) 10/22 (45%) with AAD	0.3 0.06

A-E fistula = atrio-esophageal fistula; AF = atrial fibrillation; CVA = cerebrovascular event; PV = pulmonary vein; PVI = pulmonary vein isolation; STE = ST segment elevation in electrocardiogram; TIA = transient ischemic attack

right PVs. No overt neurological sequel or symptomatic pulmonary stenosis or atrio-esophageal fistula was observed.

Four vascular access site complications (pseudoaneurysm without the need for a vascular surgery) and three transient ST elevations in inferior leads occurred in group I after injecting dye through the Brockenbrough needle.

Since these cases we have changed our protocol regarding two issues:

1) we infuse protamine-sulfate post-procedure before removing the sheaths from the groin and prescribe new oral anti-coagulants (NOACs) post-procedure in order to avoid bridging for warfarin with low-molecular weight heparin (LMWH);

2) we no longer inject contrast through the Brockenbrough needle after trans-septal puncture. Since the application of these changes in daily practice, no such complication has been seen (group II) (Table 3).

Despite a difference in the amount of contrast medium injected in the two groups we observed no worsening in renal function tests in both groups, except for one patient in group I in whom calculated GFR worsened from normal to mild renal dysfunction the day post-procedure (p = 0.3).

We observed no acute complication related to the injection of contrast media in group II. The contrast was injected and was irrigated prior to the application of RF ablation.

Acute Success

For one patient in group I and one in group II, PV isolation could not be proven for all PVs, either due to anatomy of very small PVs and instability of the catheter at PV ostium (group I) or due to phrenic nerve stimulation in the RSPV that prevented us from isolating this vein (group II). Thus the acute success rate was 97% for nMARQ™ (group I) and 97.5% for nMARQ™ with contrast (group II) (Table 3).

One-Year Follow Up

One-year follow up was available for 35 patients in group I and 24 patients in group II. One year freedom from AF in those patients was 77% in group I and 83% in group II (p = 0.56) (Table 3). Twenty-two percent of those free of AF in group I were treated with anti-arrhythmic drugs AADs, versus 50% in group II (p = 0.13).

One-year freedom from AF after two PVI procedures was 83% in group I and 92% in group II (p = 0.3) (Table 3). Twenty-one percent of those free of AF in group I were treated with AAD, versus 45% in group II (p = 0.06).

Discussion

The irrigated multi-electrode electro-anatomically guided nMARQ™ catheter was recently launched in the market for AF ablation.[1] Despite its advantages (EAM-based, TissueConnect™ feature), the first generation nMARQ™ system consists of an 8.4F catheter with an adjustable circular array of 20–35 mm diameter and no guiding wire.

The learning curve of this technology might be long for new operators since the localization of the catheter in PV ostium is difficult without a guiding wire. In addition, for some PV anatomies, the relatively large diameter of the nMARQ™ catheter and the lack of a guiding wire frequently causes technical difficulties and some uncertainty regarding the exact location of the catheter relative to the PV ostia, despite EAM usage. PVI guided by EAM integrated with magnetic resonance/computed tomographic images of the left atrium LA (Cartomerge™ technology) may serve as a solution to these cases,[8,9] but their availability might be sub-optimal in some centers.

In order to overcome this difficulty, we connected the steerable long sheath to a closed-loop automatic injector contrast delivery system. This helped us in localizing the catheter at the PV orifice by using short injections of contrast media through the deflectable sheath while the catheter was in the PV antrum before RF ablation of the vein (Figure 1). This study investigated the applicability of this option in selective cases.

Procedural Differences

Mean procedure time and fluoroscopy time were comparable for both groups. However, the number of applications was larger when we used the injector and the total burning time tended to be longer.

We suspect that this stems from those situations where we think that the catheter is in the right place, but then, when we inject contrast media, we find that the catheter is not in an optimal location, despite satisfactory EAM, and that we need to ablate more (Figure 1). This is true especially for very large PVs and common PVs.

Acute End-Point and Success Rate

The acute success rate (isolation of all PVs) was high and similar for the two groups with or without contrast injection (Table 3). One case of anatomic difficulties in group I and another case of phrenic nerve stimulation all over PV ostium in group II resulted in acute success rates of 97% and 97.5%, respectively (p = 0.9). The contrast system could not help in this regard.

One-year follow up was similar for both groups after either one PVI or two, but with a trend of using more AAD during this period of time in group II (p = 0.06).

Safety

The overall complication rates were similar versus point-by-point ablation techniques, with one tamponade out of the whole study population (1.3%).[10] This tamponade was not related to injection of contrast media. There was a high rate of vascular access site complications and transient ST elevation in inferior leads in group I. Changes in procedure protocol were described above and resulted in no such complications in group II patients that followed group I in time.

No patient showed symptoms related to cerebral thromboembolism.

Although there was an absence of clinically noticeable cerebral thromboembolic injuries, we cannot exclude or quantify possible asymptomatic cerebral events, which have been described with all available ablation techniques used for PVI,[11,12] because no cerebral MRI scan was performed.

No symptomatic pulmonary stenosis was observed. However, the development of PV stenosis might occur after a delay of several months or weeks, which cannot be excluded by our present set of data.

In order to avoid esophageal damage with nMARQ™,[4] our practice was to set the power during ablation along the posterior wall with a maximum energy level of 15 Watts (Unipolar only) and maximum impulse duration of 40 seconds. A nasal-gastric tube marked the esophagus location. Since no clinical signs for esophageal damage appeared, no endoscopy was performed. Thus, no data can be given for possible thermal esophageal lesions by ablation.

Despite a difference in amount of contrast injection in the two groups we observed no worsening in creatinine level and eGFR in Group II versus group I (Table 3). We believe that our common practice to treat group II patients preventively with intravenous saline (1000 mL/24h) during the procedure or until the day after has a role in those calming results.

We observed no acute complication related to the injection of contrast media in group II. The contrast media was injected and was irrigated prior to the application of RF ablation. The fact that this system is irrigation-based prevents the contrast media from sticking to the catheter. We observed no char on the catheter in all cases.

Target Population

Although the purpose of the study was to evaluate mainly feasibility and safety of the nMARQ™ catheter with contrast injection, our study showed no benefit in using this method routinely in every patient. On the other hand, we believe that this method should be taken into consideration in selective clinical scenarios:

In group II patients – in most PVs with "normal" anatomy, the selective angiograms done before introducing the catheter, the PV potentials, the fluoroscopy, the impedances, and the EAM guidance have provided sufficient information to assure us regarding proper catheter location.

However, in cases of large PVs and common PVs, the newly described introduction of a contrast delivery system, the ACIST CVi System, surely helped us localize the catheter at the PV orifice and avoid ablation inside the PVs (Figure 1). Further validation of this technique is needed.

In addition, we realized that another advantage of the contrast injections during catheter manipulation is its role in training new operators with the multi-electrode ablation system: especially when there is no "anchoring wire" and the learning curve to recognize the signals of the multi-electrode catheter takes time. Knowing the exact catheter location gives the operators online feedback.

Limitations

We could not rule out that the tendency for longer ablation time and larger number of applications in group II were related to the contrast media covering the electrodes, but we saw no change in temperature, power, and impedances of the electrodes before and after injecting the dye; thus we believe it is mostly the result of a better catheter-PV contact after more attempts of manipulations of the catheter.

Another limitation of the study is the sequential nature of the two groups. The fact that increasing experience level could have influenced outcome cannot be ruled out.

Conclusion

Addition of contrast injections to standard nMARQ™ procedure is feasible and safe. Although it does not prolong the procedure significantly, it involves more applications. It does not have a benefit for a routine use in every patient, but this tool may have an added value to EAM in catheter localization by newly trained operators and in selective cases of large/common PV anatomy. Future studies are needed to prove its advantage in selective cases.

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Peak Early Diastolic Transmitral Velocity As A Surrogate Marker Of Short-Term Atrial Fibrillation Recurrence After Electrical Cardioversion

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Abstract

Objectives: The aim of this study was to assess if peak early diastolic transmitral velocity (E-wave) can be used as a surrogate marker of short-term atrial fibrillation (AF) recurrence.

Methods: We prospectively studied 57 consecutive patients who underwent electrical cardioversion (ECV) for AF and successfully converted to sinus rhythm. N-terminal brain natriuretic peptide levels (BNP) before and after ECV was measured in all patients. The follow-up included physical examination and a 12-lead electrocardiogram 14 days and one month after the ECV.

Results: In 42.1% patients AF recurred during one-month follow-up period. Gender, presence of mitral regurgitation, treatment with angiotensin II receptor blocker and left atrium diameter independently influenced E-wave velocity before ECV. E-wave velocity fell immediately after successful ECV (94.0±27 cm/s vs 79.7±23 cm/s, P<0.0001). E-wave velocity before ECV>94 cm/s and E-wave velocity after ECV >80 cm/s were predictors of one-month AF recurrence [(Hazard Ratio) HR=3.62 with 95% CI=1.49-8.78 and HR=3.76 with 95% CI=1.40-10.10, respectively]. E-wave velocity before and E-wave velocity after ECV remained predictors of AF recurrence but only in non-hypertensive patients (HR=1.01 with 95% C.I=1.01-1.03 and HR=1.03 with 95% C.I=1.01-1.06, respectively). Similarly, BNP levels before and after ECV were associated with an increased the risk of AF recurrence (HR=1.14 with 95% C.I 1.01-1.28 and HR= 1.16 with 95% C.I 1.03- 1.31, respectively). The addition of BNP levels to E-wave velocity before ECV appeared to have incremental value on short-term AF recurrence but at a marginally statistical significance (LR chi2=3.28, p=0.07).

Conclusions: E-wave velocity before and after ECV appears to be a marker of short-term recurrence of AF.

Introduction

Atrial fibrillation (AF) has a high risk of recurrence mainly in the first month after electrical cardioversion (ECV).[1] Several clinical and echocardiographic entities have been proposed as predisposing factors to AF recurrence such as: gender, age, AF duration before cardioversion, number of previous recurrences, left atrial size, left ventricular (LV) function, left atrial appendage velocities and the presence of coronary heart disease.[2-6] Furthermore, Doppler transmitral flow indices have been investigated as risk factors of AF[7] and several studies have investigated the changes in transmitral velocity pattern and N-terminal brain natriuretic peptide levels (BNP) after ECV.[8,9] The rational of this study was to find a simple echocardiographic index like peak early diastolic transmitral velocity as a surrogate marker of predicting short-term atrial fibrillation recurrence and to explore if the addition of BNP had an incremental value over this marker.

Key Words:

Transmitral Pattern, Atrial Fibrillation, BNP.

Disclosures:
None.

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Methods

Patients

We prospectively studied 57 consecutive patients who underwent ECV at the Onassis Cardiac Surgery Center for AF and who were successfully converted to sinus rhythm. The recruitment period was from January 2006 to December 2006.

The objective of the study was to assess if a simple echocardiographic diastolic index (E-wave) can be used as a surrogate marker of short-term AF recurrence in patients who successfully converted to sinus rhythm.

All patients continued the same antiarrhythmic medication and other drugs before, during and after the ECV. All patients received anticoagulation (per os acenocoumarol or warfarin) with a target INR 2-3 for 3 weeks before and 4 weeks after ECV in order to avoid embolic complications.

All patients underwent echocardiographic study before ECV including M-Mode, and 2D-examination as well as pulsed wave, continuous wave and color Doppler evaluation. We examined left

Table 1: Baseline clinical and echocardiographic characteristics of patients

	All patients N =57	SR Maintenance N =33	AF recurrence N =24	P
Mean age±SD (years)	65.2±12	65.9 ±11	64.2±13	0.607
Gender (male: female)	44:13	28:5	16:8	0.106
Fractional shortening±SD	30±13	31±15	30±9	0.671
LA size AP dimension±SD (cm)	4.7±0.8	4.7±0.7	4.7±0.9	0.879
LA Area±SD (A4C) (cm2)	35±12	35±11	35±12	0.998
Underlying disease n (%)				
CAD	15 (26.3%)	10 (30.3%)	5 (20.8%)	0.423
Mitral regurgitation	8 (14%)	5 (15.2%)	3 (12.5%)	0.776
Hypertension	34 (59.6%)	24 (72.7%)	10 (41.7%)	0.018
Diabetes Mellitus	7 (12.3%)	4 (12.1%)	3 (12.5%)	0.996
Lone AF	6 (10.5%)	2 (6.1%)	4 (16.7%)	0.198
Medication n (%)				
AT II Inhibitors	26 (45.6%)	13 (39.3%)	13 (54.2%)	0.206
Amiodarone	39 (68.4%)	22 (66.7%)	17 (70.8%)	0.716
Propafenone	5 (8.8%)	3 (9.1%)	2 (8.3%)	0.816
Sotalol	2 (3.5%)	2 (6.1%)	0 (0%)	0.214
Beta-Blockers	20 (35.1%)	12 (36.4%)	8 (33.3%)	0.567

LA=Left atrium, SD=Standard Deviation, A4C=Apical 4-chamber view, CAD=Coronary Artery Disease, AF=Atrial Fibrillation, AT II Inhibitors=Angiotensin Receptor II Inhibitors

ventricular function (measurement of fractional shortening) and left atrial size (measurement of left atrial diameter and area). Transmitral flow velocity was measured at the tip of mitral valve leaflets on long-axis view of the left ventricle. The peak atrial systolic (A) and peak early diastolic velocities (E) were measured from transmitral flow velocity. The function and anatomy of cardiac valves were also studied.

All blood samples were drawn by venipuncture and collected in EDTA-containing tubes. The samples were then centrifuged and plasma was stored in aliquots at -20oC within 30 minutes. Levels of plasma NT-proBNP were determined using an Elecsys 1010 Roche Diagnostics Pro-BNP (Roche Diagnostics, Germany) Electrochemiluminescence sandwich immunoassay. The analytical range extends

Figure 1: Boxplots of E-wave velocity before and after ECV between the two groups

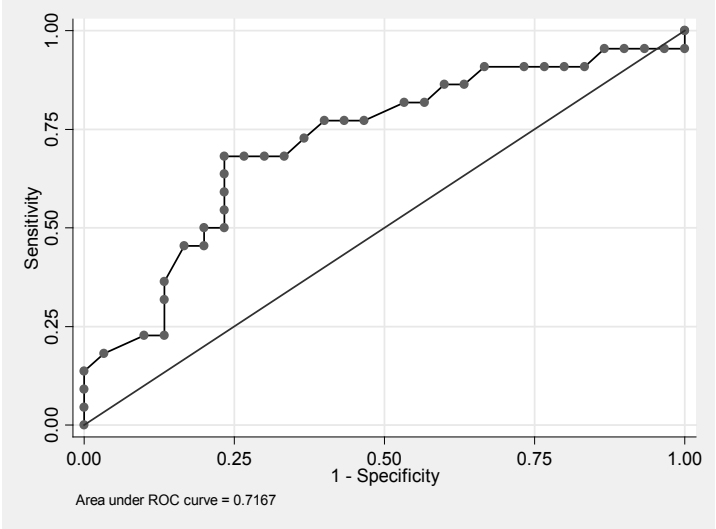

Figure 2: ROC analysis for E-wave velocity before ECV. Area Under Curve (AUC)=0.717, P=0.008

from 20 to 35,000 pg/mL.

The prospective follow-up of the patients included physical examination and an ECG 14 days and one month after the ECV. In addition to this, we advised every patient of our study that whenever he had symptoms, such as palpitations, or whatever would have suggested an AF recurrence to come for an urgent visit in order to perform an ECG and detect any possible recurrence of the arrhythmia.

The study complies with the Declaration of Helsinki and an informed consent of the subjects has been obtained.

Statistical Analysis

Categorical data were summarized as frequencies or percentages. Continuous data were summarized as mean ± Standard Deviation (S.D). We used t-test for independent samples to compare means of continuous variables and chi-square test for qualitative variables. We used the Kolmogorov-Smirnov test for normality in order to evaluate assumption of t-test. The natural logarithm of the variables BNP before and BNP after (as independent variables) was used to evaluate assumption of linear regression analysis. Cut-off analysis using Receiver-Operating-Characteristic (ROC) analysis revealed the level of early diastolic transmitral peak velocity with best combination of sensitivity and specificity that discriminate patients according to whether they had an AF recurrence or not. Discriminant analysis after calculating λ-Wilk's showed which of the continuous variables had the best discriminating ability for the outcome. We used linear regression analysis in order to identify linear correlations between continuous variables using R-square. Multiple linear regression analysis was conducted using the "backward stepwise" estimation with p-value (Wald test) for entry equal to 0.05 and p-value (Wald test) for removal equal to 0.10 beginning with full model. A Cox proportional hazard model was used to assess the association of baseline variables with the end point of AF recurrence during the first month of follow-up after the successful electrical ECV. The Cox analysis used to evaluate Hazard Ratios (HR) (and their 95 % C.I) of early diastolic transmitral peak velocity and BNP as predictors of one-month AF recurrence. We used likelihood ratio test to evaluate incremental value of BNP levels added on E-wave before ECV value on short-term AF recurrence using the Cox models.

We considered the results significant when the p value was <0.05.

Data was analyzed using STATA 9.1 College Station, Texas, USA.

Results

Follow-Up

During the one month follow-up period 24 patients (42.1%) had AF recurrence. Patient baseline demographic, clinical characteristics and echocardiographic variables are shown in Table 1.

Clinical Characteristics And Medication

There were no differences in age, gender and underlying diseases (All Ps>0.05) except for hypertension between patients with or without AF recurrence. Specifically, 34 patients (59.6%) had a history of arterial hypertension. The group of AF recurrence had significantly lower prevalence of history of hypertension compared to other group (27.3% vs 72.7% respectively, P=0.018). There were no differences concerning the antiarrhythmic medication and beta-blocking agents (Table 1).

Echocardiographic Parameters And AF Recurrence.

There were no differences in left atrial diameters, LV fractional shortening, before and after ECV, and in the prevalence of mitral regurgitation (All p-values>0.05). The early diastolic transmitral peak velocity before the ECV (E-wave before) was higher in patients with one-month AF recurrence compared to group with SR maintenance (104±28 cm/s vs 84.5±22 cm/s, P=0.006). Similarly, the early diastolic transmitral peak velocity after ECV (E-wave after) was higher in patients with AF recurrence compared to group with SR maintenance (88.3±19 cm/s vs 73.6±21 cm/s, P=0.012) (Fig. 1). Receiver-Operating-Characteristic (ROC) analysis identified appropriate cutoff values of E-wave before and E-wave after with best combination of sensitivity and specificity for predicting one-month AF recurrence (Figure 2 & 3) (Area Under Curve (AUC)=0.717, P=0.008 and AUC=0.693, P=0.018, respectively). The cutoff values of E-wave before was more than 94 cm/s (sensitivity=68%, specificity=77%) and of E-wave after ECV greater than 80 cm/s (sensitivity=76%, specificity=64%) provided the best discrimination between patients without and with AF recurrence. According to the above cutoff points, 27 patients (47.4%) had E-wave before > 94 cm/s and 31 patients (54.4%) E-wave after >80 cm/s.

Table 2: Results from univariate linear regression analysis using as independent variable E-wave before ECV. We present β regression coefficient with corresponding C.I and Wald test P-values

Dependent variable	β	95% C.I	P
Gender (male vs Female)	-28.81	-39.70 to -5.91	0.009*
Age (years)	0.60	0.03 to 1.18	0.039*
Underlying Disease			
CHD	10.70	-6.52 to 27.93	0.218
Mitral regurgitation	13.00	-7.13 to 33.13	0.201
History of hypertension	-0.58	-15.37 to 14.20	0.937
Treatment			
ATII Blockers (0: No vs 1: Yes)	12.90	-0.91 to 26.72	0.067
Beta-blockers (0: No vs 1: Yes)	-5.82	-21.42 to 9.76	0.455
Echocardiographic parameters			
LA diameter (mm)	0.67	-0.29 to 1.65	0.169
Fractional shortening	0.50	-0.32 to 1.34	0.224
*P<0.05			

ECV=Electrical cardioversion, LA= Left Atrium, CHD=Coronary Heart disease, AT II Blockers=Angiotension Receptor II blockers

Table 3: Results from multivariate linear regression analysis using as independent variable E-wave before Cardioversion. We present β regression coefficient with corresponding Confidence Intervals and P-values of Wald tests. Age, beta blockers treatment, History of hypertension, presence of CAD and ejection fraction were excluded from the final model

Dependent variable	β	95% C.I	P
Gender (male vs Female)	-28.56	-48.05 to -9.07	0.005*
Underlying Disease			
Mitral regurgitation (0:No vs 1:Yes)	26.66	4.84 to 48.47	0.018*
Treatment			
ATII Blockers (0:No vs 1:Yes)	19.44	5.43 to 33.45	0.008*
Echocardiographic parameters			
LA diameter (mm)	0.87	-0.06 to 1.81	0.068
*p<0.05			

LA= Left Atrium, CHD=Coronary Artery disease, AT II Blockers=Angiotensin Receptor II blockers.

Early diastolic transmitral peak velocity became lower after successful ECV than before ECV (94.0±27 cm/s vs 79.7±23 cm/s, P<0.0001).

Correlation Of E-Wave Before ECV With Clinical And Echocardiographic Predictors Of AF Recurrence.

We tried to correlate linearly E-wave before ECV with clinical and echocardiographic predictors. Firstly, we performed univariate linear regression analysis using several dependent variables. Results are shown in Table 2. Finally, multivariate linear regression analysis revealed that gender, presence of mitral regurgitation, antihypertensive treatment with angiotensin receptor II inhibitors (AT II inhibitors) and LA diameter (mm) influenced independently E-wave levels before ECV (Table 3). Specifically, female patients had greater E-wave levels than males (P=0.005) and patients with mitral regurgitation had higher E-wave levels (P=0.018)

Prediction Of Short-Term AF Recurrence Based On Clinical And Echocardiographic Parameters.

Univariate Cox regression analysis revealed that E-wave before >94 cm/s and E-wave after >80 cm/s were predictors of one-month AF recurrence, followed by E-wave before ECV and E-wave after

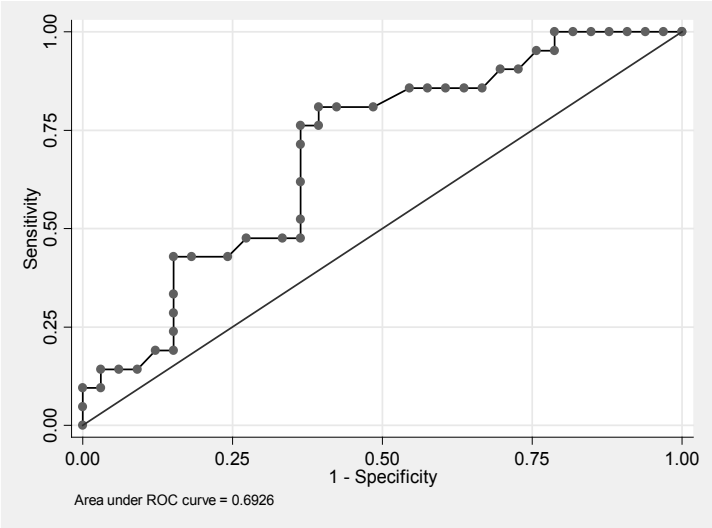

Figure 3: ROC analysis for E-wave velocity after ECV. Area Under Curve (AUC)=0.693, P=0.018

Table 4: Predictors of one-month AF recurrence. Results from univariate Cox regression analysis

Predictors	HR	95% C.I	P
Gender (male vs Female)	0.49	0.21 to 1.15	0.105
Underlying disease			
CAD	0.68	0.25 to 1.82	0.446
Mitral regurgitation	0.83	0.24 to 2.79	0.766
Echocardiographic parameters			
LA diameter (mm)	0.99	0.93 to 1.05	0.814
Fractional shortening	0.99	0.96 to 1.03	0.845
A-wave after ECV (cm/s)	1.01	0.97 to 1.03	0.954
E-wave before ECV (cm/s)	1.03	1.01 to 1.06	0.013*
E-wave after ECV	1.02	1.01 to 1.05	0.020*
E-wave >94 cm/s before ECV	3.62	1.49 to 8.78	0.004*
E-wave >80 cm/s after ECV	3.76	1.40 to 10.10	0.008*

*P<0.05

HR=Hazard Ratio, C.I=C.I, ECV=Electrical cardioversion, LA= Left Atrium, CAD=Coronary Artery disease

ECV as continuous variables (Table 4)

As far as the medication is concerned beta-blockers, Angiotensin Receptors II inhibitors did not seem to have influence on AF recurrence (All p values>0.05) (Data not shown).

Discriminant analysis showed that E-wave before ECV (λ-Wilk's=0.827) was the best discriminator for AF recurrence among all the aforementioned predictors followed by E-wave after ECV (λ-Wilk's=0.866) (Data not shown in texts or tables).

Log rank test showed that there was a difference between AF recurrence experience of patients with E-wave before >94 cm/s and those with <94 cm/s (P=0.002) (Fig. 4). As well, log rank test revealed a difference between the AF recurrence experience of patients with E-wave after >80 cm/s and those with <80 cm/s (P= 0.004) (Fig. 5).

Prediction Of Short-Term AF Recurrence Based On Clinical And Echocardiographic Parameters In Hypertensive And Non-Hypertensive Patients (Sub-Group Analyses)

In order to investigate whether the history of hypertension acts as a confounding factor to the relationship between the early diastolic transmitral peak velocity and the short-term AF recurrence we performed separate Cox regression analyses.

E-wave before and E-wave after (as continuous variables) remained predictors of AF recurrence during the follow-up only in non-hypertensive patients (HR=1.01 with 95% C.I=1.01-1.035, P=0.035 and HR=1.03 with 95% C.I=1.01-1.06, P=0.023, respectively). The corresponding HRs of Cox regression model in hypertensive patients were the following: HR=1.01 with 95% C.I=0.99-1.045, P=0.15 and HR=1.01 with 95% C.I=0.98-1.05, P=0.278.

BNP And Short-Term AF Recurrence

E-wave before and after ECV correlated linearly with natural logarithm of BNP levels before and after ECV (p=0.027 and p= 0.001).

It is interesting that logarithm of BNP levels dropped rapidly after successful ECV (6.9±0.9 vs 6.3±1.1, P<0.0001).

NT-pro BNP levels before and after ECV had a significant effect on short-term AF recurrence (HR=1.14 with 95% C.I 1.01-1.28 and HR= 1.16 with 95% C.I 1.03- 1.31, respectively).

NT-proBNP levels added on E-wave before ECV had incremental value on short-term AF recurrence at a marginally statistical significance (LR chi2=3.28, p=0.07).

Discussion

In our study we investigated the prognostic role of peak early diastolic transmitral peak velocity and we found a positive association between this marker and short-term atrial fibrillation recurrence.

The Framingham Heart study revealed that a one Standard Deviation increment in ratio of the velocity-time integrals of the early and late diastolic filling waves was associated with a 28% higher risk of AF.[7] This may be due to the fact that these markers reflect increased left atrial afterload probably because of left ventricular diastolic dysfunction.[10] However, other investigators did not find any association of E-wave and AF recurrence, even if the follow-up was longer i.e. for 1 year.[11] On the other hand, in patients following first anterior myocardial infarction AF recurrence was associated with significant reduction of E-wave.[12] But this study referred to a specific sub-group of AF patients and these patients were not followed-up after a successful cardioversion.

In our study we performed sub-group analysis and we found that E-wave before and E-wave after ECV remained predictors of AF recurrence only in non-hypertensive patients. This may be due to the fact that paroxysmal atrial fibrillation in hypertension is associated with depression of left atrial contractile function and "normalization" of the pattern of left ventricular filling.[13] In our study we found that gender, presence of mitral regurgitation, ATII inhibitors treatment and LA diameter (mm) influenced independently E-wave levels before ECV. So, further studies need to investigate the association of E-wave, hypertension, ATII inhibitors treatment and LA diameter with AF short-term recurrence. Thus, we would be ready to depict the common pathophysiologic entity of the above factors and its "causal pathway".

BNP is a ventricular hormone which is secreted from myocytes with the major determinant of secretion being the degree of ventricular stretch and work.[14] Several investigators reported that plasma BNP levels fell immediately following successful cardioversion.[15] In a recent study, pre- and post-cardioversion BNP concentrations were shown to be predictive of reversion to AF, independent of age, LV function or the prophylactic prescription of β-blockers.[14,16] Furthermore, even in patients with mild congestive heart failure, BNP before cardioversion was an independent predictor of AF recurrence.[17] Also,

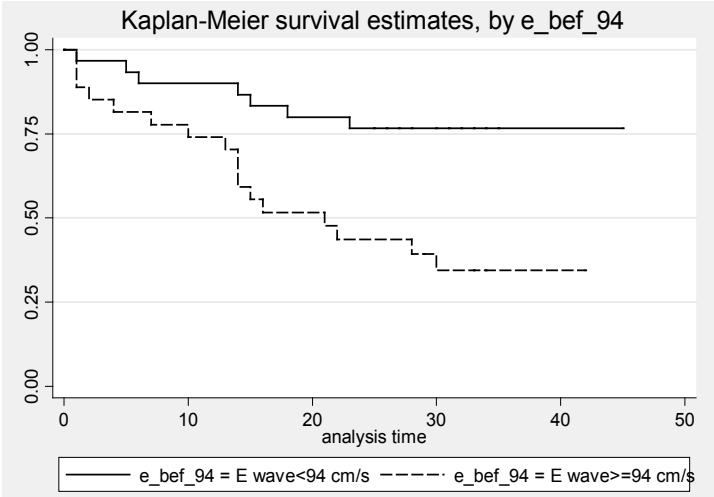

Figure 4: Kaplan-Meier Survival Estimates for patients with E wave velocity before ECV more and less than 94 cm/s

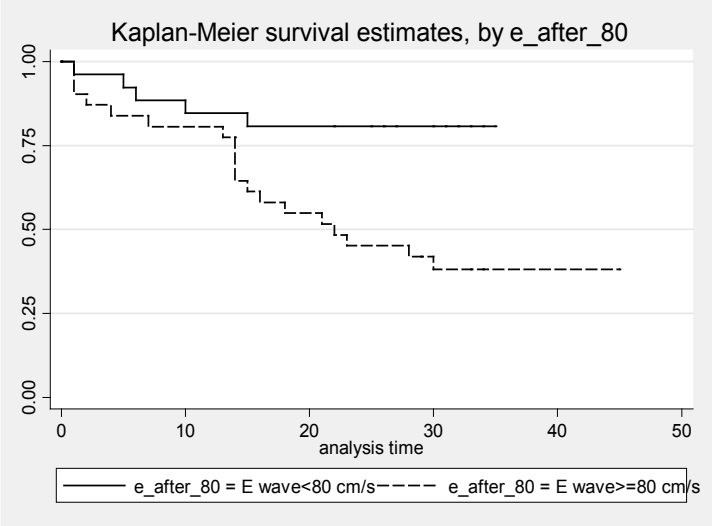

Figure 5: **Kaplan-Meier Survival Estimates for patients with E wave velocity after ECV more and less than 80 cm/s**

in a recent meta-analysis, researchers found that low preprocedural BNP levels were associated with SR maintenance.[18]

Limitations Of The Study

E-wave had prognostic significance on short-term recurrence of AF after ECV, but this was more prominent in non-hypertensive subjects. It would be of great interest to perform separate analyses of the predictive value of E-wave according to different underlying disease or to different antihypertensive medication (i.e. AT II inhibitors). But this was impossible to do because we enrolled small number of patients and, thus there was no enough statistical power to establish a difference that really exists. We cannot conclude from this study whether E-wave is a marker or an etiologic factor of AF recurrence, or whether acts as an indirect marker of left ventricular diastolic dysfunction in accordance with NT-pro BNP. We need large cohort studies after successful ECV in order to illuminate the relationship between E-wave itself, NT-pro BNP, antihypertensive therapy and AF recurrence. This study provides only an indication that these entities may play a role to a specific subgroup of patient (i.e non-hypertensive subjects), which remains to be further and better clarified with other studies. In addition to this, mitral E-wave velocity by itself does not accurately reflect left atrial function or left ventricular filling pressure as an it can be elevated due to many other conditions such as high output flow states (e.g. Anemia, tachycardia, sepsis, thyrotoxicosis and liver disease), which were not accounted for in the present study. Besides that, it seems that the use of more contemporary modalities such as tissue Doppler, Strain and speckle imaging techniques have better correlation with invasive measurements of LA pressure and LV filling pressure.

Conclusions

Peak early diastolic transmitral peak velocity had prognostic significance on short-term recurrence of AF after ECV, which was prominent in non-hypertensive subjects. The identification of predisposing factors for AF recurrence may affect the potential changes of antiarrhythmic medications or may also have consequences for choosing non-pharmacological treatment, for instance catheter-ablation.

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Left Atrial Appendage Tachycardia Termination With A LARIAT Suture Ligation

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Abstract

Left atrial appendage (LAA) is a known trigger for left atrial tachycardia (AT). The use of LARIAT epicardial suture for termination of AT arising from LAA is not yet reported.

A 66-year-old female had a history of hypertension, diabetes, sick sinus syndrome, labile INR, and symptomatic persistent AF. She underwent radiofrequency ablation after failed cardioversion and multiple antiarrhythmics. She was in AT originating from LAA on activation map. Radiofrequency endocardial LAA isolation was performed. However, the AT recurred with increased burden and symptoms. Due to her multiple hospitalization for spontaneous bleeds and labile INR, a Lariat epicardial suture ligation of her LAA was performed. With application of the Lariat suture, electrical isolation was achieved and the AT terminated. She remained AT free at 18 months.

Our case is the first to illustrate the utility of LARIAT suture in electrical isolation of the LAA in addition to its mechanical exclusion.

Introduction

The Left atrial appendage (LAA) is a known trigger for left atrial arrhythmia. While endocardial radiofrequency ablation of the LAA is well known to control atrial arrhythmias, the use of LARIAT epicardial suture for termination of AT arising from LAA is not yet reported.

Case Report

A 66 year old female with recurrent symptomatic persistent atrial fibrillation (AF) and atrial tachycardia (AT) who failed cardioversion and multiple anti-arrhythmic medications including: propafenone, dofetilide, dronedarone and sotalol with several symptomatic breakthrough episodes.

Her past medical history included also: hypertension, diabetes mellitus, non critical coronary artery disease, obstructive sleep apnea, chronic obstructive pulmonary disease, colon cancer s/p colectomy, sick sinus syndrome s/p dual-chamber pacemaker, chronic anticoagulation with warfarin for AF and recurrent lower extremity deep venous thrombosis (DVT).

Key Words:

Atrial Tachycardia, LARIAT, Left Atrial Appendage.

Disclosures:

None.

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Physical examination and labs were unremarkable. After a lengthy discussion for the available options of her symptomatic arrhythmia she requested a radiofrequency ablation. Her CT scan showed normal pulmonary veins anatomy and a moderately enlarged left atrium with no thrombus. During her procedure and just after transseptal puncture, a thrombus was noted on the sheath inside the left atrium (despite INR=2.0 and 10,000 Units of Unfractionated IV Heparin bolus at transseptal puncture). The procedure was aborted and the patient was maintained on a higher INR goal (2.5-3.5).

Unfortunately, with a supratherapeutic INR, a hematoma developed over her left elbow that had resolved later. She was rescheduled for the ablation procedure 3 months later. She was found in atrial tachycardia, cycle length (CL)= 470ms (127bpm) at the beginning of the procedure. This was tracked by her PPM (upper tracking rate 130bpm). Activation map of the tachycardia showed a reentrant tachycardia around the base and neck of the left atrial appendage (LAA) (Figure 1). She had extensive left atrial scar on voltage map. Isolation of the left atrial appendage with radiofrequency ablation successfully terminated the tachycardia and the patient converted to NSR. We continued the procedure with an isolation of her pulmonary veins and a cavo-tricuspid isthmus ablation for an induced right sided flutter.

Two weeks later, she presented with groin pain and hematoma. She was on enoxaparin subcutaneous injections for subtherapeutic INRs. CT scan showed a subacute right anterior thigh hematoma (5.9 x 2.7 cm) with no intra or retroperitoneal extension. Due to fluctuations in INRs a recommendation for new oral anticoagulants was made but the patient couldn't afford it. The bleeding events unfortunately continued. With an INR of 3.5, she was admitted to an outside

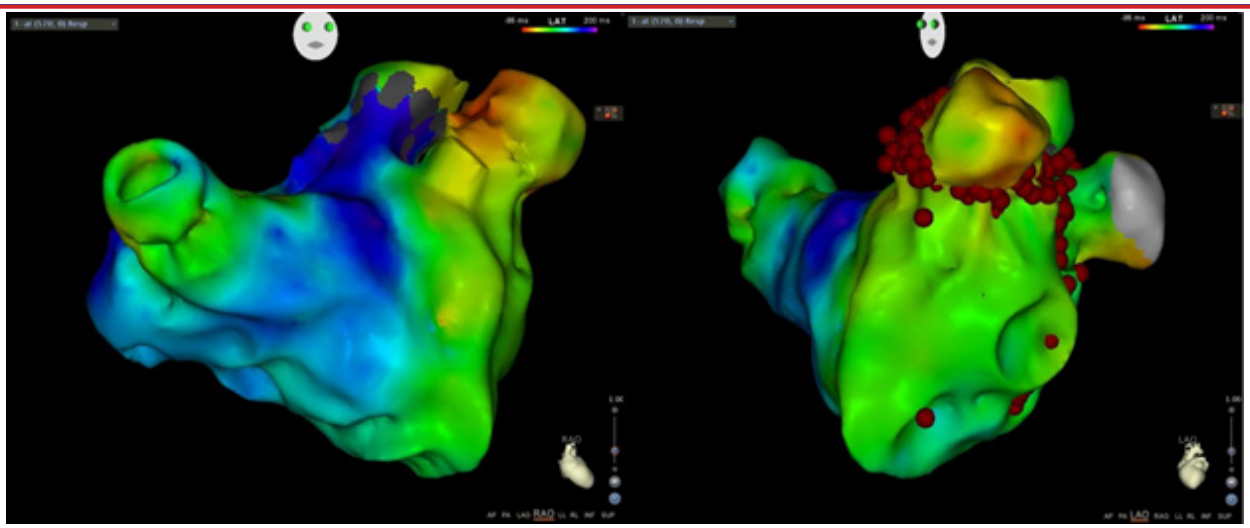

Figure 1: RAO and LAO views of the AT Activation Map. Origin from the left atrial appendage. Ablation points of the LAA ablation were listed in the LAO view

hospital for hematomas in her psoas muscle and rectus abdominis sheath.

She was in sinus rhythm at that time. She was restarted on warfarin 2 weeks after the last bleeding event. Three months later the patient was found with a recurrent atrial tachycardia with a similar cycle length around 470ms. The burden increased and later become persistent with atrial fibrillation reaching a 73% of the time on device interrogation.

With recurrent atrial tachycardia that is most likely originating from the left atrial appendage, multiple bleeding episodes from the elbow, psoas, groin and rectus sheath; increased HAS-BLED score of 5 we discussed the treatment options with our patient and she agreed for a LARIAT suture ligation for her left atrial appendage.

On the day of the procedure, and after intubation a negative trans-esophageal echocardiogram for thrombus, the patient was noted in atrial tachycardia. The CL was 470ms with ventricular pacing. The Lariat device (SentreHEART, Redwood, California, USA) consists of a compliant occlusion balloon catheter (EndoCATH), magnet-tipped guidewires and a 12-F suture delivery device (LARIAT). The procedure was done as described previously.[1] To place the suture across the LAA, a pericardial and transseptal accesses were obtained separately. The endocardial magnet-tipped guidewire was advanced into the apex of the LAA. The other magnet tipped guide wire was advanced pericardially to the tip of the LAA to establish a stable connection between the two magnet tips. A snare was then advanced over the LAA and after confirmation of closure, a pre-tied suture for LAA ligation was released and tightened (Figure 2). The tachycardia, which was present throughout the procedure, terminated two minutes after tightening the appendage and with further application of the suture (Figure 3). She remained in normal sinus rhythm during her uneventful post procedure stay.

During long term follow-up (18 months), her device interrogation always showed great control of her atrial arrhythmia. The total AT/AF burden decreased to 0.7%. She remains in AV sequential pacing 98% of the time with normal left ventricular function. Post her LAA suture ligation she remained doing well off anticoagulation and was kept only on Aspirin and Metoprolol.

Discussion

Our case demonstrated the termination of left atrial appendage reentrant tachycardia following appendage ligation with Lariat suture delivery device. In our case, initial isolation of the appendage was performed using radiofrequency ablation. However reconnection occurred and electrical isolation was maintained with Lariat suture.

Although this case was mainly performed in the setting of recurrent bleeding episodes, however, this may open the potential use of Lariat epicardial suture ligation for the treatment of atrial tachycardia

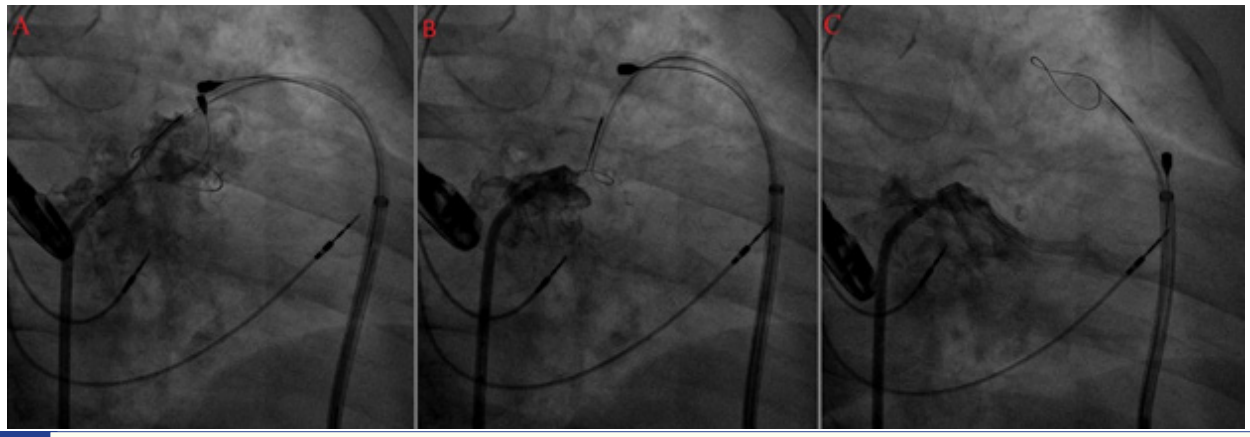

Figure 2: Left Atrial Appendage ligation with the Lariat Suture: A- The endocardial and epicardial magnet-tipped guidewires are connected and the Lariat device is placed around the neck of the appendage. B- Lariat device is tightened without releasing the suture, note that the balloon was deflated and the magnet-tipped guidewires are pulled back. C- After the satisfactory position, the Lariat suture was released, atriogram showing the final result

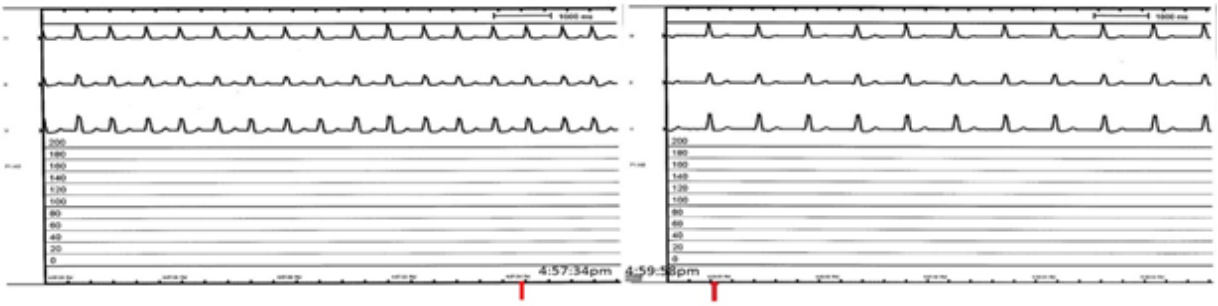

Figure 3: Electrical Isolation of the LAA with Lariat: termination of the AT was noted 2 minutes after tightening the appendage with Lariat Device/Suture

arising from the left atrial appendage. To our knowledge, this is the first case report that demonstrates this phenomenon.

LAA triggers are well known to be an important contributor for initiation and maintenance of persistent atrial arrhythmias.[2,3] If the LAA was found to be a trigger (like in this case), endocardial isolation of the left atrial appendage reduces the risk of AF/AT.[2] However, endocardial isolation of the LAA is extremely challenging as it carry a significant risk of perforation, in addition to electromechanical dissociation which may subsequently contribute to thombus formation.[2] In our patient with recurrent bleeding episodes, the choice of a LAA ligation with Lariat suture was optimal as it provided both mechanical as well as electrical isolation of the LAA. The later most likely decreased the risk of stroke in this patient with persistent arrhythmia.

A prior case report demonstrated the termination of the atrial tachycardia immediately after the placement of the AtriClip device.[4] Similarly in preclinical studies epicardial LAA exclusion has been shown to result in LAA electrical isolation.[5] In a recent study performed at our center, we demonstrated that 90% of patients had a reduction in the LAA voltage with lariat suture ligation. We were also able to demonstrate the lack of left atrial capture during bipolar pacing from the occluded LAA in 90% of the patients tested.[6] Although various other delivery devices like the watchman device and the amplatzer cardiac plug are good mechanical closure alternatives and help to prevent risk of thromboembolism, however electrical isolation cannot be achieved. Arrhythmia control was extremely helpful in our patient and she was able to remain asymptomatic while off antiarrhythmic and anticoagulation. This was recently proven in our prospective observational study, LAALA-AF, which involved 138 patients with persistent AF. A higher freedom of AF at 1year off antiarrhythmic was noted in the Lariat group (65% VS 39%, p=0.002) in addition to less need for a repeat ablation for recurrence (16% VS 33%, p=0.018).[7]

Procedure wise, Lariat ligation suture was shown to have a high success rate (96%, 89 patients) and limited adverse events rate of 3.3% (bleeding).[8] This rate was even lower in a large survey conducted in 11 US sites that involved 441 patients. The bleeding rates decreased from 3.3% (2% need for transfusion and 1.3% need for open heart surgery) to none in the remaining 231 patients and was referred to the switch from an 18-gauge Pajunk needle to micropuncture for the pericardial access.[9] The use of micropuncture needle (performed in this case) was further recommended in a multi-center study including our center. With its use, a decreased incidence of major complications and the need for surgical repair was noted.[10]

Conclusions

In conclusion, our case is the first reported which demonstrates termination of a LAA reentrant tachycardia with a Lariat suture. It may be important to consider the electrical isolation as additional benefit to patients who are selected for appendage occlusion.

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Proarrhythmic Effects Of Antiarrhythmic Drugs: Case Study Of Flecainide Induced Ventricular Arrhythmias During Treatment Of Atrial Fibrillation

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Abstract

Purpose : Flecainide is a class 1C antiarrhythmic drug especially used for the management of supraventricular arrhythmia. Flecainide also has a recognized proarrhythmic effect in patients treated for ventricular tachycardia. It is used to treat a variety of cardiac arrhythmias including paroxysmal atrial fibrillation, paroxysmal supraventricular tachycardia and ventricular tachycardia. Flecainide has local anesthetic effects and belongs to the class 1C AADs that block sodium channels, thereby slowing conduction through the heart. It selectively increases anterograde and retrograde accessory pathway refractoriness. The action of flecainide in the heart prolongs the PR interval and widens the QRS complex. The proarrhythmic effects however noted are not widely reported.

Method : We report a case of paroxysmal atrial fibrillation with structurally normal heart who was treated with oral Flecainide. There were no adverse events and no QTc prolongation was noted on ECG. Despite subjective improvement a repeat Holter detected him to have multiple short non sustained ventricular arrhythmias.

Results : Development of ventricular arrhythmias, salvos and non-sustained ventricular tachycardia after a month of initiation of oral flecainide detected by 24 hours ECG Holter lead to discontinuation of flecainide and subsequent early electrophysiological studies and successful ablation.

Conclusion : Initiation of oral Flecainide in a case of atrial fibrillation with subjective improvement and regular ECG monitoring, no QTc prolongation can still lead to development of dangerous ventricular arrhythmias. A cautious approach and thorough investigations and follow up are recommended.

Introduction

Flecainide is a class 1C antiarrhythmic drug used especially for the management of supraventricular arrhythmias such as paroxysmal atrial fibrillation (AF).[1] It causes rate- dependent slowing of the rapid sodium channel slowing phase 0 of depolarization and in high doses inhibits the slow calcium channel.[2] Flecainide also slows conduction in all cardiac fibers, increasing conduction times in the atria, ventricles, atrio-ventricular node and His-Purkinje system. Flecainide can also cause myocardial depression. In over- dose cases, flecainide can induce life treating ventricular arrhythmias and cardiogenic shock.

Case Report

Mr. RJN, 44 years male was diagnosed with paroxysmal atrial fibrillation in May 2013 and was under beta blockers and acetyl salicylic acid. He was reviewed in our hospital in September 2013 because of his disturbing symptoms of palpitations and fatigue. Beta blockers were stopped and he was started with flecainide and dabigatran with the possibility of electrical cardioversion later if required. Regular follow ups were done and he reported subjective improvement starting after 3 days. Periodic ECG done did not show any QTc prolongation. He was reassessed with Holter after one month of flecainide treatment and found to have multiple short episodes of ventricular arrhythmias [salvos and non-sustained ventricular tachycardia] while still suffering from paroxysms of atrial fibrillation. Thereafter he was admitted to CCU and flecainide was stopped. He was switched back to beta blockers and again reassessed with Holter after a week which showed persistent atrial fibrillation with no ventricular tachyarrhythmia.

Risk Profile: No hypertension or diabetes. Nonsmoker.

Physical examination: Blood pressure: 110/70 mm of Hg, pulse rate: 102/minute irregular. No evidence of heart failure.

ECG: Initial: Atrial fibrillation, ventricular rate ~110/minute. On beta blockers currently.

With Flecainide: Paroxysmal AF with multiple nonsustained ventricular arrhythmias.

Fig 1 Holter trace showing Ventricular arrhythmias Fig 2 Holter

Key Words:
Flecainide, Atrial Fibrillation, Ventricular Arrhythmias.

Disclosures:
None.

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trace showing Ventricular arrhythmias

ECHO: Atrial fibrillation, normal LV dimensions and systolic function.

He underwent electrophysiological studies and successful isolation of all four pulmonary veins for paroxysmal atrial fibrillation with termination of focal site for AF initiation near mid/proximal coronary sinus roof.

Discussion

Pharmacological Treatment For Atrial Fibrillation

Pharmacological cardioversion of AF can be achieved using a number of drugs with different pharmacological properties, including disopyramide, procainamide, quinidine (all class IA), flecainide, propafenone (both class IC), dofetilide, ibutilide, sotalol, and amiodarone (all class III). Currently, the most commonly used drugs for chemical cardioversion are flecainide, sotalol, and amiodarone. Little difference is observed between the routes of administration for cardioversion rates, although intravenous administration results in faster conversion. Indeed, in patients with recent onset AF, successful cardioversion is reported in up to 80% of cases with oral therapy, rising only to 90% with intravenous administration.[1]

Unfortunately, recurrence of AF is common, often requiring long-term drug therapy to improve maintenance of sinus rhythm. For most current antiarrhythmic agents, the relapse rate is at least 50% during the first year,[2–5] although slightly better figures are seen with dofetilide[6] and amiodarone.[7, 8] A number of studies have also demonstrated that flecainide and propafenone are effective drugs for preventing AF recurrence.[9–11] The effectiveness of flecainide is comparable to quinidine, but with fewer side effects.[12] In contrast, propafenone is more effective for maintenance of sinus rhythm than quinidine. It is as effective as sotalol.[13, 14] Generally, however, class IC drugs are preferred to class IA drugs in view of their better safety profile.[12, 13] The success of electrical cardioversion for AF has been quoted as between 75 and 93%, although this depends on left atrial size and co-existing structural heart disease, and ultimately on the duration of AF.[15–17] Where there is some concern about a successful restoration of sinus rhythm (for example, previous cardioversion failure or early recurrence of AF), concomitant amiodarone or sotalol can be used pre-cardioversion to improve the success of electrical cardioversion.[18] Such an approach is advocated by the ACCF/AHA practice guidelines 2013 on AF management.[2] The frequency of recurrence of AF after electrical cardioversion is high, and maintenance therapy with antiarrhythmic drugs such as amiodarone or sometimes b-blockers is somewhat useful to prevent AF relapses.[1] Beta-blockers are very effective at controlling ventricular rate and also may reduce the risk of AF recurrence following successful cardioversion (whether spontaneous, pharmacological, or electrical) and are currently used as first-line prophylactic agents in paroxysmal AF. Rate-limiting, non-dihydropyridine calcium channel blockers (diltiazem, verapamil) are frequently used to optimize rate control where B-blockers are contraindicated or ineffective. A rate-limiting calcium antagonists (diltiazem, verapamil) are indicated where urgent pharmacological rate control is required. Intravenous amiodarone is a useful alternative in situations where the administration of b-blockers or calcium antagonists is not feasible, such as in the presence of heart failure. All current class IA, IC, and III antiarrhythmic drugs have significant side effects. This includes non-cardiovascular effects (e.g. pulmonary fibrosis and thyroid dysfunction with amiodarone), and

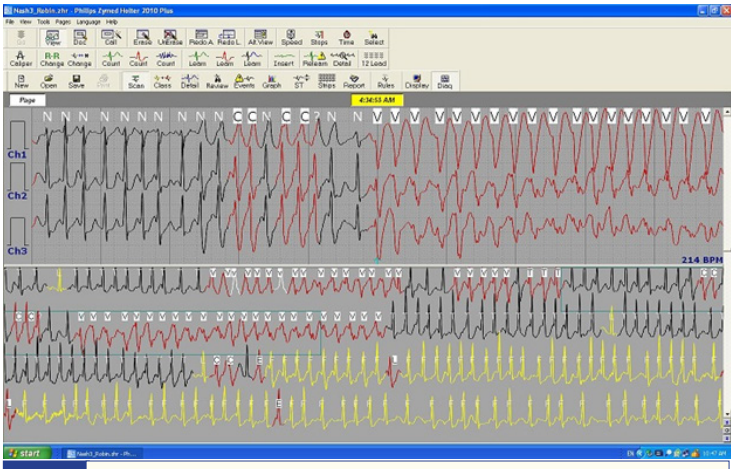

Figure 1: Holter trace showing Ventricular arrhythmias

of particular importance, the risk of life-threatening ventricular proarrhythmia including TdP in up to 5% of patients.[19, 20] Most of these antiarrhythmic drugs prevent or terminate AF by altering the function of potassium or sodium channels within the atrial cells. Blockade of potassium channels may prolong ventricular repolarization — and hence, the refractory period — resulting in QT-interval prolongation. Given the risk of severe proarrhythmia, the safety profile of many current antiarrhythmic drugs is far from ideal.

From the early twentieth century, drug therapy has played an important role in the management of atrial arrhythmias. Quinidine was the first antiarrhythmic used to successfully restore and maintain sinus rhythm in atrial fibrillation (AF). Subsequently, a large number of other drugs have become available. Although the efficacy of many of these agents is impressive, side effects are a frequent occurrence. Amongst the most worrying side effects are QT-interval prolongation and risk of proarrhythmia, including torsade de pointes (TdP)[21]

Flecainide, a class 1C anti-arrhythmic agent, depresses the rate of depolarization of cardiac action potentials producing a membrane stabilizing action. It is a very effective anti-arrhythmic agent against supraventricular arrhythmias, nevertheless flecainide is contraindicated in patients with structural heart disease because it increased mortality.[22] The proarrhythmic effect of flecainide may be related to promoting a reentry in ventricular tissue. The phenomenon is due to a rate-dependent blockade of rapid sodium channels slowing phase 0 of depolarization and an inhibition of the slow calcium channel.[23] In cases of overdose, the mortality with class Ic agents has been reported to approach 22%. Conduction disturbances began with widening of QRS complex which can rapidly progress to ventricular tachycardia, electromechanical dissociation and asystole.

Despite the large number of available antiarrhythmic agents, significant QT-interval prolongation and risk of severe proarrhythmia, including torsade de pointes, limit pharmacological opportunities in the management of atrial arrhythmias. The risk of proarrhythmia has been demonstrated in class I and class III drugs, but significant variability has been observed between agents of the same class. Electrophysiological drug effects found to be important in the etiology of proarrhythmia include QT- interval prolongation through selective blockade of the delayed rectifying potassium current (IKr), early afterdepolarizations, transmural dispersion of repolarization, and a reverse rate dependence. Interestingly, less

proarrhythmic potential is seen or anticipated with agents that are able to block multiple ion channels and those with atrial selectivity, despite moderate QT prolongation. This observation has helped steer the development of newer drugs, with some promising preliminary results.

Conclusions

In conclusion, despite the large number of antiarrhythmic agents that are currently available, modern cardiology is still waiting for the introduction of new efficient and safe drugs for the treatment of atrial arrhythmias. The ideal anti- arrhythmic agent must efficiently cardiovert AF patients and prevent relapses without proarrhythmic potential. To achieve this, it seems that such drugs should be atrial selective, should have multi ion-channel effects, should not increase transmural dispersion of repolarization, should not produce early after depolarization, and should not exhibit reverse use-dependency.

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Cardiac Resynchronization in Patients with Atrial Fibrillation

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Abstract

Atrial fibrillation (AF) occurs in one of four patients undergoing cardiac resynchronization therapy (CRT).-Without special therapy, the prognosis of AF patients with CRT has been generally worse than those in sinus rhythm. The importance of a high percentage of biventricular pacing (BIV%) was confirmed in a large study where the mortality was inversely associated with BIV% both in the presence of normal sinus and atrial paced rhythm and with AF. The greatest reduction in mortality was observed with BIV% >98%. Patients with BIV% >99.6% experienced a 24% reduction in mortality ($p < 0.001$) while those with BIV% <94.8% had a 19% increase in mortality. The optimal BIV% cut-point was 98.7%. This cutoff would appear mandatory but it would be best to approach 100%. Careful evaluation of device interrogation data upon which the BiV% is based is essential because the memorized data can vastly overestimate the percentage of truly resynchronized beats since it does not account for fusion and pseudofusion between intrinsic (not paced) and paced beats. The recently published randomized CERTIFY trial provides unequivocal proof of the value of AV junctional (AVJ) ablation in CRT patients with AF. This trial confirmed the favorable results of AVJ ablation by many other studies and two important meta-analyses and therefore established the firm recommendation that the procedure should be performed in most, if not all, patients with permanent AF as well as those with frequent and prolonged episodes of paroxysmal AF. Patients after AVJ have improved mortality with a mortality similar to those in sinus rhythm. The AVJ ablation procedure carries the theoretical risk of device failure and death in pacemaker dependent patients. An inappropriate first ICD shock for AF seems to increase mortality. Increased long-term mortality after an inappropriate shock may be due to the underlying atrial arrhythmia substrate as opposed to the effect of the shock itself.

Introduction

The major randomized controlled trials that demonstrated the efficacy of cardiac resynchronization therapy (CRT) excluded patients with atrial fibrillation (AF). Yet, AF occurs in one of four recipients of CRT.[1-2] The prognosis of AF patients with CRT is generally worse than that of patients in sinus rhythm.[3-4] because they are at a major disadvantage.[5] They exhibit loss of atrioventricular synchronicity, a higher risk for insufficient CRT delivery because of uncontrolled ventricular rates, more ICD shocks for ventricular arrhythmia, inappropriate ICD shocks, inadequate symptomatic improvement, repeated hospitalization and increased mortality.[6-17] Furthermore AF may be associated with fusion and pseudofusion beats that represent inefficient biventricular capture (Fig 1).[18,19] Such beats render the pacing counters inaccurate for assessing true biventricular capture beats. AF represents an important cause of poor long-term CRT benefit and prognosis unless aggressive efforts are made to slow the ventricular rate. The new developments in rate control can now promote the delivery of a high percentage of biventricular paced beats to the AF patient (which was challenging in the past) so as to produce an overall response virtually similar to that seen in patients with sinus rhythm despite the persistence of atrial arrhythmia.

Contemporary CRT devices are equipped with reliable and extensive diagnostic and memory features yielding full disclosure of the number, duration, and overall burden of atrial tachyarrhythmias. These advanced diagnostic features have demonstrated the high frequency of symptomatic and asymptomatic AF and atrial arrhythmias in CRT patients with heart failure (HF). Because the overwhelming majority of atrial tachyarrhythmias consist of AF, we shall refer, as do many workers, to atrial tachyarrhythmias simply as AF.[15-17, 20] Some arrhythmias stored in an implanted device may not be true AF but rather atrial tachycardias or atrial flutters with rates that exceed the programmable recording threshold. In AF the loss of atrial transport function and associated tachycardia frequently result in deterioration of cardiac function and clinical outcome.

Key Words:
Atrial Fibrillation, Cardiac Resynchronization, B Iventricular Pacing, Ablation Of Atrioventricular Junction, Implantable Cardioverter Defibrillator

Disclosures:
None.

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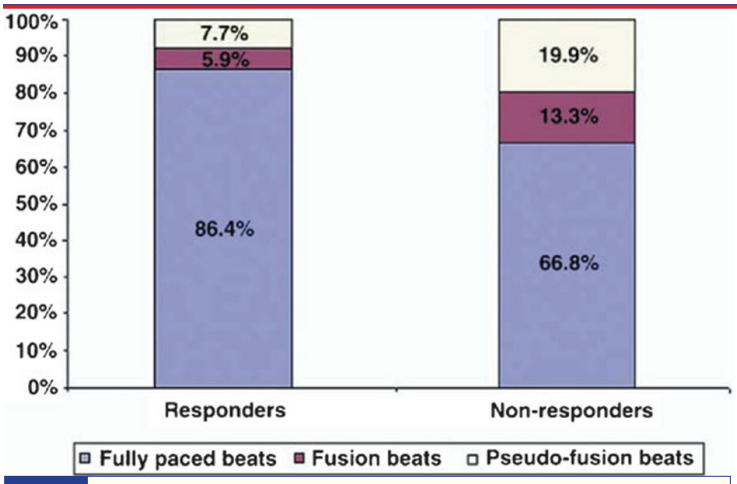

Figure 1: 24-hour Holter data for cardiac resynchronization therapy (CRT) responders and non-responders with permanent AF. CRT responders had a higher percentage of fully paced beats than non-responders. Non-responders to CRT had a significantly higher percentage of ineffective pacing because of a combination of fusion and pseudo-fusion beats (Reproduced with permission from reference.[18])

AF compromises CRT delivery due to RR interval variability and competing tachycardia, and may even result in excessive rapid ventricular pacing during atrial tracking. Arrhythmia occurrence must be confirmed by examining stored electrograms to rule out problems such as intermittent undersensing, far-field R wave sensing by the atrial channel, and electromagnetic interference. Because of intermittent atrial undersensing, a single prolonged episode may be recorded as multiple shorter episodes so that the overall arrhythmia burden may be more reliable than the number of episodes.

Device interrogation also provides estimates of the percentage of biventricular (BIV%) pacing in CRT patients, a measurement of the utmost importance in achieving a satisfactory clinical response.[18, 19] Other important data from implanted devices include the ventricular rate during atrial tachyarrhythmias and stored electrograms that permit the precise diagnosis of the atrial tachyarrhythmia (e.g. AF versus atrial flutter versus atrial tachycardia) and characterize the initiation/termination of arrhythmias. The AF burden calculated from the recordings in terms of total time in AF during a specific period is sometimes called the "electrocardiographic" AF burden. This burden can be further subdivided into total time in AF, the number of AF (re)occurrences in a specific period or duration of the AF-free period until the recurrence of AF, or a combination of these.

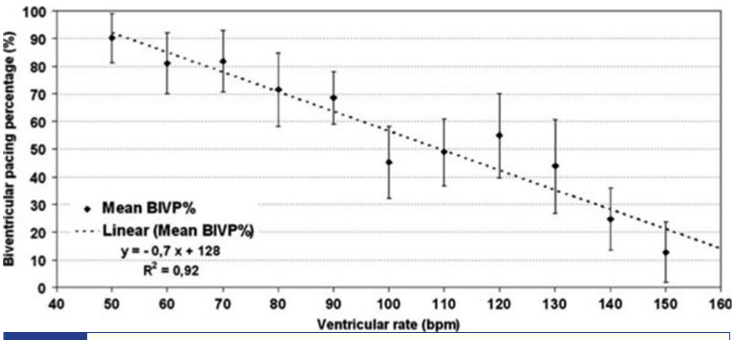

Figure 2: The percentage of effective biventricular pacing (BiVP%) during atrial fibrillation decreases linearly as a function of the ventricular rate. The faster the ventricular rate, or the shorter the R-R interval, the less biventricular pacing was present. (Reproduced with permission from reference.[21])

AF burden is a more accurate assessment of AF than the time to the first recurrence of AF.

Incidence and Prognosis of Atrial Fibrillation During Cardiac Resynchronization Therapy

Device based continuous monitoring of AF in CRT patients has improved the diagnosis and therapy of AF in this group of patients.[7] The bulk of our knowledge regarding the role of CRT in patients with permanent AF is based on non-randomized, observational data. AF and heart failure have much in common and frequently coexist. AF is independently associated with a worse outcome in heart failure. Marijon et al[16] analyzed the incidence of AF in CRT patients in a prospective study and found that 34 out of 173 (27.5%) patients developed paroxysmal AF during a follow-up of 9.9 ± 3.6 months. About half of the AF patients had a past history of AF. Boriani et al[21] evaluated 1404 CRT patients for a median follow-up of 18 months. All were in sinus rhythm at the time of entry into the study. AF was documented in 443 out of 1404 patients (32%). The duration of AF ranged from > 10 min to weeks. AF developed in 222 CRT patients without a previous history of AF (22%) and 221 CRT patients with a previous history of AF (16%). The observations of Leclercq et al[17] involving 120 CRT patients followed for a mean of 183 ± 23 days showed an AF incidence of 21%. A previous history of AF was present in 29% of patients and those with new-onset AF after CRT constituted 17% of all the patients. Thus, the incidence of AF in patients with heart failure treated with CRT ranges from 30 – 35% for paroxysmal AF and around 20–25% for permanent AF. This should not be surprising given the association of AF with the severity of HF heart failure. This association carries a worse prognosis than HF with sinus rhythm.

Boriani et al[21] found in their AF population that age (p = 0.046), and uncontrolled VR (p = 0.028) were the only independent predictors of clinical outcome assessed by the combined end-point of HF hospitalizations or death. In a study involving 1193 CRT patients (initially all in sinus rhythm) Santini et al[18] found AF in 361 patients (30%) over a mean follow-up of 13 month (The study overlapped that of Boriani et al[21]). Among 882 patients with no previous history

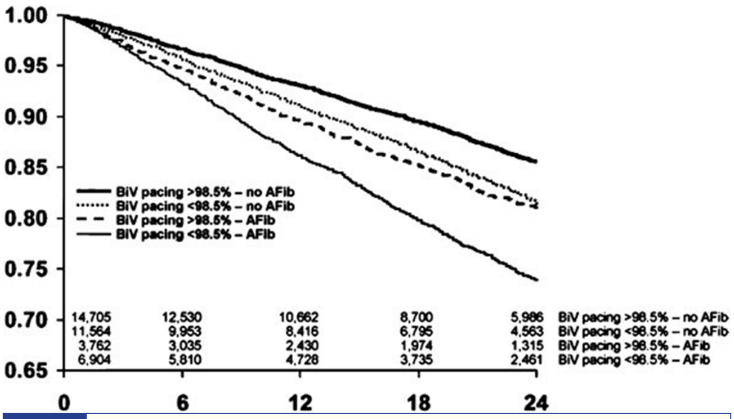

Figure 3: In a large cohort of 36,935 patients followed up in a remote-monitoring network (LATITUDE Patient Management system) a high percentage of biventricular (BiV) pacing achieved, specifically >98.5%, was associated with a reduction in mortality. As expected, patients with atrial fibrillation (AF) had a worse outcome than those without AF. However, this was lessened if the high percentage of BiV pacing could be achieved in the AF population, usually after an atrioventricular junction ablation (Reproduced with permission from reference.[24])

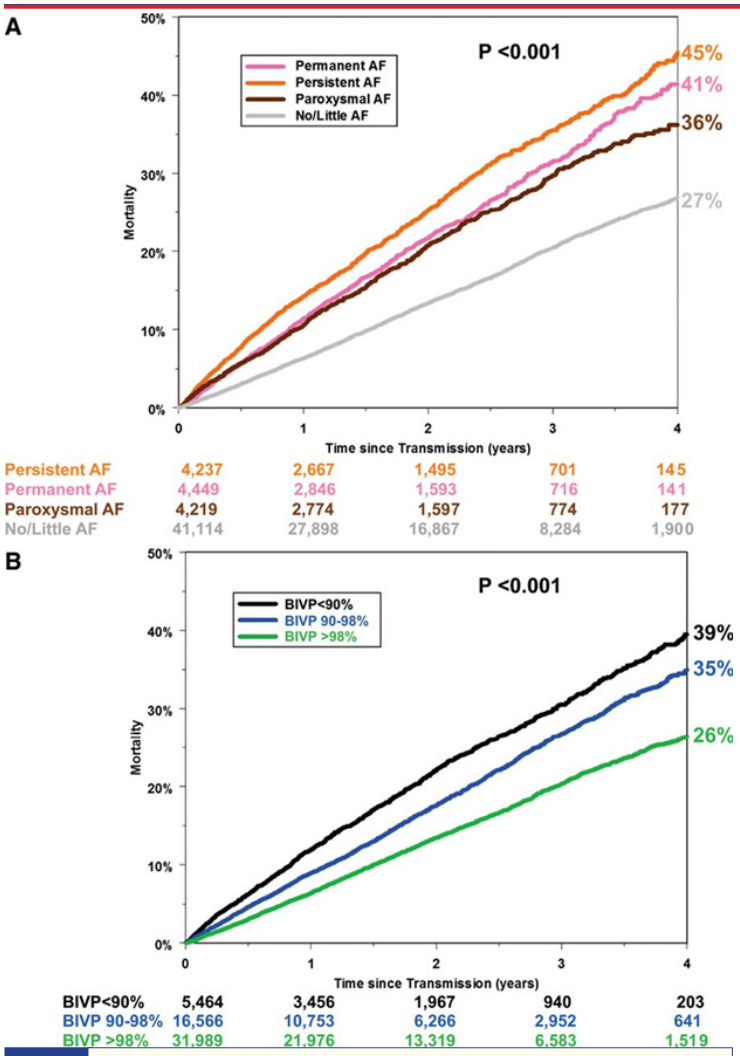

Figure 4: The epidemic of inadequate biventricular pacing in patients with persistent or permanent atrial fibrillation. Unadjusted mortality. A, Atrial fibrillation (AF) classification groups. B, Biventricular pacing (BIVP%) groups. See text for details. (Reproduced with permission from reference.[26])

of AF, 20% developed new-onset AF. The end point of deaths or hospitalizations occurred in 174 patients (14.6%). AF (especially persistent AF) was significantly correlated with the composite end point of death and HF hospitalization (p = 0.005).

Prognostic data was also obtained in a recent subanalysis of the MADIT-CRT trial where the cumulative probability of both the combined end point of HF or all-cause mortality was higher among patients who developed atrial tachyarrhythmia during the first year.[22]

Importance of The Percentage of Biventricular Pacing: More is Always Better

In the study of Boriani et al[21] the percentage of biventricular pacing (BIV%) in the AF group was 95% vs. 98% in the entire patient population. When patients with AF were in sinus rhythm the BIV% was 98% vs. 71% during AF, p < 0.01). Suboptimal CRT was defined as BIV% < 95% which was predicted by the occurrence of persistent or permanent AF (P < 0.001), and uncontrolled ventricular rate (P = 0.002). BIV% was inversely correlated to the ventricular rate (VR) in AF decreasing by 7% for each 10 bpm increase in VR (Fig 2).

Koplan et al[23] conducted a retrospective analysis in 1800 of CRT patients to evaluate the significance of BIV% and its relationship to a combined clinical end point of death and heart failure hospitalization. Patients that showed a BIV% >92% had a 44% reduction in clinical end points compared with subjects with BIV% 0–92% (p < 0.00001). Subjects with BIV% 98% to 99% had similar outcomes as the subjects with BIV% 93–97% and also similar outcomes as subjects paced 100% of the time. Subjects with a history of atrial arrhythmias were more likely to pace ≤ 92% (p < 0.001).

The importance of a high BIV% has recently been confirmed in a large cohort of 36,935 patients who participated in the US LATITUDE patient Management System in which the patients were followed in a remote monitoring network.[24] The mortality was inversely associated with BIV% both in the presence of normal sinus and atrial paced rhythm and with AF (Fig 3). The greatest reduction in mortality was observed with BIV% >98%. Patients with BIV% >99.6% experienced a 24% reduction in mortality (p < 0.001) while those with BIV% <94.8% had a 19% increase in mortality. The optimal BIV% cut-point was 98.7%.

It is important to remember that the delivery of a stimulus does not guarantee effective CRT. The percentage of BiV pacing based on device interrogation data vastly overestimates the percentage of truly resynchronized beats since it does not account for fusion and pseudofusion between intrinsic (not paced) and paced beats. Kamath et al[18] utilized 12 lead Holter monitoring to assess the incidence of ineffective capture in 19 AF patients undergoing CRT (Fig1). The study clearly demonstrated that although device interrogation showed >90% BiV pacing only 9 patients (47%) received effective BiV pacing. It is imperative to examine rhythm strips and electrocardiograms of non-responders to verify that the beats are truly resynchronized. Importantly, certain device algorithms aimed at maximizing biventricular pacing in AF patients with a relatively fast ventricular rate may also lead to a false sense of reassurance about the percentage of BiV pacing.

Importance of The Percentage of Biventricular Pacing in Patients in Sinus Rhythm

Ruwald et al[25] estimated the threshold of BIV pacing percentage percentage needed for CRT-D (D = implantable cardioverter-defibrillator, 699 patients) to be superior to ICD (no D, 520 patients) on the end-point of HF or death in patients from the Multicenter

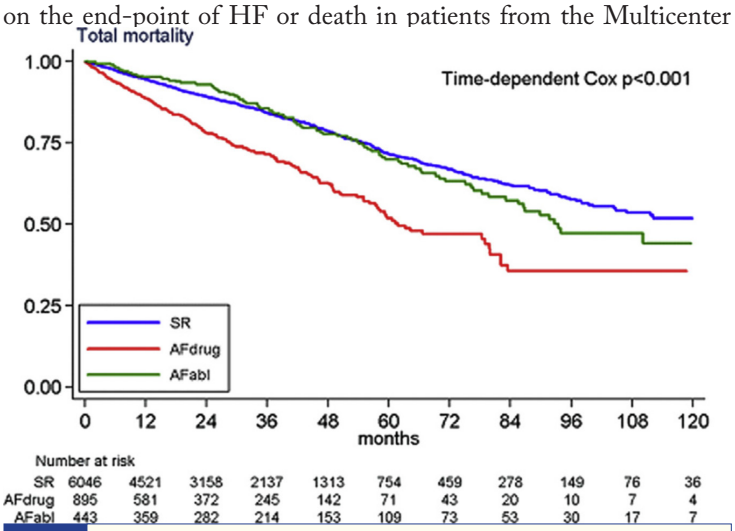

Figure 5: CERTIFY trial. Kaplan-Meier survival after cardiac resynchronization therapy (CRT) from total mortality for the 3 patient groups: sinus rhythm (SR) (blue lines); atrial fibrillation (AF) plus drugs (red lines); and AF plus ablation (green lines). (Reproduced with permission from reference.[14])

Automatic Defibrillator study. The study was comprised of individuals with depressed LV function, prolonged QRS durations, and New York Heart Association class I or II HF symptoms in sinus rhythm. No difference was seen in the risk of heart failure/death between ICD and CRT-D patients with BIV pacing ≤90%, and BIV pacing exceeding 90% was associated with a benefit of CRT-D in HF/death when compared with ICD patients. Furthermore, BIV pacing ≥97% was associated with an even further reduction in HF/death, a significant 52% reduction in death alone, and increased reverse remodeling. CRT-D with BIV ≥97% was associated with a significant 52% reduced risk of death alone, when compared with ICD patients, and a 63% risk reduction when compared with CRT-D patients with BIV pacing <97%. Within the CRTD group, for every 1 percentage point increase in BIV pacing, the risk of HF/death and death alone significantly decreased by 6 and 10%, respectively. Increasing BIV pacing percentage was associated with significant reductions in LV end-systolic volume. Interestingly a past history of supraventricular tachyarrhythmias did not influence the results.

Uncontrolled Ventricular Rates

A ventricular rate (VR) in AF controlled at rest may not be associated with rate control during exercise. Furthermore, pronounced RR interval variability in AF may decrease the number of resynchronized beats. In a study in 2011 when the benefit of AVJ ablation was already being appreciated, Boriani et al[21] calculated the average VR of each patient at 115 ± 15 bpm In an AF group of 443 patients. An uncontrolled VR occurred in 150 of 443 (34%) of the patients. In the AF patients with new-onset AF after CRT, 93 of 222 patients (42%) were found to have uncontrolled VR while in those with a known history of AF before CRT, 43 of 221 patients (26%) exhibited uncontrolled VR (p = 0.001). An uncontrolled VR which occurred in about one-third of CRT patients was associated with a worse clinical outcome of combined heart failure, hospitalization or death (p = 0.046).

The Epidemic of Inadequate Biventricular Pacing

In a study evaluating inadequate biventricular pacing, CRT defibrillator patients were classified as permanent (daily mean AF burden ≥23 hours), persistent (≥7 consecutive days of AF ≥23 hours/d), paroxysmal (≥1 day with AF ≥6 hours), or no/little AF (all others) using device-detected AF during the 6 months postimplant (Fig 4).[26]

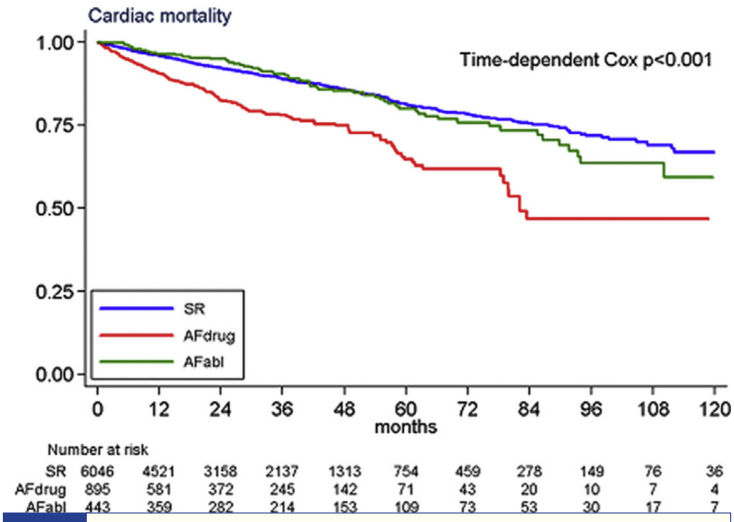

Figure 6: CERTIFY trial. Kaplan-Meier survival after cardiac resynchronization therapy (CRT) from total mortality for the 3 patient groups: sinus rhythm (SR) (blue lines); atrial fibrillation (AF) plus drugs (red lines); and AF plus ablation (green lines). (Reproduced with permission from reference.[14])

Subsequent all-cause mortality was evaluated using a multivariable Cox proportional hazard regression. Among 54 019 patients, 8% of patients each had permanent (N=4449), persistent (N=4237), and paroxysmal AF (N=4219). A high proportion of patients with permanent (69%) and persistent (62%) AF did not achieve high BIV% (>98%).[25] Relative to patients with BIV % >98%, patients with reduced BIVP had increased mortality after adjusting for age, sex, AF, and shocks (90%–98%: hazard ratio=1.20 [1.15–1.26]; P<0.001; <90%: hazard ratio=1.32 [1.23–1.41]; P<0.001). High BIVP% was associated with the greatest mortality improvement in permanent AF among the AF classifications. Nearly half (47%) of the patients with persistent AF had <90% BIV% during AF. High BIV% (> 98%) was not achieved in two thirds of 8686 patients with persistent or permanent AF, and these patients had an increased risk of death independent of each other and age, sex, or ICD shocks.[25]

Analysis of the RAFT Study in Patients with Permanent Atrial Fibrillation: Suboptimal Dose of Cardiac Resynchronization?

The results of the Resynchronization for Ambulatory Heart Failure Trial (RAFT AF) study were published in 2012 and constitutes to date the largest, randomized report examining the role of CRT in patients with permanent AF[27] The findings were disappointing, contrary to prevailing belief that AF patients improve with CRT though somewhat less than in patients in sinus rhythm. The RAFT AF study illustrates the importance of BIV%. The RAFT study enrolled 1788 patients with a follow-up of 40 ± 18 months. Healy et al randomized all the 229 patients with permanent AF (12.7%) and compared 115 patients who received only an ICD vs. 114 patients who received a CRT device and an ICD (CRT-D device). Patients with permanent AF were required to have a resting heart rate of ≤60 beats per minute and ≤90 beats per minute after a 6-minute walk test to be eligible for the study. All patients received optimal medical therapy. Only 1 patient had an AV junction ablation before or within 6 months after randomization. During the first 6 months after randomization, there were 34.3% of CRT-treated patients with ≥95% biventricular pacing and 47.1% with biventricular pacing ≥90% of the time. There was no statistically significant difference in the risk of or those receiving <95% ventricular pacing versus ≥95% (P=0.65) reaching a composite endpoint of all-cause deaths or hospitalization for heart failure receiving <90% ventricular pacing versus ≥90% or those receiving <95% ventricular vs. ≥95% . The study demonstrated a strong trend toward a 42% decrease in heart failure hospitalizations with CRT, closely missing statistical significance with a P value of 0.052.

Only one third of CRT patients in the RAFT trial received ≥95% ventricular pacing during the first 6 months. Even this may bean overestimate, because Holter monitoring studies have shown that, when device logs indicate ≥90% ventricular pacing inpatients with permanent AF but without AV junction ablation, 53% of these paced beats are actually fusion or pseudofusion. Furthermore, the CRT-ICD arm had the conducted AF response algorithm (Medtronic) enabled. This feature regularizes the pacing rate by adjusting the pacemaker escape interval after each ventricular beat. In this way the delivery of biventricular pacing was enhanced at a rate that closely matches the relatively fast spontaneous ventricular rate. Therefore

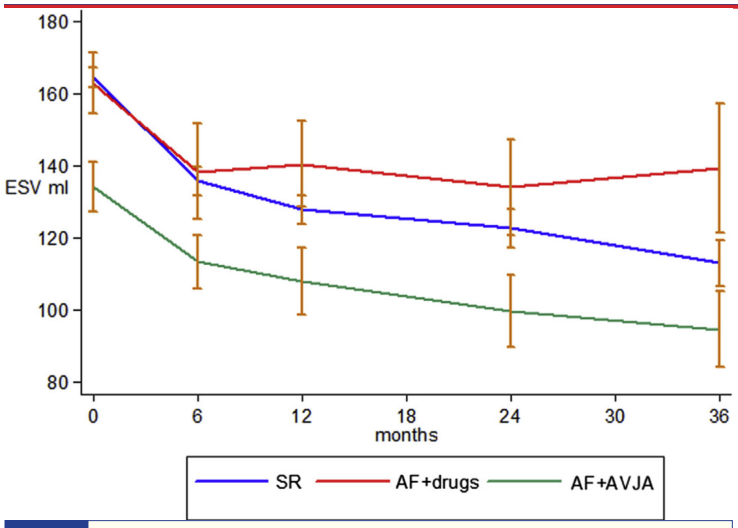

Figure 7: **CERTIFY trial. Left Ventricular Reverse Remodeling after cardiac resynchronization (CRT). Progression in left ventricular end-systolic volume (ESV) after therapy CRT throughout the 3-year follow-up for the 3 groups: sinus rhythm (SR) (blue line); atrial fibrillation (AF) plus drugs (red line); and AF plus atrioventricular junction ablation (AVJA) (green lines). (Reproduced with permission from reference.[14])**

the BiV% may have been overestimated in the CRT-D patients. The investigators of the RAFT AF study indicated that their data suggests that the standard medical rate control of permanent AF in RAFT was not sufficient to allow effective delivery of CRT therapy. The potentially misleading conclusions of the RAFT trial were forcefully and correctly challenged by Gasparini and Boriani.[28]

Control of The Ventricular Rate and Need For Ablation of The AV Junction

Many reports have emphasized that the control of the ventricular rate with AV blocking drugs is difficult and often yield suboptimal results. During AF one must not rely solely on the pacemaker counters to determine the percentage of biventricular pacing because of prevailing fusion and pseudofusion beats liable to produce an inaccurate count of true bipolar capture beats. It seems reasonable to start with pharmacologic therapy to optimize rate control in AF patients requiring CRT. When after careful clinical evaluation including device interrogation, repeated Holter monitoring, and exercise testing, the amount of "true" biventricular pacing is suboptimal, atrioventricular node ablation should be considered. The limiting value of suboptimal pacing has gradually increased so that ≥ 95% may no longer be acceptable.[24]

AV junctional (AVJ) ablation should be considered in all CRT patients when AF engenders a fast ventricular rate despite adequate doses of AV nodal active drugs or when such drugs are not tolerated or when antiarrhythmic medications are ineffective or call contraindicated.

The importance of achieving 100% BIV pacing by AVJ ablation was first highlighted by Gasparini et al in 2006.[7] They demonstrated that permanent AF patients (48 subjects) treated with negative dromotropic drugs and receiving biventricular (BIV) pacing as high as 88% (considered at that time 'adequate') fared poorly compared to AF patients (114 subjects) treated with CRT and AVJ ablation in whom the global effective CRT dose approached 100% effective BIV pacing. This study showed that only those AF patients who had undergone AVJ ablation developed significant improvements in left ventricular (LV) ejection fraction, LV end-systolic volume, and exercise capacity. Furthermore, a significantly higher proportion of responders (response defined as a ≥10% reduction in LV end-systolic volume relative to baseline) were observed in the AVJ ablation group (68%) compared with the non-ablated group (18%) at 12 months.

Gasparini et al.[8] in 2008 presented more extensive data on 1285 consecutive CRT patients (1042 in sinus rhythm, 243 (19%) in AF). Of the 243 AF patients, 125 underwent rate control with drug therapy. Those with > 85% BIV pacing were continued with rate control (BIV > 85% pacing was considered as "sufficient" CRT delivery at the time but is no longer considered as satisfactory as discussed later). The other 118 AF patients underwent AVJ ablation for inadequate BIV capture during follow--up defined arbitrarily as < 85% BIV capture. At a median follow-up of 34 months, all-cause mortality and cardiac mortality was similar in the sinus rhythm group and the AF group.

In the above study, the long-term total mortality was statistically lower in the AVJ-ablation group with11 deaths out of 118 patients during pacing 98.7 ± 1.8% of the time, compared to the AF group in the drug-treated group with[28] deaths out of 125 patients The difference was mostly due to a reduction of deaths from progressive HF which was 4.3 in the ablated AF group vs. 15.2 per 100 person-year in the drug-treated AF group ($p < 0.001$).

The beneficial role of AVJ ablation in AF patients has been confirmed by others.[29-32] However, a few small studies claim that conservative therapy without AVJ ablation produces results similar to those seen after AVJ ablation.[33-38] Finally, the recently published randomized CERTIFY trial provided unequivocal proof of the value of AVJ ablation in CRT patients with AF.[14]

CERTIFY Trial

The study was conducted because no randomized controlled trial of CRT had addressed whether CRT confers similar benefits on AF patients (25% of CRT patients) with or without AVJ ablation (A despite the high prevalence of AF in the patient population undergoing CRT. The trial compared clinical outcomes of patients with permanent AF undergoing CRT combined with either AVJ ablation (A) (n = 443) or rate-slowing drugs [(AF+drugs = 895] to outcomes in patients who were in sinus rhythm (n = 6,046).[14] The study found that after median follow-up of 37 months: all-cause mortality (6.8 vs 6.1 per 100 person year) and cardiac-related mortality (4.2 vs 4.0) were similar in patients with AF+AVJA and in patients who were in sinus rhythm (both p = not significant). In contrast, the AF+ drugs drugs group had a higher rate of total and cardiac-related mortality than both the sinus rhythm and the AF+AVJA groups (11.3 and 8.1, respectively; $p<0.001$) (Figs 5 and 6). The authors also reported that on multivariable analysis the AF plus AVJA group had a total mortality (Hazard ratio [HR]: 0.93, 95% confidence interval CI 0.74-1.67) and cardiac mortality (HR: 0.88, 95% CI 0.66-1.17) similar to the sinus rhythm group, independent of known confounders. The AF+ drugs group, however, had a higher total mortality (HR: 1.52, 95% C.I. 1.26-1.82) and cardiac mortality (HR: 1.57, 95% C.I. 1.27-1.94) mortality than both the sinus rhythm and AF+AVJA groups (both $p<0.001$). The AF+AVJA group was associated with 52% lower mortality than the AF+drug group, independent of age, sex, etiology of heart failure, New York Heart Association class, device type, LV ejection fraction (LVEF), and QRS duration. The investigators concluded that long-term survival after CRT in patients with AF+AVJA is similar to that observed in patients in sinus rhythm. Mortality is higher in AF patients treated

with rate-slowing drugs.

All 3 patient groups namely, the AF+AVJA, AF +drugs, and sinus rhythm groups showed improvements in LVEF at 6 months. The increase in LVEF observed in the AF+AVJA and sinus rhythm groups was higher than that observed in the AF+drugs group (p < 0.001 and p ¼ 0.003, respectively). Similarly, the 3 groups showed a reduction in LV end-systolic volume (LVESV) at 6 months (all p < 0.001). Although there was no further reduction in LVESV after 6 months in the AF+drugs group, the reduction in LVESV for the sinus rhythm group and AF+AVJA group was sustained over the 3-year follow-up. The difference in LVESV between the AF+AVJA group and AF+drugs group increased from 25 ml at 6 months to 50 ml at 3 years (p < 0.001) (Fig 7).

The mean biventricular pacing percentage was significantly higher in the AF+AVJA group (96±6%) than in the AF+drugs group (87±14%; p < 0.001); this difference in all likelihood played an important +role in the different mortality observed in these 2 groups

The results of the CERTIFY trial confirmed the findings of 2 meta-analyses[39-40] that had suggested that in CRT patients with AF, AV junctional ablation is associated with a reduction in all cause-mortality, compared with rate-slowing drugs. One of the meta-analyses ablation showed a substantial reduction in all-cause mortality (risk ratio 0.42) and cardiovascular mortality (risk ratio 0.44) and improvements in New York Heart Association functional class (risk ratio 0.52), compared with CRT without AV junctional ablation. Based on these results, organizational guidelines now emphasize the importance of AV junctional ablation for the control of ventricular rate in CRT patients with AF(Class IIa, Level of evidence: B). According to the ESC, a lower level of evidence (Class IIb, Level of Evidence C belongs to CRT for patients with atrial fibrillation. treated with rate-slowing drugs.

The impressive results following AVJ ablation suggests that the procedure should be performed in most, if not all, patients with permanent AF as well as those with frequent and prolonged episodes of paroxysmal AF. With regard to timing, some cardiologists have suggested the use of routine AVJ ablation at the time of CRT implantation and others prefer to do it 1 month later after verification of proper device function or even later if reverse LV remodeling has occurred.

There are no reports of increased mortality associated with AVJ ablation. The procedure carries the theoretical risk of device failure and death in pacemaker dependent patients. Following ablation, attempts at restoring sinus rhythm in selected patients should not be abandoned because restoration of AV synchrony in HF is superior to AF with a controlled biventricular paced rate.

Organizational Guidelines for Cardiac Resynchronization

The 2010 European Society of Cardiology (ESC) guidelines state that "there is consensus that essentially complete ventricular capture is mandatory in order to maximize clinical benefit and improve the prognosis of patients with permanent AF. This often requires creation of complete heart block by ablation of the AV junction given the frequently inadequate efficacy of pharmacological treatment of ventricular rate control at rest and during exercise."[41] Frequent pacing was defined as BIV% ≥95% in 2010, but it is now defined as 98%. The 2012 ESC state that the routine use of AV junction ablation ensures adequate biventricular pacing in patients with AF.[42] Such patients are considered as eligible to receive CRT with a Class II a indication with the added specification of AV nodal ablation." AF patients with LVEF≤35%, heart failure with an intrinsic QRS ≥120ms and who remain in NYHA functional class III and ambulatory IV despite adequate medical treatment are classified as a class IIa provided BiV pacing is achieved as close to 100% as possible.

The 2012 American College of Cardiology/American Heart Assocation/ Heart Rhythm Society (ACC/AHA/HRS) guidelines state that the prospective experience among patients with permanent AF and with decreased LV systolic function suggests that benefit may result from biventricular pacing when the QRS duration is ≥120 ms, although it may be most evident in patients in whom atrioventricular nodal ablation has been performed such that right ventricular pacing is obligate.[43] Thus, the 2012 ACC/AHA/HRS guidelines indicate that CRT can be useful in patients with AF and LVEF less than or equal to 35% on guideline-directed medical therapy if a) the patient requires ventricular pacing or otherwise meets CRT criteria and b) AV nodal ablation or pharmacologic rate control will allow near 100% ventricular pacing with CRT. (Level of Evidence: B).

The 2012 guidelines certainly did not consider AVJ ablation as controversial. The class IIa indication for CRT in the guidelines is probably based on the incorporation of relatively few AF patients in the major CRT trials and the lack of large randomized trials guideline-directed medical therapy comparing patients in sinus rhythm with those in AF. We believe that AF should now be a class Ia indication for CRT based on the favorable impact of AVJ ablation and our better understanding of rate control and the importance of aiming for the highest percentage of biventricular pacing.

Implantable Cardioverter-Defibrillators

AF is the most common cause of inappropriate shocks in CRT patients and is related to a baseline history of AF. AF is associated with an increased risk of appropriate and inappropriate defibrillator therapy and is an independent risk factor for mortality.[44-46] AF also causes an increased risk of heart failure deterioration. Appropriate shocks are related to AF may be an expression of a poor cardiac function, but this relation could also be due to a reduced amount of biventricular pacing during periods of paroxysmal or persistent AF with subsequent less electrical remodeling. This could not only lead to mortality, but also result in a higher frequency of ventricular arrhythmias and consequently of appropriate shocks. Powell et al[44] found that no mortality risk was associated with an inappropriate first shock such as "benign rhythms" (sinus tachycardia or supraventricular tachycardia) or nonarrhythmia events (noise, artifact, and oversensing). This group had similar survival to those who did not receive a shock. Although some workers have claimed that inappropriate shocks were not associated with increased mortality, Powell et al found that an inappropriate first shock for AF/A flutter increased mortality. These data suggest that increased long-term mortality after a shock is due to the underlying arrhythmia as opposed to the shock itself.

Fisher et al[47] found that the most powerful programmable variable associated with shocks was the detection rate threshold. A detection threshold of 167 bpm was associated with an increase in shocks, independent of other variables. This is consistent with previous reports demonstrating that lower 1-year inappropriate shock rates occur when utilizing detection thresholds of 181 to 188 bpm as compared with detection thresholds of 150 to 170 bpm. More complex algorithms have been recently developed to produce a marked reduction of inappropriate shocks due to AF.[48]

Impact of Structural Changes on the Development of Atrial Tachyarrhythmias During Cardiac Resynchronization

The change in the left atrial volume and incidence of atrial tachyarrhythmias was evaluated in a substudy of the MADIT-CRT trial.[22] In the total population of 1820 patients there were 139 patients with atrial tachyarrhythmis (AF 47%). A low left atrial volume (LAV) reduction was defined as a <20% and a high LAV reduction as ≥20%. Based on the 1 year follow- up echocardiographic data, the mean percent reduction of LAV was 3-fold higher in patients treated with a CRT-D (D = ICD) device compared to the ICD-only group. The median reduction in LAV was 29% (20 – 30%) in the CRT-D group versus 10% (5 – 14%) in the ICD-only group (p < 0.001). As expected, reduction in LAV was highly correlated with reduction in the LV end-systolic volume.

The cumulative probability of atrial tachyarrhythmias (at 2.5 years) in MADIT-CRT was lowest among high LAV responders to CRT-D (3%) and significantly higher among both low LAV responders to CRT-D (9%) and ICD-only patients (7%; p = 0.03 for the difference among the 3 groups). Multivariate analysis showed that high LAV responders experienced a 53% reduction in the risk of subsequent atrial tachyarrhythmias compared to low LAV responders in the CRT-D group and patients in the ICD-only group (p = 0.01).

The potential influence of CRT on the risk of new-onset AF or a beneficial effect of CRT on the burden of paroxysmal AF remains unknown but CRT is associated with conversion of persistent or permanent AF to sinus rhythm in a minority of patients.

Atrial High Rate Episodes

Shanmugam et al[49] conducted a trial of 560 patients with CRT prospectively followed for a mean of 370 days, using remote monitoring technology. The study defined atrial high rate episode (AHRE) as an atrial rate >180 pulses/minute and included patients with and without a prior history of AF. The investigators did not adjudicate individual AHRE, but defined them as significant if they were documented for at least 1% of any day or 14 minutes. Thromboembolic complications developed in 2% of patients and were nine times more likely to develop among patients who had ≥3.8 hours of AHRE detected during any day.

However, patients with AHRE < 3.8 hours/day still had a trend toward an increased risk of thromboembolism, with a hazard ratio of 4.3, P= 0.11. The ASSERT study did not demonstrate a strong temporal relationship between AHRE and thromboembolic events. The median interval between the most recent prior AHRE and the thromboembolic complication was 47 days and only 27% of patients with AHRE who suffered a thromboembolic complication were in AF at the time of that event. This is in keeping with the TRENDS trial[50] (Is There a Critical Value of Daily Atrial Tachyarrhythmia Burden From Device Diagnostics That Raises Stroke Risk?) which found that in patients with AHRE and a thromboembolic event, only 30% were in AF at the time of the event, and in the remaining patients, the most recent AHRE was an average of 168 ± 199 days earlier.[50] This challenges our traditional understanding of the relationship between AF and stroke.

Witt et al[51] recently reported an observational study of patients who received CRT and no history of AF. They were screened for early detected AHREs longer than 6 minutes occurring before 6-month follow-up, and the longest duration of AHREs was recorded.[51] Of 394 eligible patients, 79 patients (20%) had early AHRE detected. During a median follow-up of 4.6 years, patients with early detected AHREs had an increased risk of clinical AF (HR 2.35; 95% CI 1.47-3.74; P < .001) and thromboembolic events (HR 2.30; 95% CI 1.09-4.83; P = .028). For patients with AHREs longer than 24 hours, these associations were stronger. The risk of mortality was not higher with early detected AHREs (HR 0.97; 95% CI 0.64-1.45; P = .87). Of the 27 patients with thromboembolic events, only 10 patients (37%) had AHREs detected within a 2-month period before the thromboembolic event. Therefore detection of early AHREs after CRT is associated with a significantly increased risk of clinical AF and thromboembolic events.

At this time, the critical duration, rate, and definable burden of AHRE or AF associated with a significant risk of a stroke that would warrant anticoagulation remain unknown though patients with a CHADS 2 or CHA2DS2-VASc score should be strongly considered.[52] AHRE monitoring may help us understand more about the natural history of AF by revealing the circumstances predictive of progression from asymptomatic to symptomatic AF and the transition from paroxysmal to sustained AF. Such data may become useful in the future. Although there appears to be a strong association between AHRE and stroke, more data are needed before routine oral anticoagulation. Can be recommended. Randomized trials of anticoagulation with respect to AF burden and frequency of AHRE are needed.

Return Of Sinus Rhythm. Implantation Of An Atrial Lead

Gasparini et al[53] indicated that about 10% of CRT patients with permanent AF revert to sinus rhythm spontaneously mostly in the first year but late reversion even at 5 years is possible. These workers identified 4 predictors of reversion: 1. Smaller LV end-diastolic diameter, shorter QRS duration after CRT, smaller left atrial diameter, and AVJ ablation. Patients with 3 predictors had a 60% likelihood of spontaneous reversion and those with 3 predictors had a 25% chance of reversion. Patients with the spontaneous return of sinus rhythm showed an 87% reduction in mortality after 1 year. Gasparini et al[49] suggested that implantation of an atrial lead should be considered at the time of CRT implantation. The parameters suggesting a favorable atrial response might be useful in determining which patients are likely to respond to various therapies aimed at restoring sinus rhythm.[53, 54]

Conversion to Sinus Rhythm

Rhythm control should be considered in selected patients with persistent symptoms attributable to AF. The parameters defined by Gasparani et al[53] to predict the spontaneous return of sinus rhythm after CRT could also be used to predict a favorable response to therapies used to restore sinus rhythm. Cardioversion of permanent AF should be considered in the first 3 – 6 months particularly in patients demonstrating significant LV remodeling.[55] There are no official guidelines about drug therapy, cardioversion or AF ablation (excluding the AV junction) in patients with CRT devices. There are no data about the role of pulmonary vein isolation in in CRT patients with AF.[56] Ongoing trials may provide data about this potentially important procedure.[56]

Conclusions

AF in CRT patients is associated with an increase in heart failure hospitalizations and death mainly because uncontrolled ventricular rates reduce the delivery of an optimal "dose" of BiV pacing. ICD shocks in AF may be contributory. Although the ventricular rate in

AF can be controlled with drugs in some patients, AV junctional ablation is now the preferred choice especially on the basis of the recent CERTIFY trial. AV junctional ablation permits CRT delivery close to 100% of the time with regularization of the RR intervals, elimination of fusion and pseudofusion beats and discontinuation of some AV nodal blocking drugs. Patients who have undergone AV junctional ablation derive as much benefit from CRT as patients in sinus rhythm provided the ventricular rate is controlled by AV junctional ablation. It is incumbent on the physician to achieve the highest possible BiV% pacing because prognosis depends on it. The greatest mortality reduction in CRT patients with AF occurs with BIV% pacing ≥ 97-98%. One should always aim for a BIV% pacing of 100%. More is better and small gains in BIV% pacing are important. The latest organizational guidelines recommend a class IIa indication for CRT in patients with AF and a controlled ventricular rate that may require AV junctional ablation. The guidelines should now show CRT in AF as a class 1a indication for CRT in patients with a controlled ventricular rate that virtually always requires AV junctional ablation.

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Atrial fibrillation - Who Needs Catheter Ablation And Which Approach?

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Abstract

Catheter ablation therapy for atrial fibrillation (AF) has gained a significant role during maintenance of sinus rhythm compared to antiarrhythmic medication. Catheter ablation techniques are also improved and progressed over years in parallel to better understanding of disease mechanisms and technological advancements. However, due to invasive nature of the therapy with its pertinent procedural risks, both appropriate patient selection and use of relevant approach should be considered by all electrophysiologists before decide to perform catheter ablation.

Introduction

Atrial fibrillation (AF) affects approximately 30 million individuals worldwide and is known as a major cause of stroke, heart failure, hospitalizations and death.[1] The recognition for the first time that, in a subset of patients, AF was triggered by a rapidly firing focus and could be "cured" with a localized ablation procedure eventually led to the progressive innovations in catheter ablation technologies.[2] Percutaneous catheter ablation is now an evidenced and established therapeutic option for rhythm control in selected AF patients with reasonable safety and efficacy.[3] However, success rates for persistent AF ablation still remain far lower than paroxysmal AF, despite a large spectrum of ablation strategies.[3] Therefore, appropriate AF patient selection with relevant catheter ablation technique should be considered by all electrophysiologists during treatment of AF via rhythm control strategy.

This review addresses current approaches in the field of catheter ablation for AF.

Why Ablation?

A number of systematic reviews have been performed to evaluate the efficacy of catheter ablation versus antiarrhythmic drug therapy for AF.[4-6] The efficacy of radiofrequency catheter ablation for maintaining sinus rhythm (SR) has been found to be superior to current antiarrhythmic drug therapy for providing freedom from symptomatic AF and improving quality of life in selected patient populations.[7-9] Studies have also demonstrated a reduction of AF-related symptoms.[10] However, evidence is insufficient to determine whether catheter ablation reduces all-cause mortality, stroke, or heart failure (HF).

Evidence supporting the efficacy of catheter ablation is strongest for paroxysmal AF in younger patients with little or no structural heart disease.[11]

Who to Ablate?

First, reversible causes of AF should be investigated thoroughly prior to giving consideration to catheter ablation. These include evaluation for hyperthyroidism, pulmonary embolism, myocardial ischemia/infarction, heavy alcohol consumption, recent cardiac surgery and other acute inflammatory/infectious processes. Supraventricular arrhythmias, such as atrioventricular (AV) nodal reentry, AV reentry tachycardia, or atrial tachycardia may also serve as triggers for AF, therefore eliminating those supraventricular tachycardia episodes may help limit or eliminate episodes of AF.

Beyond these, determining whether a patient is an appropriate candidate for catheter ablation depends on various factors, including the type of AF (paroxysmal, persistent, or long-standing persistent), severity of symptoms, presence of structural heart disease, candidacy for alternative options such as rate control or antiarrhythmic drug therapy, likelihood of complications, and patient preference.[3] When patient preference is excluded, the primary selection criterion for catheter ablation should be the presence of symptomatic AF.[3]

ACC/AHA guidelines[11] have stated that AF catheter ablation:

a) Is useful for symptomatic paroxysmal AF [Class I, level of evidence (LOE): A];

b) Is reasonable for selected patients with symptomatic persistent

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AF (Class IIa, LOE: A);

c) May be considered for symptomatic long-standing (>12 months) persistent AF (Class IIb, LOE: B) refractory or intolerant to at least 1 class I or III antiarrhythmic medication when a rhythm control strategy is desired.

The difference in recommendations of HRS/EHRA/ECAS guidelines[3] from ACC/AHA guidelines is that AF catheter ablation is reasonable for selected patients with symptomatic persistent AF refractory or intolerant to at least 1 class I or III antiarrhythmic medication with Class IIa, LOE: B indication.

ESC guidelines[12] have recommended catheter ablation of symptomatic paroxysmal AF in patients who have symptomatic recurrences of AF on antiarrhythmic drug therapy and who prefer further rhythm control therapy (Class I, LOE: A). They have also stated that catheter ablation of AF should be considered as first-line therapy in selected patients with symptomatic paroxysmal AF as an alternative to antiarrhythmic drug therapy, considering patient choice, benefit, and risk (Class IIa, LOE: B).[12] HRS/EHRA/ECAS guideline[3] have additionally mentioned that catheter ablation as first-line therapy could be considered in persistent AF (Class IIb, LOE: C) and might be considered in long-standing persistent AF patients (Class IIb, LOE: C).

It is not recommended to perform catheter ablation for AF in patients who cannot receive anticoagulant therapy during and following the procedure (Class III, LOE: C).[11]

At last but not least, when catheter ablation is found appropriate for a patient, some patient characteristics that are known to increase the incidence and burden of AF should be corrected prior to catheter ablation to improve procedural outcomes. For instance, recent studies have demonstrated the importance of weight loss and sleep apnea treatment prior to ablation.[13]

Catheter Ablation in Special Patient Populations

The safety and efficacy of catheter ablation are less well established for some populations of patients, especially very elderly patients, and patients with significant HF.[3]

In Patients with HF

Restoring sinus rhythm has a positive impact on heart failure as atrial contraction and AV synchrony are important contributors to total cardiac output. In patients who suffer from symptomatic AF recurrences on amiodarone therapy, catheter ablation remains as the sole choice for escalated rhythm control therapy. It is indicated to improve AF-related symptoms (EHRA score II–IV).[12]

Studies evaluating the role of catheter ablation for AF in HF patients have demonstrated an acceptable rate of successful sinus rhythm maintenance with improvements in left ventricular ejection fraction (LVEF) and symptoms.[14-16] Therefore, most clinicians reserve AV node ablation/biventricular pacing for elderly patients, patients with significant comorbidities who would not tolerate catheter ablation for AF, or patients with preexisting biventricular implantable cardioverter defibrillators and AF with ventricular response rates rapid enough to limit the amount of biventricular pacing.

The degree of LVEF improvement varies according to patient characteristics.[17] For instance, where the LV dysfunction is thought to be due to AF itself, AF catheter ablation and maintenance of sinus rhythm may result in a marked improvement. Improved rate control or cardioversion with antiarrhythmic drug therapy may help predict the outcomes of catheter ablation in such cases. On the other hand, in patients with HF who develop AF, a rhythm-control strategy is not superior to a rate-control strategy.[18]

Due to the extent of remodeling and underlying heart disease, recurrence[19] and complication rates are higher in this population. A meta-analysis had reported that the single-procedure efficacy of AF catheter ablation was lower in patients with systolic dysfunction, but a similar success rate could be achieved among patients with and without systolic dysfunction with repeat procedures.[20] Recently, in a study including 81 patients with LVEF≤45%, Rillig et al.[21] showed that single-procedure success rates after PVI during 6 years of follow-up were low (35.1%). In patients with single- or multiple-procedure ablation success, a higher improvement of LVEF was observed. Another long-term follow-up study has shown that at 5 years, 60.7% of patients with systolic heart failure had clinical recurrence of AF.[22] In a systematic review[23] including 26 randomized controlled trials, clinical trials, and observational studies of patients with left ventricular systolic dysfunction undergoing catheter ablation for AF, efficacy in maintaining sinus rhythm at a mean follow-up of 23 months was found to be 60%. Left ventricular ejection fraction significantly improved during follow-up by 13%. A recent meta-analysis of 4 trials (n=224) which randomized HF patients (LVEF<50%) with persistent AF to a rate control or AF catheter ablation strategy, AF catheter ablation has been reported to be superior to rate control in improving LVEF, quality of life and functional capacity.[24]

Other than systolic heart failure, severe diastolic left ventricular dysfunction has also been shown to result in a higher risk of AF recurrence after catheter ablation.[25]

Elderly Patients

Age was shown to be an independent predictor of AF recurrence following catheter ablation for AF.[26] Hsieh et al.[27] compared outcomes after catheter ablation for AF and AV node ablation in 71 patients >65 years at a mean follow-up of 52 months. Patients who had ablation of AF were more likely to have symptomatic AF, less persistent AF, better New York Heart Association functional class and less heart failure than the patients who underwent AV node ablation. However, the prevalence of stroke, mortality and other complications were similar between the AF ablation and AV node ablation groups. Corrado et al.[28] showed that catheter ablation for AF in 174 patients older than 75 years resulted in a clinical efficacy of 73 and 80% after single and repeat ablation procedures, respectively at a mean follow-up of 22 months. Zado et al.[29] also compared the safety and efficacy of catheter ablation in three groups of patients: <65, 65-74, and ≥75 years over a 27 month follow-up period. Patients over the age of 75 were more likely to demonstrate a partial response to ablation and require antiarrhythmic drug therapy. Another study had stratified 1548 patients who underwent AF ablation according to age <45, 45–54, 55–64 and ≥65 years. Outcomes, defined as rare or no AF with or without antiarrhythmic drugs, were similar in all groups with an 82–88% success rate.[30] In another study, 35 octogenarians undergoing AF ablation were compared to 717 younger patients also undergoing RF ablation. They found similar success rates of 78 and 75%, respectively.[31] Another study looked prospectively at 103 octogenarians compared with 2651 younger patients, and found 69% of octogenarians were free of AF compared with 71% of their younger peers.[32] However, both Spragg et al.[33] and Shah et al.[34] reported that older age has been significantly associated with a higher risk of complications, suggesting careful assessment of the risk/benefit profile in

these patients before catheter ablation for AF.

Patients With Hypertrophic Cardiomyopathy (HCM)

ACC/ AHA guidelines[11] have stated that AF catheter ablation can be beneficial in patients with HCM in whom a rhythm-control strategy is desired when antiarrhythmic drugs fail or are not tolerated (class IIa, LOE: B). Contreras-Valdes et al.[35] have compared long-term arrhythmia control among patients with HCM and a non-affected cohort and found that the efficacy of AF ablation is significantly lower compared with non-affected patients, irrespective of the number of procedures or use of antiarrhythmic drugs and when present, left ventricular outflow obstruction could be a strong predictor of recurrence. Gaita et al.[36] have demonstrated that 64% of 24 AF patients with HCM had AF-free survival at a mean follow-up of 19 months following catheter ablation. Similarly, Bunch et al.[37] have shown that 1 year AF-free survival was 62% in 33 patients with HCM. Okamatsu et al.[38] have reported that during a mean follow-up of 21 months, sinus rhythm was maintained in 59% of HCM patients who underwent catheter ablation for AF. On the other hand, Bassiouny et al.[39] have reported that only 29% of HCM patients who underwent catheter ablation had no documented recurrent atrial arrhythmia after a single procedure after a follow-up of 35 months.

Patients with Mechanical Mitral Valve (MMV)

Previous studies have demonstrated that catheter ablation of AF in patients with MMV is feasible and safe but is associated with higher recurrence than in patients with native valve.[40-43] Lakkireddy et al.[42] have shown that at 12 months, 80% of patients in the mitral or aortic prosthetic valve group were in sinus rhythm after an average of 1.3 procedures. Hussein et al.[43] have reported that of 81 patients with MVR, 56 (69.1%) were arrhythmia free while not taking antiarrhythmic drugs, 11 (13.6%) had their arrhythmia controlled with antiarrhythmic drugs that had previously failed, and 14 (17.3%) had drug-resistant AF and were managed with rate control. In this study, all MMV patients underwent ablation under therapeutic international normalized ratio. No entrapment of catheters or stroke had occurred and there were no differences in terms of procedure-related complications between the groups.

A recent study has compared the efficacy and long-term outcome of pulmonary vein (PV) antrum isolation (PVAI) alone versus extended PVAI plus non-PV trigger elimination for the treatment of AF in patients with MMV.[44] It was found that compared with the standard PVAI alone, a strategy including extended PVAI and non-PV trigger elimination was associated with a higher 12-month and long-term arrhythmia-free survival in patients with MMV undergoing AF ablation. Very late recurrence occurred in up to 18.8% of patients undergoing extensive ablation, with focal AT being the most common type of recurrent arrhythmia.

Athletes

ACC/AHA guidelines[11] state that radiofrequency (RF) catheter ablation (RFCA) can be considered in athletes with AF episodes.[45]

Re-Ablation

Recovery of PV conduction may necessitate re-ablation in certain patients.[46] Patients with persistent AF are more likely to need a repeat ablation than those with paroxysmal AF.[47] Current guidelines do not specify when re-ablation should be performed; however, it is generally recommended to withhold repeat procedures for a 3-month period after the first procedure as residual areas of conduction in the PVs may take time to become clinically apparent.[3]

Other

Recent studies have demonstrated that severity of atrial fibrosis was associated with decreased response to catheter ablation.[48-51] The tissue characterization of the LA wall regarding atrial fibrosis on DE-MRI was found to be correlated with electroanatomic voltage mapping (EAVM).[49] Relying on this, identification and acute targeting of gaps in atrial ablation lesions sets have been investigated using a real-time MRI system.[52,53] Major limitation is that this modality requires extensive MRI experience, and its reproducibility is still under investigation.

Approaches in AF Ablation

The early percutaneous catheter ablation procedures were designed to mimic a surgical Cox maze procedure, which was based on the 'multiple wavelet hypothesis' for AF. This hypothesis suggested that, as long as the atrium had a sufficient area with adequately short refractory periods, AF could be initiated and then indefinitely perpetuated. Therefore, the early attempts at interventional AF treatment aimed to decrease arrhythmia perpetuation by compartmentalizing the atrium into smaller regions incapable of sustaining the critical number of circulating wavelets.

Today, the most common goal, particularly for ablation of paroxysmal AF in younger patients whose atria have undergone little or no atrial remodelling, is complete PV isolation (PVI) with unidirectional or bidirectional conduction block. PVI alone is much less successful for AF control dominated by "substrate" (persistent and long-standing persistent AF) when there has been extensive and irreversible atrial remodelling. In such cases, some other strategies including successful isolation of sites of non-PV triggers; elimination of sites harboring complex fractionated atrial electrograms (CFAE); linear ablation with bidirectional block; ablation of sites harboring ganglionated plexi (GP); ablation utilizing electrogram analysis to eliminate sites of AF rotors or other drivers; ablation with a goal of conversion to SR during ablation; or ablation until the absence of any atrial arrhythmias during attempts at re-induction must be considered.

Following PVI, data supporting the use of any particular strategy over another for improved long-term clinical outcomes is inconsistent and adjunctive strategies to PVI are often selected based on operator experience and preference.[54-57] Heterogeneity between patient populations may be explanatory to explain the variation in the results of outcome studies. Besides, the different end-points, follow-up periods and protocols often limit comparisons of studies (Also see "Success rates of AF ablation").

Ablation Approaches Targeting PVs

Rapidly firing foci initiating paroxysmal AF arise most commonly from LA myocardial sleeves that extend into the PVs.[2] These observations led to the development of segmental PVI as the cornerstone for ablation strategies.[58] An ablation strategy of encircling the PVs with RF lesions guided by 3D electroanatomical mapping was subsequently developed by Pappone et al.[59] Strategies then shifted to target the atrial tissue located in the antrum rather than the PV itself ("segmental PV ablation" or "wide area circumferential ablation") following the recognition of both PV stenosis as a complication of RF delivery within a PV, or the PV antrum. And today, circumferential isolation of PVs has become the standard therapy for paroxysmal AF.

Most clinicians have identified their primary endpoint for PV ablation as the elimination (or dissociation) of the PV potentials re-

corded from a circular multipolar electrode catheter. 10% rely on exit block as an endpoint for the ablation procedure.[3]

Ablation Approaches not Targeting PVs

Additive strategies to PVI have been sought, particularly in persistent and long- standing persistent AF patients, to improve outcomes of catheter ablation.

Linear Ablation

The rationale underlying creating linear LA lesions[60] originates from the surgical Cox maze procedure, and follows the 'multiple wavelet hypothesis' that postulates that compartmentalizing the LA into smaller regions incapable of sustaining micro re-entry will improve outcomes. Added benefits include the potential effect on the macro re-entrant tachycardias that can occur post-AF ablation.

Unfortunately, achievement of complete conduction block across linear lesions can be very difficult to achieve since the lesions have to be both contiguous and transmural. Thus, whereas complete lines may prevent recurrent arrhythmias, if incomplete they may be proarrhythmic and result in higher prevalence of LA flutter.[61] Therefore, the addition of linear lesions confers no benefit when compared to PVI alone in paroxysmal AF patients.[56,62] A slight advantage has been suggested in persistent AF patients where two small, randomized trials have demonstrated a significant benefit.[62,63] However, the recent Substrate and Trigger Ablation for Reduction of Atrial Fibrillation Trial Part II trial (STAR- AF II) has failed to show any beneficial effect of linear ablation in addition to PVI in persistent AF patients.[57]

Non-PV Triggers

The sites of origin for non-PV atrial triggers include the posterior wall of the LA, the superior vena cava, the inferior vena cava, the crista terminalis, the fossa ovalis, the coronary sinus, behind the Eustachian ridge, along the ligament of Marshall, and adjacent to the AV valve annuli.[64] Furthermore, re-entrant circuits maintaining AF may be located within the right and left atria. In selected patients, elimination of only the non-PV triggers has resulted in elimination of AF.[65,66]

Ablation of CFAES

Complex fractionated atrial electrograms are regarded to represent areas of slow conduction, conduction block, or 'pivot' points for a local AF perpetuating re-entry. The primary endpoints during RF ablation of AF using this approach are either complete elimination of the areas with CFAEs, conversion of AF to sinus rhythm, and/or non- inducibility of AF. For patients with paroxysmal AF, the endpoint of the ablation procedure using this approach is non- inducibility of AF. For patients with persistent AF, the endpoint of ablation with this approach is AF termination. Similar to linear lesion, studies have demonstrated that CFAE ablation as a lone ablation strategy is inadequate for both paroxysmal and persistent AF.[67,68] Likewise, in the paroxysmal AF population there appears to be limited benefit for adjunctive CFAE ablation.[62,67,69,70] In those with persistent AF, observational and randomized studies have demonstrated that ablation of CFAE areas, in addition to PVI, improves the procedural outcome.[62,67,71,72] Recent STAR- AF II trial, on the other hand, has failed to demonstrate any beneficial effect of CFAE ablation in addition to PVI in persistent AF patients.[57] One of the limitations of targeting CFAEs with ablation has been the extensive amount of ablation needed. Half of the clinicians have stated that they routinely employed CFAE-based ablation as part of an initial ablation procedure in patients with long-standing persistent AF.[3]

Ablation Of GPs

Adding GPs to other ablation targets has been shown to improve ablation success.[73,74]

Other Unestablished Ablation Strategies

A) Voltage Map-Guided Substrate Modification: Box Isolation Of Fibrotic Areas (BIFA)

The regional localization and the extent of the fibrotic LA substrate can be visualized during the intervention in sinus rhythm applying EAVM; this allows the use of a new patient-tailored ablation strategy, BIFA, for the circumferential isolation of the significantly affected fibrotic areas (e.g., <0.5 mV). An individualized substrate modification using BIFAs may be added to circumferential PVI in patients with paroxysmal AF, or who have very substantial regional LA fibrosis detected in the first ablation session. However, in patients with massive fibrosis, failure of the initial ablation is likely regardless of the applied ablation concept, and further ablation procedures should be discouraged and avoided.

There are several limitations of methods for identifying substrates. Voltage maps using point-by-point mapping not only take time, but the measured voltage also depends on the rhythm (sinus, atrial fibrillation, atrial extrasystole), the electrode contact with tissue, and the atrial myocardium thickness. Therefore, clear limits or definitions for a normal voltage (e.g., >1.5mV, >2.0mV) and a highly abnormal voltage (e.g., <0.5 mV) do not exist.

B) Focal Impulse and Rotor Modulation (FIRM)

The follow-up results of FIRM strategy, in which a 64-pole basket catheter is advanced into the left and right atria to demonstrate focal impulse and rotors, have revealed that patients who underwent FIRM-guided ablation maintained higher freedom from AF versus those who underwent conventional ablation.[75] AF sources were analyzed to be co- incidentally ablated in 45% of conventional cases.[76] These results were also confirmed in a multicenter study.[43]

Ensuring Durable Isolation

Various techniques have been proposed to identify regions of incomplete ablation and/or residual gaps within the index ablation line. One technique is the use of intravenous adenosine to differentiate permanent PV-atrial block from dormant conduction. Not all studies have been in agreement concerning adenosine application.[77-81] Results of Adenosine Following Pulmonary Vein Isolation to Target Dormant Conduction Elimination [ADVICE] trial has recently been published,[82] supporting that adenosine administration should be considered for incorporation into routine clinical practice. An alternative strategy is the 'pace-capture guided' approach, where, after completion of PVI, the antral ablation line encircling the ipsilateral PVs is mapped while pacing from the ablation catheters distal electrode pair.[83,84] Where local LA capture is identified, additional ablation can be performed with the goal of closure of the residual gaps. And also, to attain durable PVI, waiting time after PVI is also important. In a study, Yamane et al.[85] demonstrated that provocation and elimination of time- and ATP-induced early PV re-connection is recommended not only at 30 minutes but also at 60 minutes after PVI to improve its efficacy.

Energy Sources

Radiofrequency energy is by far the dominant energy source that has been used for catheter ablation of AF. RF energy achieves myocardial ablation by the conduction of alternating electrical current through myocardial tissue. The tissue resistivity results in distribution

of RF energy as heat, and the heat then conducts passively to deeper tissue layers. Most tissues exposed to temperatures of 50°C or higher for more than several seconds will show irreversible coagulation necrosis, and evolve into non-conducting myocardial scar. High power delivery and good electrode–tissue contact promote the formation of larger lesions and improve procedure efficacy. Most clinicians employ irrigated tip catheters for delivering RF energy.[3] Comparative trials of irrigated tip and large tip RF technologies versus conventional RF electrodes have demonstrated increased efficacy and decreased procedure duration in the ablation of AFlu,[86,87] but only limited trials of large tip and open irrigation catheters have been performed in patients undergoing AF ablation.

Cryoablation has more recently been developed as a tool for AF ablation procedures. Cryoablation systems work by delivering liquid nitrous oxide under pressure through the catheter to its tip or within the balloon, where it changes to gas, resulting in cooling of surrounding tissue. This gas is then carried back through the reciprocating vacuum lumen. The mechanism of tissue injury results from tissue freezing with a creation of ice crystals within the cell that disrupts cell membranes and interrupts both cellular metabolism and any electrical activity in that cell. In addition, interruption of microvascular perfusion may interrupt blood flow, similarly producing cell death. Complete vein occlusion is required for the creation of circumferential PV lesions and electrical PVI using the cryoballoon ablation catheter.[88]

The reported complications related to catheter ablation of AF may include vascular access complications such as hematoma, retroperitoneal bleeding, pseudoaneurysm, arteriovenous fistula; myocardial perforation and pericardial tamponade; pulmonary vein stenosis; phrenic nerve palsy; thromboembolic events including transient ischemic attacks and stroke; atrioesophageal fistula; and death.

Cryoablation is known to cause less patient discomfort and require lower doses of conscious sedation when compared with RFCA. It also carries a low risk of thrombus formation[89] and therefore, a decreased risk of embolization and stroke. Cryoenergy leaves the connective tissue matrix intact and theoretically, is less likely to lead to myocardial perforation and tamponade compared with RFCA. However, a recent study of 133 consecutive patients undergoing AF ablation has found a similar incidence of pericardial effusions between those treated with cryoballoon ablation and radiofrequency ablation.[90] Otherwise, both procedures have similar risks of injury of adjacent structures (esophagus, phrenic nerves, vagus nerves, lung parenchyma). Although ostial cryoablation reduced the incidence of PV stenosis significantly, the risk still has not been eliminated. Despite animal models showing greater risk of PV stenosis with RFCA[91] and lack of evidence of collagen deposition or PV stenosis 3 months post-cryoablation,[92] PV stenosis may also complicate cryoablation. Clinical data from a small series have shown esophageal ulcerations with cryoablation, but no progression to fistula.[93]

Although point-by-point RF energy and cryoballoon ablation are the two standard ablation systems used for catheter ablation of AF today, balloon-based ultrasound ablation,[94] and laser based ablation systems[95] also have been developed for AF ablation.

Novelties In Ablation

Multielectrode Circumferential Ablation Catheters

The principal purpose of the multielectrode circular ablation catheter systems is to provide ablation and mapping on a single platform.[96,97] The PV ablation catheter (PVAC, Medtronic Ablation Frontiers, Carlsbad, CA) is a 9F deflectable circular multi-electrode catheter that enables mapping and circumferential PV ablation. The latter is the irrigated multi-electrode nMARQ ablation system (Biosense Webster, Inc., Diamond Bar, CA, USA), which allows multi-electrode ablation. The key difference in the nMARQ system is its integration into the CARTO3 platform (Biosense Webster, Inc., Diamond Bar, CA, USA) allowing full visualization of the catheter loop and electrodes, as well as the fact that the catheter is irrigated with 10 irrigation holes per electrode (completely surrounding the electrodes). Recently, multicenter registries including patients referred for paroxysmal or persistent AF underwent PVI by the nMARQ ablation system have shown high acute success rates and shorter procedural times.[98,99] However, several recent studies have reported a higher incidence of silent microemboli following ablation with a multielectrode ablation catheter.[100,101]

Electroanatomic Mapping Systems

Electroanatomic mapping systems combine anatomic and electrical information by a catheter point-by-point mapping, allowing an accurate 3D anatomic reconstruction of the targeted cardiac chamber. There are two different electroanatomic mapping systems that are widely used in clinical practice. The current generation of the CARTO mapping system (CARTO-3, Biosense Webster, Diamond Bar, CA, USA) relies on both a magnet-based localization for visualization of the ablation catheter and an impedance-based system that allows for both tip and catheter curve visualization as well as simultaneous visualization of multiple electrodes.[102] The second electroanatomic mapping system is an electrical impedance mapping system (NavX, St. Jude Medical Inc., Minneapolis, MN, USA) using voltage and impedance for localization.[103] The use of these 3D mapping systems has been demonstrated to reduce fluoroscopy duration.[102,103] To further improve anatomic accuracy of the maps, the 3D images may be integrated with computed tomography (CT) or magnetic resonance imaging (MRI).[104] However, it should not be forgotten that CT or MRI images are not real-time images, and that the accuracy of image integration is dependent on the accuracy of the image fusion. Furthermore, another potential limitation of electroanatomic mapping is the relatively static nature of the geometry, which may need to be updated during the procedure because of changes in anatomy (volume status and tissue edema) or if the location reference has moved. The development of 3D intracardiac echo (ICE) probes may overcome the limitations in geometry creation as one could navigate the real-time 3D image. It has been demonstrated that RFCA of paroxysmal AF using the CARTO 3 system and ICE could be performed safely without fluoroscopy.[105]

Overall, studies on the use of mapping systems on safety and efficacy of AF ablation have revealed contradictory results.[106-108] Most clinicians prefer using these systems when performing AF ablation excluding cases where a balloon-based ablation system is used.[3]

Special Issues in Catheter Ablation

It has been shown that RFCA of AF performed under therapeutic international normalized ratio (INR) does not increase bleeding risk and reduces the risk of emboli.[109,110] Although in guidelines, it is recommended to use novel oral anticoagulant agents with caution for patients undergoing catheter ablation because of the lack of approved antidotes in the event of cardiac tamponade,[11] recently in Active-controlled multi-center study with blind-adjudication designed to evaluate the safety of uninterrupted Rivaroxaban and uninterrupted vitamin K antagonists in subjects undergoing cathEter

ablation for non-valvular Atrial Fibrillation (VENTURE- AF) trial, it has been shown that the use of uninterrupted oral rivaroxaban was feasible and event rates were similar to those for uninterrupted VKA therapy.[111]

Periprocedural protamine administration following catheter ablation to reverse heparin- mediated effects have been shown to allow quicker sheath removal and minimize the risk of potential vascular complications without causing an increase in thrombotic events.[112-114]

Success Rates Of AF Abalation

A meta-analysis of 4 prospective, randomized clinical trials reported that 76% of patients treated with catheter ablation were free of AF compared with 19% of patients randomized to antiarrhythmic drugs.[115] Another meta-analysis involving 63 AF ablation studies reported that the single-procedure success of ablation with no antiarrhythmic drug therapy was 57%, the multiple-procedure success rate with no antiarrhythmic drug therapy was 71%, and the multiple procedure success rate with antiarrhythmic drugs was 77%. In comparison, the success rate for antiarrhythmic drug therapy was 52%.[6]

Medical Antiarrhythmic Treatment or Radiofrequency Ablation in Paroxysmal Atrial Fibrillation (MANTRA-PAF) trial[116] compared first-line catheter ablation of AF to antiarrhythmic drugs in 294 patients. At 2 years, significantly more patients in the ablation group were free from any AF and symptomatic AF. Quality of life was significantly better in the catheter ablation arm. In Radiofrequency Ablation vs. Antiarrhythmic Drugs as First-Line Treatment of Paroxysmal Atrial Fibrillation (RAAFT-2) trial,[9] the recurrence rate of AF was significant lower after ablation compared with antiarrhythmic drugs after 2 years among 127 patients with paroxysmal AF without previous antiarrhythmic drug treatment. Quality of life improved in both treatment groups. Takigawa et al.[117] have reported long-term follow-up results of catheter ablation of paroxysmal AF in 1220 patients. AF recurrence–free survival probabilities at 5 years were 59.4% after the initial catheter ablation and 81.1% after the final catheter ablation (average, 1.3 procedures). Similar results were found when cryoenergy was used for ablation of AF for treatment-naive patients in Sustained Treatment of Paroxysmal Atrial Fibrillation (STOP- AF) trial.[118] There is only little evidence from prospective, randomized, multicenter clinical trials in patients with chronic AF. However, the recently published prospective randomized Tailored Treatment of Persistent Atrial Fibrillation (TTOP-AF) trial in patients with persistent and long-standing persistent AF demonstrated a significant greater reduction of AF at 6 months after ablation compared with medical treatment.[119] Despite an identical outer shape with the first-generation (Arctic Front; Medtronic Inc, Minneapolis, MN) (Arc- CB), modifications to the refrigerant injection system has allowed improved cooling of the distal balloon hemisphere in the second-generation cryoballoon (Arctic Front Advance; Medtronic Inc, Minneapolis, MN) (Arc- Adv- CB). Several studies have compared the safety and efficacy of cryoablation in patients who underwent ablation with either first or second-generation cryoballoon[120-123] and have shown that Arc-Adv-CB attained high rates of acute PV isolation within a significantly faster and less complex procedure. Recently, Metzner et al.[124] have reported that the use of second-generation 28-mm cryoballoon for PVI resulted in 1-year success rates of 81% for PAF, 77% for short-term persistent AF. Mugnai et al.[125] have reported that at a mean follow-up of 23 months, the success rate was similar for both RFCA and cryoablation groups. Procedural times were significantly shorter in the cryoablation group. Complication rates were similar in both groups except for phrenic nerve palsy that was uniquely observed in the CB group. Wasserlauf et al.[126] have compared 1 year outcomes of cryoballoon and RFCA and shown that cryoballoon ablation was associated with equivalent 1-year freedom from AF rate as RFCA for paroxysmal AF. Procedure and fluoroscopy times were shorter for cryoballoon ablation. Aryana et al.[127] have recently shown that freedom from AF/atrial flutter/tachycardia at 12 months following a single procedure without antiarrhythmic therapy was statistically significantly greater with CB-2 (76.6%) versus RF (60.4%). This difference was evident in patients with paroxysmal AF, it did not reach significance in those with persistent AF.

Currently, there is a lack of evidence and a large debate about the optimal ablation strategy in patients with non-paroxysmal AF. A previous meta-analysis of studies reporting the results of catheter ablation of persistent and long-standing persistent had concluded that the success rate of different strategies is similar, provided that pulmonary vein isolation was performed.[128] A recent systematic review and meta- analysis of randomized and non- randomized controlled trials reporting clinical outcomes after catheter ablation for persistent atrial fibrillation, which included 46 studies containing 3819 patients, has concluded that catheter ablation results in a significantly greater freedom from recurrent AF compared with medical therapy. The most efficacious strategy was reported to be the combination of isolation of the PVs with limited linear ablation within the LA.[129]

It should not be forgotten that although most trials evaluate success of ablation in terms of long-term maintenance of SR, clinical improvement following ablation is often under-evaluated in studies. This clinical improvement may be attributed to a decreased AF burden, alteration in the severity of AF, or changes in overall cardiac function, both in patients with paroxysmal[130,131] or persistent AF.[132] A study has shown that catheter ablation significantly improved quality of life for patients with persistent AF whereas medical therapy had no appreciable effect.[133] There is currently no data on the impact of catheter ablation on mortality. Its impact on mortality (and other secondary outcomes) is being explored in the ongoing Catheter Ablation vs Anti-Arrhythmic Drug Therapy for Atrial Fibrillation (CABANA) trial.

Conclusions

Rhythm control strategy using an invasive catheter ablation therapy is both effective and safe, however, selection of both appropriate patients and ablation technique should be personalized considering various factors like availability of the devices, operators' experience, patient co-morbidities, presence of structural heart disease and patient consent. Thus, we can propose that one strategy does not fit to all AF patients when catheter ablation was chosen as an therapeutic option.

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Home Screening for Detecting Subclinical Atrial Fibrillation

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Abstract

The advent of cardiac implanted electronic devices with accurate atrial arrhythmia diagnostic capabilities has revealed a large burden of "silent " atrial fibrillation that is present in the cardiac population. Many studies have been completed, and many more are ongoing, to determine the correct treatment course when these atrial arrhythmias are detected. Alongside the development of accurate atrial diagnostics within the devices, has been the growth an entire network of wireless home monitoring capability. It is now possible to see, over the internet, individual patients' atrial arrhythmia burden on every day. This capability has tremendous promise for patient care, with the possibility of reducing strokes, decreasing heart failure, preventing cardiomyopathies, and likely substantially reducing health care costs. As this innovative diagnostic capability is generating large amounts of data, protocols for what should be done with the plethora of new information are being developed. In the pages that follow, we will present what is known about home monitoring for silent atrial fibrillation, and present the results of recent studies published in this arena.

Prevalence of Atrial Fibrillation (AF) in the Cardiac Implantable Electronic Devices (CIED) Population

Patients with CIEDs have a unique advantage over cardiac patients who do not have a continuous arrhythmia monitor in place because clinically silent arrhythmias can be detected. The incidence of previously unrecognized AF has been reported to range from 30-60%. Older studies, performed before device diagnostics were sophisticated and before home monitoring was available, reported an incidence of device detected AF in about half of the population. Gillis et al. reported atrial arrhythmias in 68% of 231 patients with pacemakers implanted for sinus node disease.[1] More recently, the ASSERT trial and the MOST study also found that AF was present in about 50% of unselected populations of patients with implanted pacemakers.[2,3]

Studies specifically designed to exclude subgroups of patients who may have had AF in the past (history of AF, history of oral anticoagulation use, history of anti-arrhythmic drug use), have found an incidence of newly detected AF (NDAF) or "silent AF" in about 30% of device patients. For example, patients from the TRENDS trial (1,368) who had no prior history of AF, no previous stroke/TIA, and no warfarin or antiarrhythmic drug use were analyzed to look for NDAF.[4] NDAF was defined as device-detected atrial arrhythmias lasting at least 5 minutes on any day of the study. Thirty percent of patients (416) experienced NDAF. The incidence of NDAF was consistent across patients with intermediate (virtual CHADS2 score of 1) (30%), high (virtual CHADS2 score of 2) (31%), and very high (virtual CHADS2 score of ≥3) (31%) stroke risk factors ($p = 0.92$). (A virtual CHADS score is calculated in a patient who has never previously had AF.) However, a significant increase was seen in the proportion of patients having days with >6 hours of AT/AF as the virtual CHADS2 score increased; 12%, 15%, and 18% for intermediate, high, and very high risk, respectively; $p = 0.04$.

In another analysis from the TRENDS trial, NDAF was analyzed in patients (319) who had a prior history of stroke or TIA.[5] Patients (156) with a documented history of AF, warfarin use, or antiarrhythmic drug use were excluded from analysis. NDAF was again defined as device-detected atrial arrhythmias lasting at least 5 minutes on any day of the study. NDAF was identified by the implantable device in 45 of 163 patients (28%) over a mean follow-up of 1.1 years.

In the ASSERT trial, a study of 2,580 patients with a history of hypertension and no prior history of AF, NDAF (defined as lasting at least 6 minutes in duration) was detected at least once in 34.7% of the patients over a mean follow-up of 2.5 years.[6] Only 10% of

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Table 1: Summary of Studies Regarding AF Detected by Dual-Chamber CIEDs and Thromboembolic Risk

Year	Trial	Number of patients	Duration of Follow-up	Atrial Rate Cutoff	AF Burden Threshold	Hazard Ratio for TE Event	TE Event Rate (below vs. above AF burden threshold)
2003	Ancillary MOST[47]	312	27 months (median)	>220 bpm	5 minutes	6.7 (p=0.020)	3.2% overall (1.3% vs. 5%)
2005	Italian AT500 Registry[49]	725	22 months (median)	>174 bpm	24 hours	3.1 (p=0.044)	1.2% annual rate
2009	Botto et al.[50]	568	1 year (mean)	>174 bpm	CHADS2+AF burden	n/a	2.5% overall (0.8% vs. 5%)
2009	TRENDS[51]	2486	1.4 years (mean)	>175 bpm	5.5 hours	2.2 (p=0.060)	1.2% overall (1.1% vs. 2.4%)
2012	Home Monitor CRT[52]	560	370 days (median)	>180 bpm	3.8 hours	9.4 (p=0.006)	2.0% overall
2012	ASSERT[31]	2580	2.5 years (mean)	>190 bpm	6 minutes	2.5 (p=0.007)	(0.69% vs. 1.69%)

the patients (1/3 of those who ultimately developed NDAF) had the NDAF detected in the first 3 months of the study.

Prevalence of AF in Cryptogenic Stroke Patients with Insertable Cardiac Monitors (ICMs)

When it was discovered that implanted pacemakers and implantable cardioverter defibrillators (ICDs) were identifying atrial arrhythmias in patients who had no prior AF history and were entirely asymptomatic, it became clear that there may be a need for an insertable monitor whose sole purpose would be to detect previously undiagnosed arrhythmias such as AF. The most recent version of these monitors are ideally suited to look for AF in the cryptogenic stroke population. Several studies have used ICMs to look for AF in the cryptogenic stroke population.[7-12] According to the results, the rate of detection of AF by ICMs in cryptogenic stroke patients ranges from 15-30% and is a function of: length of monitoring, the definition of what duration of AF constitutes an episode, the interval from the index stroke to the start of monitoring, and patient selection.[13] These numbers are remarkably similar to the incidence of AF found in the CIED population in general. Data from ICMs can also be monitored remotely allowing clinicians to act as soon as AF is discovered.

Stroke Risk Associated with Device Detected AF

Several studies that have evaluated the thromboembolic (TE) risk of device detected AF episodes have demonstrated an increased stroke rate associated with the AF episodes. A minimum of five minutes of AF was found to have clinical relevance first in 2003 in the ancillary MOST trial.[14] 312 patients were enrolled and followed for 27 months. When AF (lasting at least 5 mins in duration) was detected, the hazard ratio for TE event was 6.8 (p=0.020) (Table 1). Alternative burden cut-points have been explored over the last 10 years ranging from 5 minutes to 24 hours. In the AT500 Italian Registry[15] (725 patients, 22-month follow-up), AF episodes longer than 1 day were associated with a 3.1 fold increased risk of embolism (95% CI 1.1 - 10.5, p = 0.044) after adjustment for known embolism predictors (Table 1). In the TRENDS trial[16] (2486 patients, 14-month follow-up), 30 day windows with AF burden > 5.5 hours on any day conferred an increased risk of stroke that was more than double that of 30 day windows with no AF detected. (HR 2.2 (95% CI 0.96 – 5.05, p=0.06) . Thirty day windows with low AF burden (< 5.5 hours/day) had an hazard ratio of 0.98 (95% CI 0.34-2.82, p=0.97) compared to zero burden (Table 1).

Pooled data analysis from two prospective, multi-center, international, observational studies in patients with ICDs with Cardiac Resynchronization Therapy (CRT-Ds) everesT and HomeCARE[17] (570 patients, 1-year follow-up) demonstrated that patients with NDAF or a prior history of AF were more likely to develop TE events than patients without NDAF or prior AF history. Patients with AF lasting > 3.8 hours per day were nine times more likely to develop TE complications (p = 0.006) than patients without AF(Table 1).

The ASSERT Trial6 (2580 pts, 2.5-year follow-up) showed that 6-minutes of AF detected in a 3 month period was associated with a doubling of TE risk (HR 2.49 95% CI 1.28 to 4.85, p = 0.007). When patients were stratified according to the longest duration of AF episodes by quartiles,(≤0.86 hours, 0.87 to 3.63 hours, 3.64 to 17.72 hours, and >17.72 hours), the annual rates of stroke or systemic embolism were 1.23 (95% CI, 0.15 to 4.46), 0 (95% CI, 0 to 2.08), 1.18 (95% CI, 0.14 to 4.28), and 4.89 (95% CI, 1.96 to 10.07), respectively. Accordingly, patients with AF episodes longer than 18 hours seemed to carry the greatest risk in that study. In a pooled analysis of 10,016 patients from 3 large clinical trial data bases, 1 hour of AF doubled the risk of stroke after adjustment for stroke risk factors and anticoagulation use[18] (Table 1).

A combination of AF burden and clinical risk scores has also been tested to identify patients at lower/higher risk. Botto et al[19] studied 568 patients with implanted pacemakers and a history of AF followed for 1 year. Three AF groups were considered: patients with <5-minutes AF (AF-free); patients with >5-minutes AF but <24 hours (AF-5 minutes); and patients with AF episodes >24 hours (AF-24 hours). By combining AF presence/duration with CHADS2 score, two subpopulations with markedly different risks of TE events (0.8% vs 5%, p = 0.035) were identified. The low risk group included patients who were AF-free with CHADS2 ≤2, AF-5 minutes with CHADS2 ≤1, and AF-24 hours with CHADS2 = 0. The high risk group included patients who were AF-free with CHADS2 >3, AF-5 minutes with CHADS2 ≥ 2, and AF-24 hrs with CHADS2 ≥ 1 (Table 1). In all of these studies the AF threshold cutpoints were arbitrarily chosen, or were the results of the data itself (i.e., median values). There is still uncertainty regarding the minimum duration of device detected AF that increases TE risk. Risk seems to be increased by relatively brief AF episodes. What does seem to be consistent is the finding that the appearance of NDAF increases TE event rates and that TE risk is increased by a mere 5 minute episode.

Temporal Proximity of Silent AF Episodes to Thromboembolic Event

There does not seem to be a proximate temporal relationship of device detected AF to the occurrence of stroke, despite the fact that patients who have AF are at increased risk of stroke. Several

Table 2: Temporal Proximity of Silent AF Episodes to TE

Year	Trial	Definition of AF	Any AF prior TE	AF only after TE	No AF in 30 days prior TE	AF at the time of TE
2011	TRENDS	5 minutes	50%	15%	73%	n.a
2012	Home CARE + EveresT	14 minutes per day>180 ppm	64%	n.a.	n.a.	27%
2014	ASSERT	6 minutes	35%	16%	84%	n.a
2015	IMPACT	36/48 atrial beats>200 ppm	29%	13%	94%	n.a

studies have highlighted this point and are outlined in Table 2.[17, 20-22] As seen, in the majority of patients (73-94%) there was no AF on the device recordings in the 30 days prior to the TE events. These data imply that, in the majority of device patients with AF and TE , the mechanism of stroke may not be solely related to the AF episodes. Other vascular disease risk factors may play a role in thromboembolism.

Early Detection of AF by Remote Monitoring

Despite a very high sensitivity of CIEDs for AF detection, detection in asymptomatic patients may be difficult because of infrequent office visits. Remote monitoring of CIEDs, with automatic alerts for AF, provides an opportunity for early identification of AF, potentially reducing stroke risk, heart failure, and mortality. This is critical, because lack of symptoms from AF does not translate to freedom from risk of thromboembolic, heart failure, or mortality sequelae. Furthermore, continuous monitoring may allow monitoring of the efficacy of individual patient treatment regimens, and the opportunity to modify therapy early in the course of disease.

The ability of RM to early detect AF has been consistently demonstrated by several observational and randomized trials. Initially, 276 consecutive patients[23] implanted with pacemakers that had automatic daily remote monitoring capability were studied in 2005. AF was documented within 1 year of follow-up in 10.5% of patients, with details of AF arrhythmia episode number and duration. Most patients were asymptomatic and unaware of their arrhythmias. In another single-center study[24] of 166 patients (73% pacemakers; 27% ICD) followed for 16 months, 20% had alerts triggered by AF, of which 88% needed clinical interventions, such as drug therapy modification, device reprogramming, or electrical cardioversion. The median reaction time to AF was advanced 148 days compared to standard scheduled follow-up.

In the worldwide Home Monitoring database analysis[25],3,004,763 transmissions were sent by 11,624 patients with pacemakers, ICDs and CRT-Ds. AF was responsible for more than 60% of alerts in pacemakers and CRT-D devices, and for nearly 10% of alerts in dual chamber ICDs. RM has been demonstrated to have a sensitivity of nearly 95% for true AF detection,[26] with 90% of AF episodes triggering alerts being asymptomatic.[24] Even when using an inductive RM system (without automatic alerts) RM performed better than standard follow-up in pacemaker patients for detection of AF in the randomized PREFER trial (980 patients).[27] The number of events reported per patient after 1-year follow-up was significantly higher in the remote monitoring arm (0.061 vs 0.037 for new onset AF and 0.198 vs 0.105 for AF lasting more than 48 hours) than in the standard scheduled follow-up arm.

1,339 ICD patients were followed for 15 months in the randomized TRUST trial.[28] AF detection occurred at 5.5 days in the remote monitoring arm versus at 40 days in the standard follow-up arm (34.5 days earlier). In the randomized CONNECT trial[29] (1,997 ICD patients followed for 15 months) the interval between detection of an AF episode longer than 12 hours and the clinical reaction was 8 times shorter with remote monitoring when compared with standard follow-up (3 versus 24 days). In that same study, high ventricular rates during AF (>120 beats per minute for at least six hours) were detected within 4 days with remote monitoring versus 23 days with standard follow-up.

Due to this strong evidence from published trials, remote monitoring use for the early detection and quantification of AF has a Class of Recommendation I, Level of Evidence A, in the recent HRS Remote Monitoring Consensus Statement Recommendations.[30]

AF Alert setting and Clinical Reaction Planning

Comprehensive diagnostic data regarding AF that can be obtained from RM include AF Burden Trends, AF Episode Histogram and Log, Ventricular Rate during AF, Stored Electrogram (EGM) records with EGM details (event markers, refractory markers and event intervals), and with some devices, a chronologic plot of all AF events and their individual durations that have occurred in the last year.

AF alert setting may be challenging for individual patients. First, there are major differences in proprietary systems, either in the alert setting itself (web based or directly in the implanted device) or in the available options for programming alert triggers for burden level, arrhythmia duration, internal EGM strips, and ventricular rate in AF. Some systems will transmit only during scheduled transmissions, or during manual transmission at the time of symptoms. Others will automatically transmit when an arrhythmia is detected based on previously programmed parameters. The availability of daily alerts for single short episodes may increase clinic work burden, and make it more difficult to identify clinically meaningful events. Alert settings should be modified during follow-up for individual patients according to the individual clinical profile of each patient.

An additional void that RM can fill is the assessment of success rates of AF therapies, in particular of catheter ablation. AF recurrences are often asymptomatic even in patients who were previously severely symptomatic. It has been suggested that RM could help determine whether anticoagulation therapy could be discontinued during follow-up.[31]

AF Impact on Heart Failure and Mortality and Role of RM

Several epidemiologic studies have shown strong associations between AF and risk of developing heart failure, and AF and increased mortality.[32-38] In addition, studies have demonstrated a relationship of AF to heart failure specifically in patients with implanted CRT devices.[39] Potential deleterious effects of unrecognized AF in CRT patients include inappropriate ICD shocks, thromboembolism, and loss of CRT therapy leading to increased sympathetic tone, hemodynamic compromise, heart failure exacerbations, and increased frequency of hospitalizations. In one large multicenter study (1,193 CRT-D patients), AT/AF >10 min occurred in 361 (30%) patients during a median follow-up period of 13 months. Freedom from the composite endpoint of death, heart transplantation, or heart failure hospitalization was significantly higher for patients without vs. those with AF during follow-up (hazard ratio: 2.16, $p = 0.032$).[40] In the pooled data analysis from EveresT and HomeCARE, patients with a prior history of AF and NDAF were at higher risk for heart failure

hospitalization than those without prior AF history and no NDAF (16.5% vs 5.1%, p = 0.001).[17]

Prevention Of AF Related Stroke, Heart Failure, and Mortality With RM

At present, there is no definitive evidence for stroke risk reduction, or decreased hospitalizations for AF related heart failure or mortality due to remote monitoring despite promising results of initial studies. Data generated by running repeated Monte Carlo simulations based on a real population of 166 patients suggested that daily monitoring could reduce the 2-year stroke risk from 18% to 9% for an absolute reduction from 0.6% to 0.2% per every 2 years, compared to conventional follow-up at intervals of 6 to 12 months.[41] In the COMPAS trial the incidence of hospitalizations for atrial arrhythmias and related stroke was 7.3% in the control group and 2.4% in the RM group (p=0.02), with stroke rates of 3.3% and 0.8% respectively.[42] In the HomeGuide Registry[26] patients (1650) were followed remotely for 20±13 months; stroke incidence was extremely low (0.4% at 4 years), lower than that expected for the estimated TE risk profile of the enrolled population.

In the prospective randomized study (IMPACT) of oral anticoagulation therapy for AF guided by RM,[22] there was no improvement in the outcomes of stroke or all cause mortality for the intervention group (RM) compared with controls. The study protocol called for discontinuation of oral anticoagulation if there was no AF detected for 30 days in patients with 1 or 2 CHADS2 scores, and no AF detected for 90 days in patients with 3 and 4 CHADS2 scores. The primary outcome of TE or bleeding event was similar in the two arms at 5 years of follow-up (2.4% patient-years vs. 2.3%; p = 0.78). Mortality rates were also similar (5.4% patient-years vs. 5.1%; p = 0.66). Poor compliance to anticoagulation plan and per protocol discontinuation of oral anticoagulation in case of no AF recurrences may be responsible for this finding. Considering the temporal dissociation of atrial fibrillation events and stroke events previously discussed, it may be that oral anticoagulation should not be stopped in any subgroups at any time once there is an indication.

The Future

Many studies are currently ongoing in this field of silent AF. Some are looking merely to determine the incidence and prevalence of silent AF. Some are looking to see if the pattern and progression of AF can be elucidated. Some are investigating starting and stopping oral anticoagulation based on information from the device diagnostics, and treating patients ONLY when they are actually in AF and sparing them the risks of bleeding when the rhythm is normal. In addition, studies are ongoing randomizing patients who have silent AF detected to: oral anticoagulation vs. ASA alone. All of these studies take into account CHADSVASC risk factors when prescribing treatment regimens.

Conclusions

The absense of symptoms due to AF does not translate into freedom from risk of thromboembolic events, heart failure hospitalizations , or mortality. We have shown that the prevalence of silent AF in patients with CIEDs, including patients with implanted cardiac monitors is as high as 30%. As is written in the recent Heart Rhtyhm Society guidelines, remote monitoring should be offered to all patients for the early detection and quantification of AF (Class I, Level A). We have also shown that there is an increased risk of TE events in patients who have AF detected by their implanted devices. Remote home monitoring is an accurate way to monitor every atrial arrhythmia episode in every patient every day, thereby being highly effective for early detection AF. Studies are ongoing to demonstrate potential benefit of RM for hard endpoints such as stroke prevention, heart failure hospitalizations, and mortality.

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Managing Antiplatelet Therapy and Anticoagulants in Patients with Coronary Artery Disease and Atrial Fibrillation

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Abstract

Oral anticoagulation (OAC) is essential in patients with atrial fibrillation (AF). Interestingly coronary artery disease coexists in 20–30% of these patients.[1,2] Balancing the risk of bleeding and thromboembolism is very important for the management of patients on OAC, especially than when such patients require percutaneous coronary intervention (PCI). Lack of data and clear societal guidelines for peri-procedural and post-procedural management of anticoagulated patients has resulted in diverse clinical practices among clinicians, hospitals, and countries. Furthermore with expanding number of available oral antiplatelet and anticoagulant agents, the uncertainty regarding optimal combination therapy in this growing pool of the patients with overlapping clinical indications is also growing. Given the high proportion of patients with atherothrombosis and requiring OAC for conditions particularly like AF, it is important that physicians are aware of the clinical implications and management of these overlapping syndromes.

In this article we discuss; this evolving dilemma of peri-procedural and post-procedural management of anticoagulated patient's, burden of the disease, available data, risk factors that could identify high risk patients and propose a well-balanced management strategy.

Introduction

Long-term oral anticoagulation (OAC) is the cornerstone in the treatment of patients with atrial fibrillation (AF) at moderate to high risk of stroke, those with prosthetic heart valves, cardiogenic thromboembolism, recent deep vein thrombosis or pulmonary embolism. Approximately 70–80% of all patients in AF have an indication for continuous OAC, and coronary artery disease coexists in 20–30% of these patients.[1,2] Balancing the risk of bleeding and thromboembolism is crucial in the management of patients on OAC, and this is never more apparent than when such patients require percutaneous coronary intervention (PCI). The periprocedural management of anticoagulated patients is very important, but clinical practice varies widely between clinicians, hospitals, and countries, driven by a lack of data on which to draw guidance. Furthermore as the number of available oral antiplatelet and anticoagulant agents continue to grow, so does the uncertainty regarding optimal combination therapy in this growing pool of the patients with overlapping clinical indications. Given the high proportion of patients with atherothrombosis and requiring OAC for conditions particularly like AF, it is important that physicians are aware of the clinical implications and management of these overlapping syndromes.

Key Words:
Lariat, Embolic Stroke, Anticoagulant Therapy.

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None.

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Burden of the Atrial Fibrillation, Valvular Heart Disease and Venous Thromboembolism Disease

The prevalence of atrial fibrillation (AF) in the United States is approximately 6 million patients and is on the rise.[3] More than 17 million patients have coronary artery disease (CAD), and over 6 and 8 million Americans, respectively, have suffered a stroke or have peripheral arterial disease.[4] The prevalence of AF in patients with established atherothrombosis (11.7%) or risk factors for atherothrombosis (6.2%) is substantially higher compared with the general population (2.3%).[5,6] Another challenging patient population is those with valvular heart disease who underwent mechanical valve replacement. Approximately 90000 valve substitutes are now implanted in the United States and 280 000 worldwide each year; approximately one fourth of the US valve replacements are mechanical valves requiring long term OAC.[7] Venous thromboembolism (VTE) causes significant morbidity and mortality with an estimated annual incidence of 900,000 patients with clinically evident VTE in the U.S., resulting in an estimated 300,000 deaths from PE.[8] Keeping in mind the burden of various diseases requiring long term OAC, it is estimated that 5–7% of patients undergoing percutaneous coronary interventions (PCI) have indications for chronic oral anticoagulant therapy.[9, 10]

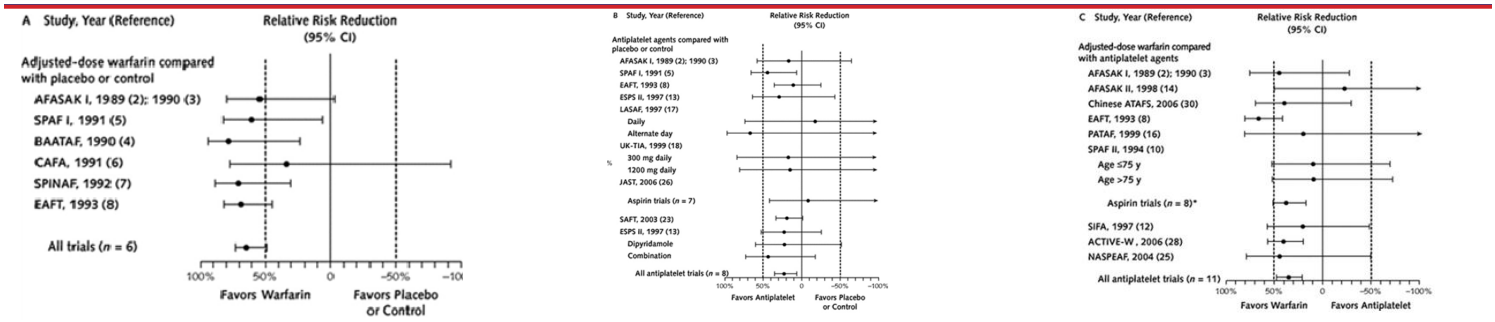


Figure 1: **Reveals relative effects of antithrombotic therapies on all types of strokes from randomized trials in patients with atrial fibrillation. Horizontal lines represent 95% CIs around point estimates.**
A. Adjusted-dose warfarin compared with placebo or no treatment in 6 randomized trials

Understanding the Problem

The mechanisms of thrombus formation differ between that associated with thromboembolic diseases like AF and that of coronary artery disease and stent thrombosis. Plasma factors (i.e., coagulation factors) are more important in the development of thromboembolic events during AF and cellular factors (i.e., platelets) are more important in the pathophysiology of atherothrombotic events.[11] Consequently, oral anticoagulant therapies are mainstay of treatment for stroke prevention in atrial fibrillation (AF), as-well as prevention of pulmonary embolism in the recent deep vein thrombosis or pulmonary embolism and antiplatelet agents are of greater benefit in the prevention of ischemic events, including stent thrombosis, in patients undergoing PCI.

AF is the most common cardiac arrhythmia and is associated with a small but significant incidence of stroke and systemic thromboembolism.[12] It is well established that oral anticoagulants reduce the incidence of stroke and systemic embolism in these patients.[13] A meta- analysis of 29 trials showed that warfarin reduced stroke by 64% as compared with placebo and by 39% as compared with aspirin in patients with non-valvular AF[14] (Figure-1). Furthermore several trials including ACTIVE-W have confirmed the superiority of warfarin in reducing embolic events over dual antiplatelet therapy (DAPT) with aspirin and clopidogrel in patients with both paroxysmal and sustained AF and at least 1 additional stroke risk factor[15] (Figure-2).

As a result, the ACC/AHA guidelines recommend oral anticoagulant therapy with warfarin for those patients with at least 1 additional risk factor for stroke and suggest the use of aspirin only for those at low risk for stroke such as patients without risk factors.[12] Dual antiplatelet therapy (DAPT) is the standard of care to reduce recurrent ischemic events after acute coronary syndrome (ACS) and to prevent stent thrombosis after percutaneous coronary intervention (PCI). Furthermore dual antiplatelet therapy has also been proven to be superior in terms of safety and efficacy when compared with anticoagulation with Warfarin following coronary stenting. Data from Stent Antithrombotic Regimen Study (STARS) trial, in which 1653 patients who had successful placement of the stent were randomly assigned to one of three regimens: aspirin alone (557 patients), aspirin and warfarin(550 patients), and dual antiplatelet therapy (DAPT) with aspirin and ticlopidine (546patients), revealed that DAPT reduced the occurrence of death, target lesion revascularization, stent thrombosis, and recurrent MI at 30 days from 3.6% with aspirin alone and 2.7% for aspirin and warfarin compared to only 0.5% for aspirin and ticlopidine16 (Figure-3). Because clopidogrel, a second-generation thienopyridine, has fewer adverse effects than ticlopidine, such as thrombotic thrombocytopenic purpura and severe neutropenia, it rapidly became the thienopyridine of choice.[17,18] Current ACC/AHA guidelines recommend DAPT in patients with an STEMI for at least 1 year for BMS and DES. In patients with unstable angina or NSTEMI receiving a BMS, DAPT should be given for at least 1 month and preferably for 1 year.[19,20] In patients who receive an elective DES, the current recommendations are for one year of DAPT.

Three antithrombotic drug combinations have been used most in practice: triple therapy (oral anticoagulation and dual antiplatelet therapy with aspirin and clopidogrel), oral anticoagulation, and 1 antiplatelet agent (aspirin or clopidogrel), or rarely, DAPT alone without oral anticoagulants. Although there are wide variations in type and duration of therapy in practice, triple therapy is the most common treatment regimen in this setting. Several studies demonstrate that the risk of bleeding rises with an increased number of antithrombotic agents. In one study of 21,443 elderly patients followed on average for 22 months after an acute MI, bleeding was 1.7 times more frequent with DAPT and 1.9 times more frequent with aspirin plus warfarin when compared with aspirin monotherapy.[21] Similarly, in a nationwide registry of 40,812 patients with acute MI in Denmark, the risk of bleeding was 2.6% for aspirin, 4.6% for clopidogrel, 4.3% for DAPT, 5.1% for aspirin plus an oral anticoagulant, 12.3% for clopidogrel plus an oral anticoagulant, and 12.0% for triple therapy over a mean follow-up of 16 months[22] (Figure-4). Hence patients taking combination of oral anticoagulants with aspirin and clopidogrel ("triple therapy") pose a significant dilemma for the cardiologist because of the increased risk of major bleeding.

In one study among patients on triple therapy with aspirin, clopidogrel, and warfarin, major bleeding occurred in 4.7%, and approximately 50% of these patients died within 6 months.[23] In a meta-analysis involving 13 retrospective studies (Figure-5A) and registries assessing antithrombotic regimens in patients with AF undergoing PCI risk of major bleeding was 1.5% at 30 days and 5.2% at 1 year with triple AT (aspirin + warfarin + clopidogrel/ticlopidine). Dual antiplatelet therapy (aspirin + clopidogrel/ticlopidine) was associated with 2.4% annual risk of major bleeding.[24] Similarly, in another meta-analysis involving 9 randomized controlled trials (Figure-5B), patients with triple antithrombotic regimen had significant reduction in ischemic stroke (odds ratio [OR] is 0.29, 95% confidence interval [CI] is from 0.15 to 0.58; and P = 0.0004) as compared with dual antiplatelet therapy. While there was a two-fold

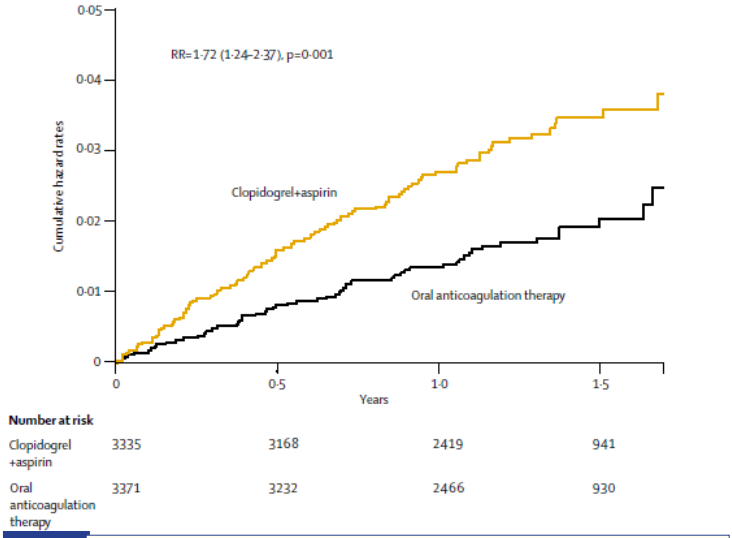


Figure 2: **Depicts that compared with clopidogrel plus aspirin, oral anticoagulation therapy reduced all strokes. (RR 1.72, 95% CI 1.24–.37; p=0.01) indicating that oral anticoagulation therapy is superior to clopidogrel plus aspirin for prevention of vascular events in patients with atrial fibrillation at high risk of stroke, especially in those already taking oral anticoagulation therapy.**

increased risk of major bleeding associated with triple antithrombotic regime (OR 2.00, 95% CI 1.41 to 2.83; and P < 0.0001). The overall incidence of death (OR 1.20, 95% CI 0.63 to 2.27, and P = 0.56) and myocardial infarction (OR 0.84, 95% CI 0.57 to 1.23; and P = 0.38) was comparable between the two regimens.[25] Both studies confirm the cardiovascular benefits of triple antithrombotic regimen by reducing ischemic stroke risk, but also demonstrated its increased risk of major bleeding.

Major bleeding is a serious complication that is associated with increased morbidity and mortality particularly when it occurs shortly after a stent procedure. Despite different bleeding definitions, both access site and non-access site bleeding has been observed across all the major trials in patients undergoing PCI. In fact, in one of a major meta-analysis using combined dataset from the REPLACE-2 (Randomized Evaluation in PCI Linking Angiomax to Reduced Clinical Events), Acute Catheterization and Urgent Intervention Triage Strategy (ACUITY), and HORIZONS-AMI (Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction) trials in 17,393 PCI patients, non-access site bleeding after PCI was found to be common, representing approximately two-thirds of all TIMI bleeding events, and was found to be associated with a 4-fold increase in 1-year mortality.[26] Furthermore, similar results have been found in other studies indicating a strong relationship between early bleeding and 1 year mortality. Results from a major meta-analysis that included 5,384 patients from 4 randomized placebo-controlled trials: ISAR-REACT, SWEET, SMART-2, and REACT-2, revealed that the 30-day occurrence of bleeding independently predicted 1-year mortality by a Cox proportional hazards model, indicating a strong relationship between the 30-day frequency of bleeding and 1-year mortality after PCI [27](Figure-6).

Bleeding severity also has been found to be directly related to mortality. In a meta-analysis involving about 26500 patients from the multicenter international GUSTO IIb, the Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy (PURSUIT), and the Platelet IIb/IIIa Antagonism for the Reduction of Acute Coronary Syndrome Events in a Global Organization Network (PARAGON) A and B trials were studied. The study demonstrated a relationship between bleeding severity and worsening 30 day mortality.[28] Interestingly, the studies aimed to investigate the long-term prognosis of patients with in-hospital major bleeding after primary PCI also show significantly increased 3-year rates of morbidity and mortality[29,30] (Figure-7).

Management

Managing the patients with AF requiring oral anticoagulants with aspirin and clopidogrel needs a thoughtful balancing act between risk of stroke or systemic embolism, risk of stent thrombosis and recurrent ischemic events as well as risk of bleeding.

Arguably, the 3 key issues appear to be:

1. Whether or not to interrupt OAC for the procedure
2. The choice of long term antithrombotic therapy that follows PCI
3. How best to modify the procedure to ensure optimal safety

Whether or Not to Interrupt OAC for The Procedure

Current guidelines offer limited guidance on long-term OAC during the peri-PCI period. Strategies like temporary replacement of warfarin by dual antiplatelet drug therapy and temporary adjustment of warfarin dosing to reach a perioperative INR of 1.5–2.0 have been proven to result in more adverse effects and inadequate for PCI or stroke prevention in AF respectively.[31,32,33] This view is supported by data showing that non-use of OAC markedly increases mortality in patients with AF after acute myocardial infarction.[34,35,36] The most common practice is to offer "bridging" with either unfractionated or low molecular weight heparin (LMWH) to cover the temporary discontinuation of OAC, if the risk of thromboembolism is considered high. While this practice makes sense and appears to be logical based on the competing pathophysiologies, this approach is based on circumstantial evidence and there are no large randomized trials to support the recommendation. Furthermore, studies have shown that patients with ACS and on home warfarin are significantly less likely to undergo coronary angiography and PCI and their waiting times

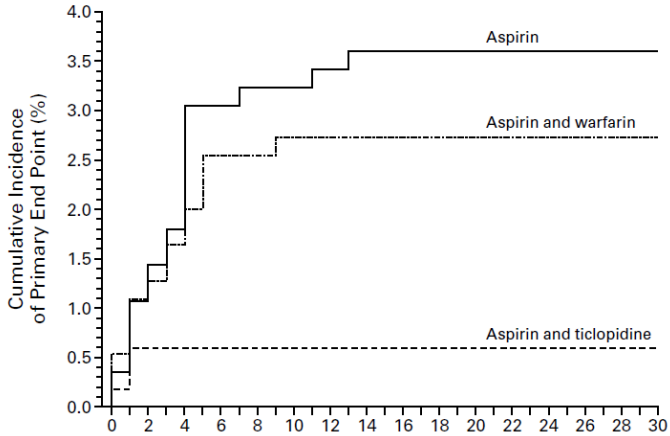


Figure:3 **1653 patients who had successful placement of the stent were randomly assigned to one of three regimens:aspirin alone (557 patients), aspirin and warfarin(550 patients), or aspirin and ticlopidine (546patients). The figure shows cumulative Incidence of the primary end point in the Three Treatment Groups. DAPT reduced the occurrence of death, target lesion revascularization, stent thrombosis, and recurrent MI at 30 days from 3.6% with aspirin alone and 2.7% for aspirin and warfarin to 0.5% for aspirin and ticlopidine.**

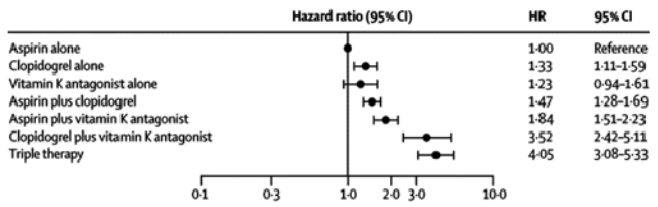


Figure:4 Reveals adjusted risk of non-fatal and fatal bleeding in 40,812 patients treated with antithrombotic drugs after first myocardial infarction HR=hazard ratio. Aspirin monotherapy is used as the reference. The risk of bleeding was 2.6% for aspirin, 4.6% for clopidogrel, 4.3% for DAPT, 5.1% for aspirin plus an oral anticoagulant, 12.3% for clopidogrel plus an oral anticoagulant, and 12.0% for triple therapy over a mean follow-up of 16 months.

for these procedures are longer than in patients not on warfarin.[37] The general perception that warfarin should be discontinued a few days prior to PCI and the periprocedural INR level should fall below therapeutic range (2.0) may contribute to these delays.

Interestingly, studies show that the incidence of bleeding or thrombotic complications is not related to peri-procedural INR levels, and propensity score analyses suggested that the bridging therapy with either unfractionated heparin or LWMH, to cover the temporary discontinuation of OAC increases the risks of peri-procedural bleeding and access site complications.[34,38,39] Supporting this view, recent findings suggest that uninterrupted anticoagulation with warfarin may be a better alternative to heparin bridging in catheter interventions with a favorable balance between bleeding and thrombotic complications.[60,61,62] Data from a major prospective multicenter European registry (Atrial Fibrillation undergoing Coronary Artery Stenting-AFCAS Registry) that recruited 963 patients with AF undergoing coronary stenting to compare the safety of uninterrupted anticoagulation (UAC), indicate that UAC does not increase perioperative complications during coronary stenting and is a simple and cost-effective alternative to conventional heparin bridging[40] (Figure-10).

Furthermore, studies have indicated advantages of PCI with UAC that includes prevention of the transient pro-thrombotic state due to proteins C and S suppression caused due to warfarin reinitiation, minimal wide and long lasting fluctuation in INR following warfarin interruption and effect of warfarin can be easily overcome by FFP or activated clotting factors II, VII,IX and X.[40,41,42]

In the European Society of Cardiology (ESC) guidelines for the management of valvular heart disease, continuation of OAC at modified doses is recommended for the majority of patients who undergo cardiac catheterization.[43] Similarly in the consensus paper of the Working Group on Thrombosis of the ESC, endorsed by the European Heart Rhythm Association and European Association of Percutaneous Cardiovascular Interventions, the UAC strategy is recommended as the preferred strategy for AF patients at moderate to high risk of thromboembolism.[44] For patients admitted with acute coronary syndrome, the risk of bleeding vs. thromboembolism becomes more complex, as these patients often require bivalirudin (a direct thrombin inhibitor) or glycoprotein IIb/IIIa inhibitors (GPI). The consensus document suggests stopping the OAC on admission in this circumstance. Exception to this may be patients at a very high risk of thromboembolism, such as those with mechanical mitral valves or recurrent venous thromboembolism, where uninterrupted OAC may be preferable to the potential risk of bleeding with interruption and heparin bridging.[44]

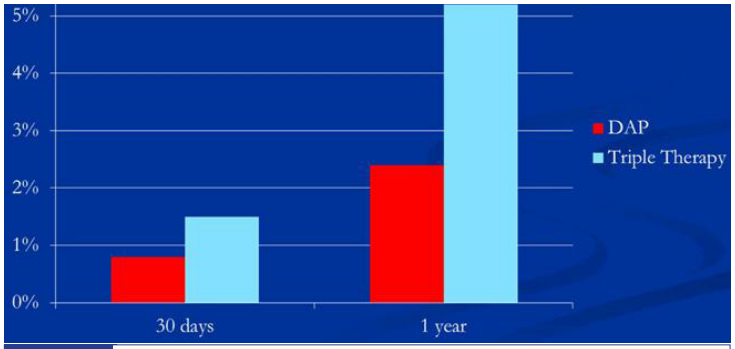


Figure: 5A Reveals results of the meta-analysis involving 13 retrospective studies and registries assessing antithrombotic regimens in patients with AF undergoing PCI, risk of major bleeding was 1.5% at 30 days and 5.2% at 1 year with triple AT (aspirin + warfarin + clopidogrel/ticlopidine). Dual antiplatelet therapy (aspirin + clopidogrel/ticlopidine) was associated with 2.4% annual risk of major bleeding.

Choice of Long Term Antithrombotic Therapy that Follows PCI

Acute coronary syndrome patients presenting with acute ST-

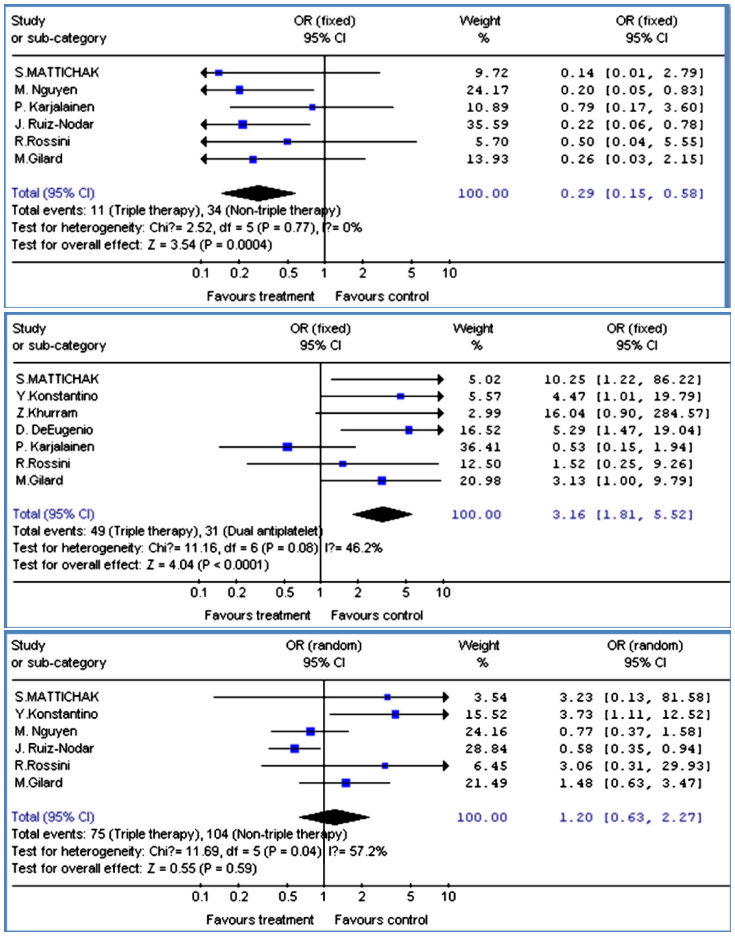


Figure: 5B Shows meta-analysis involving 9 randomized controlled trials. (a) Patients with triple antithrombotic regimen had significant reduction in ischemic stroke (odds ratio [OR] is 0.29, 95% confidence interval [CI] is from 0.15 to 0.58; and P = 0.0004) as compared with dual antiplatelet therapy.(b) While there was a two-fold increased risk of major bleeding associated with triple antithrombotic regime (OR 2.00, 95% CI 1.41 to 2.83; and P < 0.0001).(c) The overall incidence of death (OR 1.20, 95% CI 0.63 to 2.27, and P = 0.56) and myocardial infarction (OR 0.84, 95% CI 0.57 to 1.23; and P = 0.38) was comparable between the two regimens

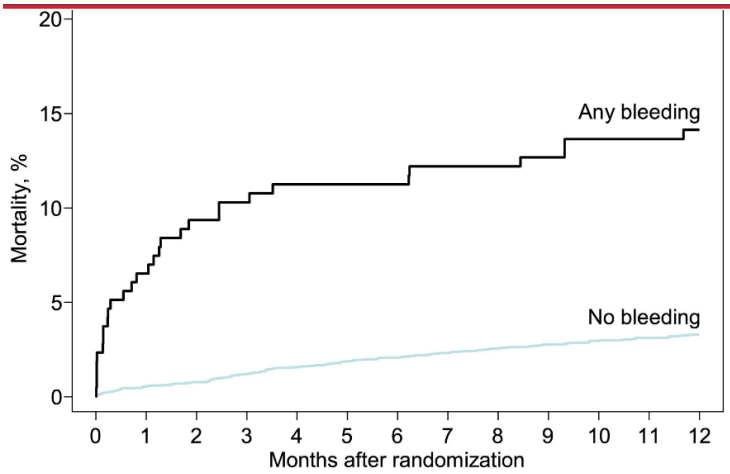


Figure:6 **Depicts. Kaplan-Meier curves of 1-year mortality among 5,384 patients from 4 randomized placebo-controlled trials. The 1-year mortality was 14.1% (n = 30) among patients in whom bleeding occurred within the 30 days after PCI versus 3.3% (n = 167) among patients who had no bleeding within the 30 days (OR 4.75, 95% CI 3.34 to 6.76, p < 0.001).**

elevation myocardial infarction (STEMI) are increasingly managed with primary PCI with additional combined antithrombotic therapy regimes.[19, 20] Those presenting with non-ST-elevation acute myocardial infarction (NSTEMI) are also managed with combined antithrombotic and anti-platelet therapy, as an early invasive revascularization strategy, is often employed based on guideline recommendations.[19,20]

The long-term results of stent usage have been blighted by the dual problem of in stent restenosis (ISR) and stent thrombosis. In particular, the increasing use of drug-eluting stents (DES) to minimize ISR necessitates long-term dual antiplatelet therapy with aspirin plus a thienopyridine (at present most frequently clopidogrel) to reduce the risk of early and late stent thrombosis. Current ACC/AHA guidelines recommend DAPT in patients with an STEMI for at least 1 year for DES and BMS.[19, 20]

As noted before, the results from ACTIVE-W trials demonstrated that combined aspirin– clopidogrel therapy cannot replace OAC in stroke prevention in patients with AF.[15] Several observational studies on clinical practice support this conclusion also in patients with AF after coronary stenting.[34, 35] Likewise OAC alone is insufficient to prevent stent thrombosis[45,46,47,48] making management of patients with Afib patients requiring stent very complicated. At present, in patients on OAC therapy, the additional use of dual antiplatelet therapy (triple therapy) seems to be the best option to prevent stent thrombosis and thromboembolism. Data from CRUSADE Registry indicates that Triple Therapy is the commonest regimen used in the setting of atrial fibrillation patients requiring PCI.[49] Similarly data from Society for Cardiac Angiography and Interventions survey (2011) reveal that 86% of interventionists prefer Triple Therapy for 1 month followed by warfarin and aspirin in case of bare-metal stent and 47.4% recommend at least 6 months of Triple Therapy after DES implantation.

As per consensus paper of the Working Group on Thrombosis of the ESC, endorsed by the European Heart Rhythm Association and European Association of Percutaneous Cardiovascular Interventions,[44] in case of elective PCI Clopidogrel 75 mg daily should be given in combination with OAC plus aspirin 75–100 mg daily for a minimum of 1 month after implantation of a BMS, but longer with a DES (at least 6 months) and clopidogrel 75 mg daily (or alternatively aspirin 75–100 mg daily, plus gastric protection with a PPI) may be continued depending on the bleeding and thrombotic risks of the individual patient. In case of the AF patients presenting with Non-ST elevation ACS like NSTEMI and unstable angina with or without PCI and at moderate to high risk of stroke it is recommended to continue/give anticoagulation therapy in addition to dual antiplatelet therapy with aspirin plus clopidogrel. However in the acute setting, patients are often given aspirin, clopidogrel, heparin (whether UFH or an LMWH, enoxaparin) or bivalirudin and with some frequency a GPIIa/IIIb inhibitor (GPI). Given the risk of bleeding with such combination antithrombotic therapies, it is recommended to stop OAC therapy, and administer antithrombins or GPIs only if INR ≤ 2. As per consensus paper, in the setting of acute STEMI with primary PCI and AF, it is recommended that patients should be given aspirin, clopidogrel, and heparin (UFH). When patients have a high thrombus load, GPIs may be given as a 'bail out' option. As an alternative to heparin plus GPI, bivalirudin might be used and has a superiority in bleeding risk as demonstrated in the ACUITY and HORIZONS-AMI trials. Given the risk of bleeding with such combination antithrombotic therapies, it may be prudent to stop OAC therapy. Ideally, GPIs would not be considered if except only in a 'bail out' option. Detailed recommendations from consensus paper of the Working Group on Thrombosis of the ESC, endorsed by the European Heart Rhythm Association and European Association of Percutaneous Cardiovascular Interventions are depicted in the Table-1.

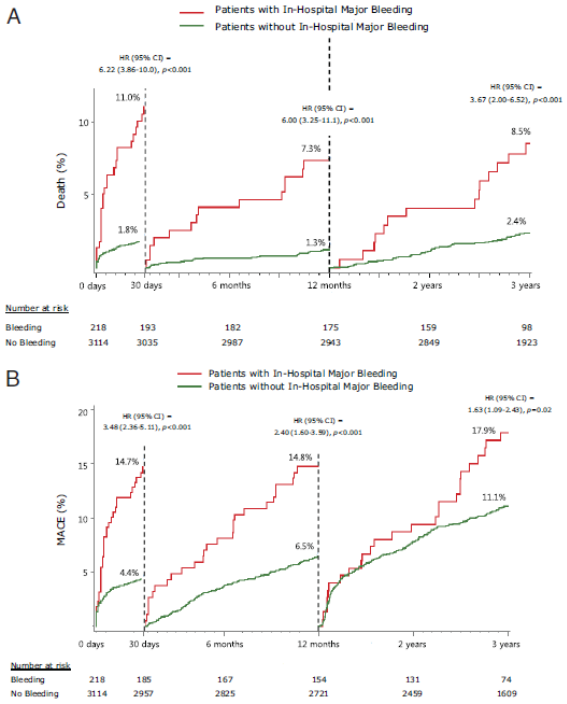


Figure:7 **Results of the HORIZONS-AMI (Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction) trial involving 3,345 patients with primary PCI. The rates of mortality and MACE were significantly higher in patients with in-hospital major bleeding (IHMB) within each time interval. The deleterious effect of major bleeding was observed within 1 month, between 1 month and 1 year, and between 1 and 3 years. IHMB was an independent predictor of mortality (hazard ratio: 2.80; 95% confidence interval: 1.89 to 4.16, p < 0.0001) at 3-year follow up.**

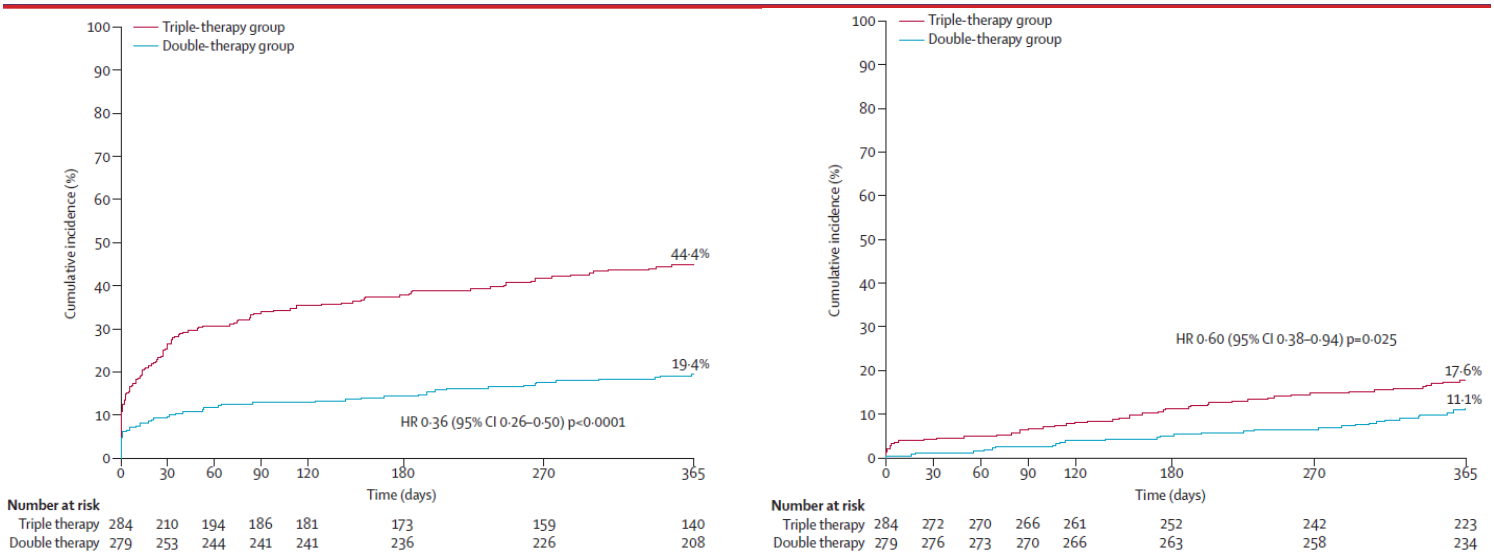


Figure 8: **Results of the WOEST (The What is the optimal antiplatelet and anticoagulant therapy in patients with oral anticoagulation and coronary Stenting) study, an open-label, randomized, controlled trial done at 15 sites in the Netherlands and Belgium involving patients taking oral anticoagulants who underwent PCI. 573 patients were enrolled and 1-year data were available for 279 (98·2%) patients assigned double therapy and 284 (98·3%) assigned triple therapy. (A). Incidence of the primary endpoint (any bleeding), bleeding episodes were seen in 54 (19·4%) patients receiving double therapy and in 126 (44·4%) receiving triple therapy (hazard ratio [HR] 0·36, 95% CI 0·26–0·50, p<0·0001).**

Dual Therapy (Warfarin+ Clopidogrel) Vs. Triple Therapy

Results from the single center WOEST trial involving 573 patients who underwent PCI with a mean follow up of 1 year clearly show that use of dual therapy (Warfarin and clopidogrel without aspirin) was associated with a significant reduction in bleeding complications with no increase in the rate of thrombotic events were observed50. Furthermore use of triple therapy was associated with higher mortality and morbidity (Figure-8). Similar observations were made in previous smaller studies51. Although data on the efficiency and safety of warfarin plus clopidogrel combination are limited, but this combination may be an alternative in patients with high bleeding risk and/or absent risk factors for stent thrombosis. Future multi-center trials will need to confirm these results.

Modifying the Procedure and Bleeding Avoidance Strategies to Ensure Optimal Safety

For optimal outcome, a delicate balance is needed between the prevention of thromboembolism, against recurrent cardiac ischemia or stent thrombosis, and bleeding risk, to individualize treatment options thus avoiding regimented common protocol. Following considerations could be used while managing a patient on anticoagulation requiring PCI.

Identify the High Risk Patient

Thromboembolism, stent thrombosis and peri-procedural bleeding are all described as complex phenomenon and dependent on several independent predictors.[68,69] (Table-2) Identification of the AF patients undergoing PCI who are at high risk for thromboembolism, stent thrombosis and peri-procedural bleeding is very important for the optimal outcome. Interestingly Faxon et al identifies patients with AF at moderate to high risk of stroke (CHADS-2 score≥1) undergoing PCI into three groups based on the risk for stent thrombosis (ST) and bleeding.[67] Low ST and low bleeding risk group, high ST and low bleeding risk group and high ST and high bleeding risk group. The management plan from each group is depicted in figure-9.

Choosing the Right Stent and Procedure

Recommendations from consensus paper of the Working Group on Thrombosis of the ESC, endorsed by the European Heart Rhythm Association and European Association of Percutaneous Cardiovascular Interventions,[44] clearly state that the use of DES of first and second generation, due to the prolonged need of dual antiplatelet therapy, should be avoided in patients with an indication for long-term OAC and high bleeding risk. However DES is recommended in the patients with high risk of stent restensois and

Table 1: **Recommended antithrombotic strategies following coronary artery stenting in patients with atrial fibrillation at moderate-to-high thrombo-embolic risk (in whom oral anticoagulation therapy is required) by European Society of Cardiology Working Group on Thrombosis, endorsed by the European Heart Rhythm Association (EHRA) and the European Association of Percutaneous Cardiovascular Interventions (EAPCI)**

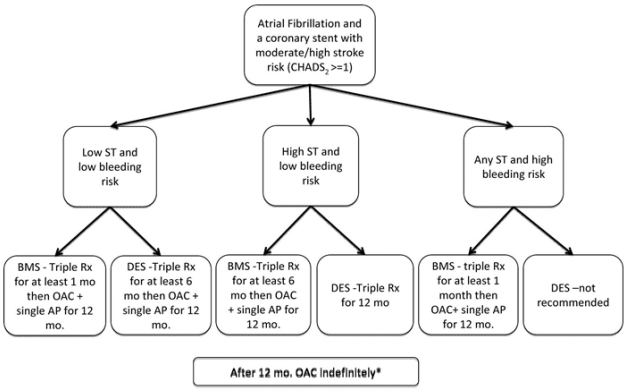
Haemorrhagic Risk	Clinical Setting	Stent Implanted	Recommendation
Low or intermediate	Elective	Bare metal	1 month: triple therapy of warfarin(INR 2.0 - 2.5) + aspirin ≤ 100 mg/day + clopidogrel 75 mg/day Lifelong: warfarin (INR 2.0 - 3.0) alone
	Elective	Drug eluting	3 (-olimus group) to 6 (paclitaxel) months: triple therapy of warfarin (INR 2.0 - 2.5) + aspirin ≤ 100 mg/day + clopidogrel 75mg/day Up to 12 months: combination of warfarin (INR 2.0 - 2.5) + clopidogrel 75mg/day (or aspirin 100 mg/day)[a] Lifelong: warfarin (INR 2.0 - 3.0) alone
	ACS	Bare metal/ drug eluting	6 months: triple therapy of warfarin (INR 2.0 - 2.5) + aspirin ≤ 100 mg/day + clopidogrel 75mg/day Up to 12 months: combination of warfarin (INR 2.0 - 2.5) + clopidogrel 75mg/day (or aspirin 100 mg/day)[a] Lifelong:warfarin (INR 2.0 - 3.0) alone
High	Elective	Bare metal[b]	2 - 4 weeks: triple therapy of warfarin (INR 2.0 - 2.5) + aspirin ≤ 100 mg/ day + clopidogrel 75 mg/day Lifelong:warfarin (INR 2.0 - 3.0) alone
	ACS	Bare metal[b]	4 weeks: triple therapy of warfarin (INR 2.0 - 2.5) + aspirin ≤ 100 mg/day + clopidogrel 75 mg/day up to 12 months: combination of warfarin (INR 2.0 - 2.5) + clopidogrel 75mg/day (or aspirin 100 mg/day); mg/day);[a] Lifelong:warfarin (INR 2.0 - 3.0) alone

INR international normalized ratio; acute cornary syndrome
[a]combination of warfarin (INR 2.0 - 2.5) + clopidogrel 75mg/day may be considered as a alternative
[b]Drug eluting sents should be avoided

where a significant benefit is expected DES when compared with BMS. Furthermore, as more studies emerge suggesting shorter duration of DAPT therapy is safe and effective in reducing stent thrombosis with second generation drug eluting stents, cardiologists will be able to reduce their patient exposure to either dual therapy or triple therapy. Reduction in the need for DAPT to 3-6 months for 2nd generation DES will make DES a more accessible option in even higher risk patients. Finally, in the extremely high risk bleeding patient, balloon angioplasty can also be considered when the angiographic result after balloon angioplasty is acceptable. In some cases also coronary artery bypass graft (CABG) might be favored over PCI if the patient is a reasonable surgical candidate otherwise.

Wise Selection of Access Site

Recommendations for the duration of triple therapy in patients with atrial fibrillation and a coronary stent (BMS or DES) with moderate/high stroke risk (CHADS2 ≥1).



BMS= bare metal stent, DES= drug eluting stent
OAC= warfarin, AP= anti-platelet agent, Triple therapy= aspirin, clopidogrel and warfarin

Faxon D P et al. Circ Cardiovasc Interv. 2011;4:522-534

Figure 9: **Recommendations for the combination and duration of triple therapy in patients with atrial fibrillation and a coronary stent (BMS or DES) with moderate/high stroke risk (CHADS2≥1. BMS indicates bare metal stent; DES, drug-eluting stent; OAC, warfarin; AP, antiplatelet agent; and triple therapy, aspirin, clopidogrel, and warfarin. In patients at high risk for atherothrombotic events including stent thrombosis, continued single antiplatelet therapy with warfarin should be considered after 12 months. The authors used the following average crude estimates of risk for each adverse outcome listed below (low and high) to be:**
• Stroke risk (CHADS2_1) on warfarin average 1.5%(1.0% for CHADS2_1–7% for CHADS2_5–6) per year (or adjusted stroke rates from 1.95%/y to _12.5%/y).
• Stent thrombosis (first year) on DAPT_1.5% (1–5%) but 5- to 36-fold higher for premature discontinuation within the first month, and 2.5- to 5-fold if between 1 and 6 months. On DAPT the risk is greatest in the first month.
• Major bleeding requiring hospitalization on triple therapy_6–15%/y; warfarin and 1 antiplatelet agent_6–12%/y; and on either DAPT or warfarin alone 2.5–4%/y. The rate is highest within the first 30 days after the procedure.

Several independent studies indicate that vascular access site selection may have a great impact on bleeding complications. Meta-analyses of randomized trials and registry studies clearly reveals that radial artery access is associated with a reduced risk of access site bleeding and other vascular complications.[52,53,54,55] Furthermore femoral access was an independent predictor (hazard ratio of 9.9) of access site complications in 523 warfarin-treated patients.[55] On the basis of current evidence, a radial approach should be always considered in anticoagulated patients, since haemostasis is rarely an issue with this access site.

Avoidance Of Newer Anti-Platelet Agents Like Prasugrel And Ticagrelor In Triple Therapy

Results from TRITON–TIMI 38 and PLATO trials, reveal higher rates of bleeding with newer anti-platelet agents prasugrel and ticagrelor respectively.[56,57,58] Therefore avoidance of newer anti-platelet agents like prasugrel and ticagrelor in the patients on OAC in the setting of ACS or requiring PCI is reasonable if a strategy of triple therapy is being pursued. Use of the newer antiplatelet therapy in setting of dual therapy with warfarin or novel oral anticoagulants are still being investigated. Please see below.

Gastric Acid Suppression With PPIs

Gastric protection with proton pump inhibitors (PPIs) is considered useful in patients on triple therapy and those prone to develop gastrointestinal bleeding (elderly, patients with a history of ulcer disease or prior gastrointestinal bleeding).[59]

Avoid Gpis

Several studies indicate that the GPI use is associated with a 3–13-fold risk of early major bleeding in warfarin-treated patients who undergo revascularization in the form of PCI.[60,61,62] In general, GPIs seem to increase major bleeding events irrespective of peri-procedural INR levels and should be used with some caution in this patient group and probably avoided if use is not indicated due to massive intraluminal thrombi. Furthermore, GPIs add little benefit in terms of reduction of ischemic events in patients with stable angina and troponin-negative ACS.[63,64]

Use of Bivalirudin

Results from HORIZONS-AMI, and ACUITY trials reveal

Table 2: Risk factors associated with an increased risk for stroke/ thromboembolism, peri -procedural bleeding[68] and stent thrombosis

Thromboembolism/ Stroke	Stent thrombosis	Peri-pocedural bleeding
Diabetes mellitus	1. Patient-related factors relating to increased thrombogenecity. Smoking, Diabetes mellitus, Chronic kidney disease, Acute coronary syndrome presentation, High post-treatment platelet reactivity, Premature discontinuation or cessation of dual antiplatelet therapy	Advanced age (>75years)
Previous stroke, transient ischemic attack, or embolism	2. Surgical procedures (unrelated to the PCI) Diffuse coronary artery disease with long stented segments, Small vessel disease, Bifurcation disease, Thrombus-containing lesions, Significant inflow or outflow lesions proximal, or distal to the stented segment	Female gender
Heart failure or moderate–severe left ventricular dysfunction on echocardiography (e.g. ejection fraction ≤40%)	3. Stent-related factors Poor stent expansion, Edge dissections limiting inflowor outflow, Delayed or absent endothelialization of stent struts, Hypersensitivity/inflammatoryand/ or thromboticreactions to DES polymers , Strut fractures, Late malposition/aneurysm formation, Development of neoatherosclerosis within stents with new plaque rupture	Renal failure
Vascular disease		Uncontrolled hypertension
Hypertension	Years	Low body weight. Patients (n)
Female gender		History of bleeding.
Renal failure	2006	Right heart catheterization
Mitral stenosis or prosthetic heart valve	2008	Anemia
		Use of GPIIb-IIIa antagonists
		Triple therapy

superiority of bivalirudin usage in the setting of primary PCI and non-ST-elevation (NSTE) ACS over combination of heparin plus GPI in terms of lesser morbidity and mortality. Furthermore data from studies support reduced both access site and non-access site bleeding with bivalirudin usage compared to heparin plus GPIs.[65,66] Although data on bivalirudin in AF patients, especially in the setting of concomitant anticoagulation with an OAC is lacking based on the current available date it is likely to be a safer and effective option in the setting of acute coronary syndromes.

Ongoing Clinical Trials

Currently several planned trials are undergoing in this field. PIONEER AF-PCI is a 3 arm study involving 2100 patients randomized to.

(a) Rivaroxiban 15mg PO daily and clopidogrel 75mg PO daily

(b) Initial period of rivaroxaban 2.5mg PO BID and dual antiplatelet therapy followed by rivaroxaban 15mg PO daily and low dose aspirin.

(c) Initial period of dose-adjusted warfarin and dual antiplatelet therapy followed by dose-adjusted warfarin and low dose aspirin.

RE-DUAL PCI ("Randomized Evaluation of Dual Therapy with Dabigatran vs. Triple Therapy Strategy with Warfarin in Patients with NVAF that have undergone PCI with Stenting"), is designed to evaluate the efficacy and safety of Dabigatran in patients with nonvalvular atrial fibrillation (NVAF) who have undergone PCI. MUSCA 2 trail will compaire dual antiplatelet therapy with triple antiplatelet therapy in patients with non-valvular atrial fibrillation undergoing PCI who are at low to moderate risk of stroke (CHADS-2 ≤ 2). The ISAR-TRIPLE is a randomized, open-label trial that examines the restriction of clopidogrel therapy from 6 months to 6 weeks after DES implantation in the setting of concomitant aspirin and oral anticoagulant. Patients are randomized in a 1:1 fashion to either 6-week or 6-month clopidogrel therapy. The primary end point is a composite of death, myocardial infarction, definite stent thrombosis, stroke, or major bleeding. The result of these trials will be critical in assessing safety and efficacy of treating these complex patients with competing indications for their disease treatments.

Conclusion

Balancing the risk of bleeding, thromboembolism and the risk for acute and late stent thrombosis in the patient who has a clear indication for oral anticoagulation and has undergone percutaneous coronary intervention, continues to remain a complex and difficult dilemma for clinicians. The need to address competing indications is further magnified in the setting of acute coronary syndromes. Risk stratification of patients, utilization of direct thrombin inhibitors, avoidance of GPIs, carefully choosing POBS, BMS, and second generation DES are critical in reducing bleeding complications. Limiting the length of exposure to DAPT in the setting of anticoagulation is also a mainstay of reducing risk. Dual therapy (single non-aspirin anti-platelet therapy coupled with anticoagulation, warfarin or a NOAC) may be a viable and safer alternative without compromising risk or long term stent outcomes. Further trials will hopefully answer whether this strategy and the concept of uninterrupted anticoagulation will be ideal approaches to treating these complex patients.

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Comparison of Phrenic Nerve Injury during Atrial Fibrillation Ablation between Different Modalities, Pathophysiology and Management

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Abstract

Atrial fibrillation ablation has emerged as an effective tool in the management of symptomatic atrial fibrillation. Currently, the electrophysiologists are striving to maximize the success while minimizing complications. Phrenic nerve injury (PNI) is one of the concerning complications, especially in cases of cryoballoon ablation. Due to anatomical proximity to atrial tissue, phrenic nerve is particularly susceptible to injury. With evolving monitoring techniques it is now possible to minimize the likelihood of a permanent PNI. However, the challenge remains to detect PNI at the earliest and to avoid further damage to the nerve. In this review, we discuss pertinent anatomical principles, techniques to avoid PNI and management in cases where PNI is encountered.

Introduction

Ablation to achieve pulmonary vein isolation (PVI) has been highly successful in the management of atrial fibrillation (AF).[1] However, it is also associated with a variety of complications including phrenic nerve injury (PNI). The anatomic course of the phrenic nerves near the pulmonary veins (PV) predisposes them to injury during the ablation. PNI has been reported as a rare complication during radiofrequency ablation (RFA) especially when a wide area circumferential ablation is deployed.[2-4] However, with the emergence of cryoballoon ablation (CBA) as an effective tool to achieve PVI, PNI has become more common with the rate ranging from 8% to 11% in some studies.[5-7] There is no reliable method to predict phrenic nerve injury prior to procedure; however, implementing vigorous monitoring of the nerve function can assure early detection and prevent permanent PNI. Hence, it is imperative for electrophysiologists and laboratory staffs to be familiar with and recognize this injury at the earliest to mitigate the damage.

Key Words:

Phrenic Nerve, Atrial Fibrillation, Ablation.

Disclosures:
None.

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Anatomy

Phrenic nerves (PN) originates from the 3rd to 5th cervical nerves and provides the only motor supply to the diaphragm as well as sensory supply to the central tendon, mediastinal pleura and pericardium. Right PN (RPN) descends vertically from its origin and continues along the right anterolateral surface of the superior vena cava (SVC). Descending down the anterolateral wall of SVC, it turns posteriorly as it approaches the superior cavoatrial junction and follows in close proximity to the right sided PVs. It is separated by only the pericardium at the anterolateral junction between the SVC and the right atrium.[8] At this level, distance between the atrial/SVC tissue and RPN on an average is between 0 to 2.3 mm. The closer relationship of the RPN to the Right Superior Pulmonary Vein (RSPV) makes it more susceptible to injury during ablation of the RSPV then during ablation of the Right Inferior Pulmonary Vein (RIPV). Similarly, left phrenic nerve runs anterior to left sided pulmonary veins and are at a danger of PNI during ablation. Furthermore, it can course close to either apex or roof of the mouth of left atrial appendage (LAA), depending upon the anatomical variation, making ablation performed in the vicinity of LAA more complicated.[9] Both the phrenic nerves run along with pericardiophrenic artery and vein form a neurovascular bundle in the fibrous pericardium. It is hypothesized that the injury to the phrenic nerve might be due to damage or infarction of the pericardiophrenic artery during cryo ablation.

Definition and Epidemiology

The stages of phrenic nerve damage can be categorized as

a) early PN injury defined as any detection of PN damage prior to

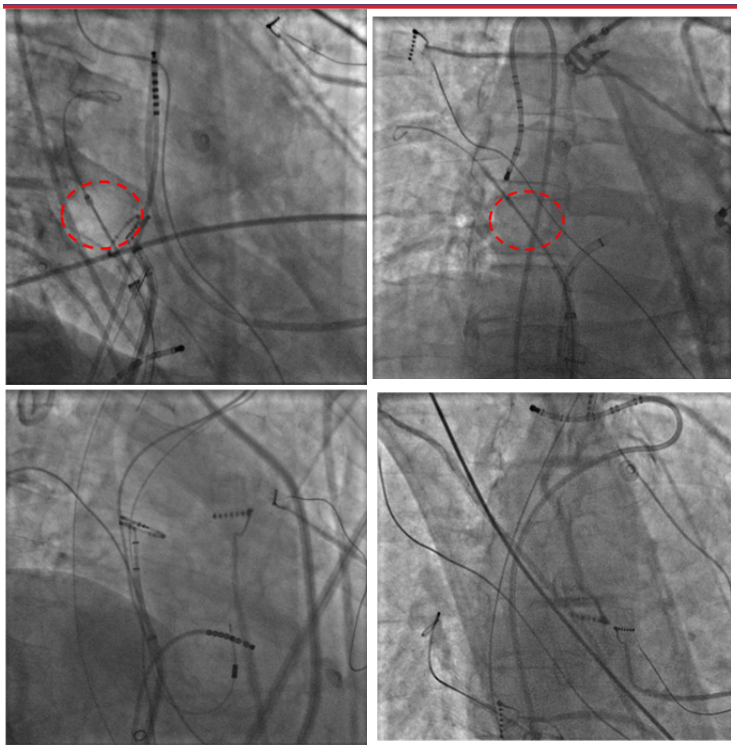

Figure:1 Position of different catheters in the superior vena cava to facilitate capture of the phrenic nerve. (A) Deflectable octapolar catheter (Bisosense Webster Diamond Bar, CA) located on the later wall of the SVC. Notice that the phrenic nerve is captured above the cryoballoon. (B) Deflectable decapolar catheter (Bisosense Webster Diamond Bar, CA) prolapsed into the SVC. Notice the retroflexed curve for better stability. (C) LASSO Circular Mapping Catheter (Bisosense Webster Diamond Bar, CA) and a more distal passion of the decapolar catheter advanced distal in the SVC (D) for stable phrenic nerve capture. Modified with permission from Kowalski M: Prevention of phrenic nerve palsy during cryoballoon ablation for atrial fibrillation. In Ngai-Yin Chan eds: The Practice of Catheter Cryoablation for Cardiac Arrhythmias. Hoboken:Wiley Blackwell, 2014, pp. 67-81

detectable decrease in diaphragmatic excursion,

b) PN injury defined as any decrease in diaphragmatic excursion resolved prior to end of the procedure,

c) PN palsy as diaphragmatic paralysis confirmed by exhalation and inhalation x-ray with elevated diaphragm lasting less than 3 months and

d) PN paralysis as any PN palsy lasting more than 3 months. 'Early PNI' and 'PNI' are often described collectively as 'transient phrenic nerve injury'.[10]

PNI is a more common complication associated with cryoballoon ablation than with radiofrequency ablation.[5,11,12] The earlier cryoballoon studies with traditional monitoring approach have reported high incidence of PNI, ranging from 4% -11%.[5,6,13-15] However, subsequent studies using novel monitoring methods in adjunction to standard pace-mapping monitoring have reported a sharp drop in this incidence to the order of 1%.[16-20] PNI is more common during the ablation of the RSPV than the RIPV due to the closer proximity of the PN to the RSPV than to the RIPV. Injury to left PN is a possibility during ablation involving LAA and rarely, with ablation of the left superior pulmonary vein (LSPV).[21,22]

Histo-Pathological Changes

Detailed examination of the histo-pathological changes occurring with PNI has provided a better understanding of the underlying mechanisms. These changes differ based upon the type of energy used and are well-characterized in pre-clinical studies[23,24] In a pre-clinical RF study, Bunch et al demonstrated a graded response to temperature rise and duration of RF applications on PN function.[23] In this study, PNI was reversible at a temperature of 47 ± 3°C after 38 ± 32 seconds, while it resulted in a permanent injury with additional RF application of 92 ± 83 seconds at a temperature of 51 ± 6°C. These dose-dependent responses were also reflective in histo-pathological changes. Permanent PNI showed manifestations of acute thermal injury such as edema, coagulation and, irreversible chromatin and cytoplasmic content damage. While transient PNI showed no signs of any nerve damage. In contrast to RF, wallerian degeneration of nerve with focal injury to large axonal neurons is the primary finding seen with cryo induced PNI.[24] This is usually distributed in subperineural fashion. Just like RF, degree of damage due to cryo-application was proportionate to the temperature changes and overall amount of energy delivered at a time. In a study done by Andrade et al, lower and earlier nadir temperature was associated with worse outcomes. In this study, nadir ablation temperature, −56.4 ± 7.3 °C with standard monitoring and −52.7 ± 9.8 °C with compound motor action potential (CMAP) monitoring were associated with higher likelihood of PNI. Also, CMAP monitoring, with 30% cutoff to interrupt cryo-application, demonstrated lesser degree of nerve damage as compared to the traditional monitoring method. These findings correspond to observations made in recent clinical studies. It also brings home the point that earlier the termination milder the damage.

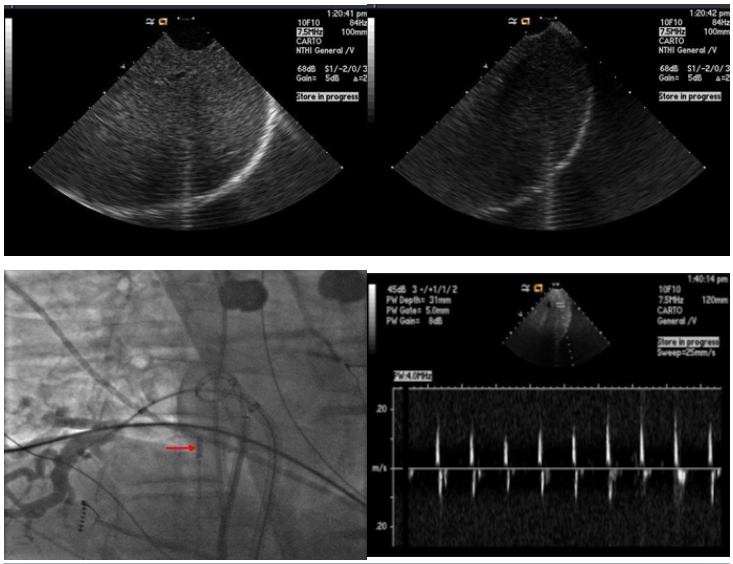

Figure:2 Intracardiac echocardiographic images of the diaphragm and the liver during phrenic nerve pacing showing the diaphragm (A) relaxing and (B) contracting. (C) Fluoroscopy image showing position of intra-cardiac echocardiography catheter (arrow) at the level of diaphragm. (Reproduced with permission from Lakhani M, Saiful F, Bekheit S, Kowalski M. Use of Intracardiac Echocardiography for Early Detection of Phrenic Nerve Injury During Cryoballoon Pulmonary Vein Isolation. J Cardiovasc Electrophysiol 2012 April 11) (D) Pulse Doppler of the liver motion during phrenic nerve pacing. If the entire liver cannot be easily visualized, a pulse wave Doppler can be placed on the liver to observe the liver exertions as a Doppler waveform. A decrease in Doppler amplitude can indicate PN injury. Notice the change in the amplitude of the velocity due to respiratory variation

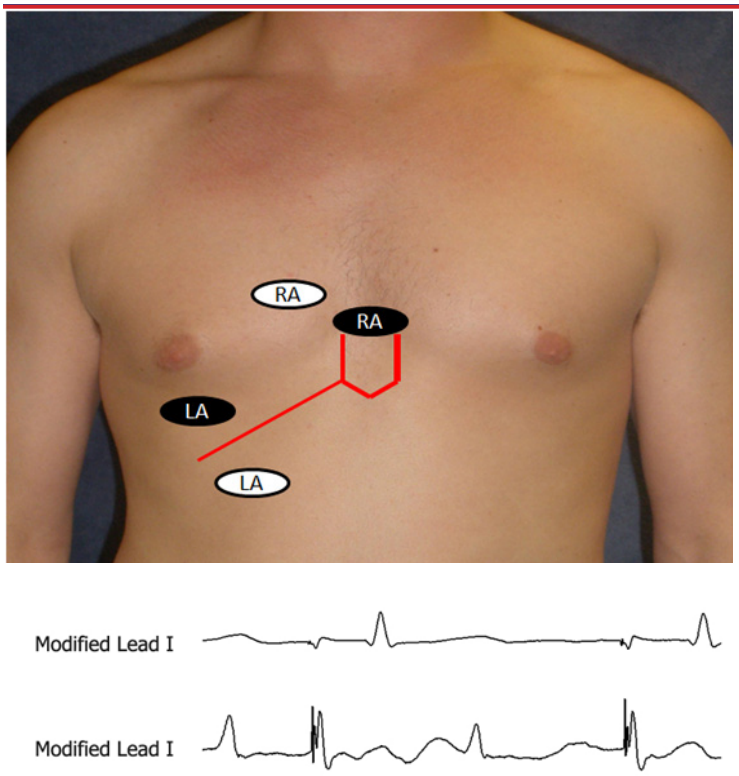

Figure:3 **Configuration of surface electrodes to record of diaphragmatic compound motor action potential on modified lead I in an obese patient. The right arm (RA black oval) surface electrode placed 5 cm above the xiphoid and the left arm (LA black oval) surface electrode is placed 16 cm from the xiphoid along the costal margin and corresponding CMAP recordings on modified lead showing low amplitude signal during PN capture (top recording). In some instances the leads require to be modified because of patient's body habitus by moving the leads to the right and more separated (white ovals) to obtain the optimal CMAP amplitude (lower recording). (Reproduced with permission from Lakhani M, Saiful F, Parikh V, Goyal N, Bekheit S, Kowalski M. Recordings of diaphragmatic electromyograms during cryoballoon ablation for atrial fibrillation accurately predict phrenic nerve injury. Heart Rhythm. 2014 Mar;11(3):369-74. PubMed PMID: 24252287. Epub 2013/11/21. eng.)**

In both of these studies, PNI occurred relatively early during the ablation and was associated with higher temperature gradient. This can be partly due to better catheter contact which may result in relatively low blood flow and higher energy delivery; or it may be just a reflection of the damage caused by the energy delivery. Furthermore, PNI is more likely to happen at subsequent energy deliveries. This may be due to the fact that nerve tissue may retain some of the effect from the previous energy deliveries, which can be potentiated by subsequent energy application.

Management

The best management strategy for PNI is to vigorously monitor phrenic nerve function and stop the ablation at the first sign of PNI. There is no reliable method of predicting PNI prior to procedure. Pre-procedural imaging of the right pericardiophrenic artery using computerized tomographic angiography can reliably locate the right phrenic nerve.[25-27] This technique may identify anatomy more vulnerable to phrenic nerve injury using balloon based ablation systems, although, their clinical utility is limited at this time primarily due to increase radiation, cost and contrast. This method is also of limited value in patients with significant dysrhythmias due to higher gating errors. Another helpful method to predicting PNI prior to energy delivery is to localize a vertical line crossing the distal SVC PN pacing catheter and the lateral edge of the cryoballoon in an anterior-posterior view. If the PN pacing catheter crossest the lateral edge of the balloon, negative predictive value for PNI is 98%[13](Figure 1).

It is now recognized that closer the phrenic nerve to the atrial tissue higher its susceptibility to temperature changes and higher the likelihood of PNI. In cases of CBA, the balloon inflation alters PV geometry and may displace PN. In a canine study conducted by Okumura et al, the inflated balloon at PV orifice extended PV diameter by 5.6 ± 3.7 mm anteriorly and 2.7 ± 3.5 mm posteriorly to the original PV diameter.[28] This prominent distortion displaced the phrenic nerve closer to the atrial tissue by 4.3 ± 2.9 mm. The degree of this distortion can further be amplified if the balloon is inflated inside the PVs to minimize peri-balloon leak. This is a prime reason why PNI were common with 23- mm diameter cryoballoons. A 23-mm balloon is more likely to be advanced deeper inside the PV as compared to a 28-mm balloon. To overcome this issue of inflation inside the veins, the depth of the balloon can be assessed by a 'pullback' method. According to this method, the balloon is pulled back slightly after complete occlusion is demonstrated. By

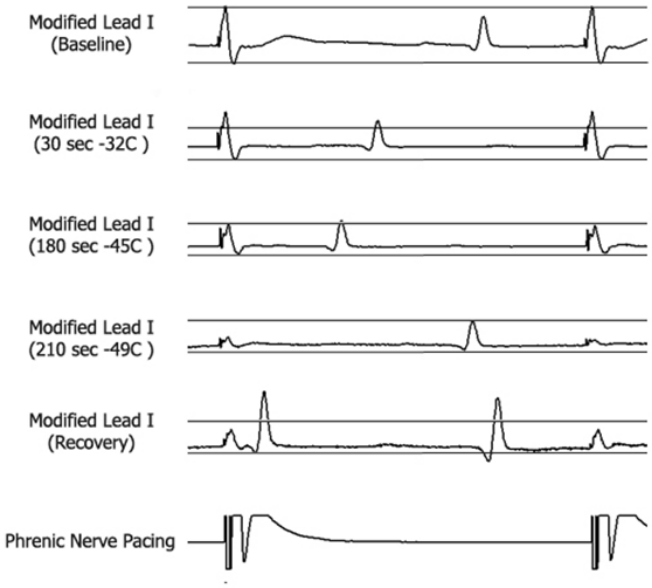

Figure:4 **Recordings of the diaphragmatic CMAP during pacing from the multipolar catheter at a CL of 1000 ms located in the SVC. The CMAP amplitude was measured at baseline (top panel) and was continuously monitored during RSPV ablation by placing horizontal calipers on the screen of a recording system at the level of 35% below the baseline CMAP amplitude (Panel 2). Note attenuation of CMAP amplitude by > 35% from baseline amplitude at 180 seconds of cryoballoon application (Panel 3). At the time of phrenic nerve palsy (210 sec) the CMAP amplitude was a fraction of the baseline CMAP amplitude (Panel 4). The amplitude of CMAP, despite some recovery two minutes after discontinuation of cryo-energy, did not return to baseline value (Panel 5). (Reproduced with permission from Lakhani M, Saiful F, Parikh V, Goyal N, Bekheit S, Kowalski M. Recordings of diaphragmatic electromyograms during cryoballoon ablation for atrial fibrillation accurately predict phrenic nerve injury. Heart Rhythm. 2014 Mar;11(3):369-74. PubMed PMID: 24252287. Epub 2013/11/21. eng.)**

Table 1: Pros and cons of various PN monitoring strategies

Method	Description	Advantages	Disadvantages
Fluoroscopy	Direct visualization of diaphragmatic motion	• Sensitive method for monitoring diaphragmatic motion	• Additional radiation exposure to the patient and the operator • Does not predict early PN injury
Palpation	Palpation of diaphragmatic excursion	• Reliable and practical method for monitoring diaphragmatic motion • Abundant data	• Requires additional staff member • The palpable strength of diaphragmatic excursion may vary with respiration
Electromyography	Recording of diaphragmatic compound motor action potential (CMAP) by two standard surface electrodes positioned across the diaphragm or by advancing a quadripolar catheter in the right-hepatic vein during PN pacing	• Earliest detection of PN injury • Simple reliable and easily applicable • The only technique that predicts PN injury	• CMAP signals might be susceptible to respiratory variations. • The baseline amplitude must be adequate • Affected by paralytic agents
Auditory cardiotocograph	Decrescendo pitch on fetal heart monitor (placed across patient's chest that can detect diaphragmatic contractions)	• Auditory cue to the operator • May portend PN injury prior to palsy	• Extra equipment difficult to record in obese patients
Intracardiac echocardiogram (ICE)	Direct visualization of diaphragmatic excursion	• minimal radiation exposure to the patient and the operator	• Requires additional venous access and intra-cardiac ultrasound
Modified pediatric blood pressure cuff	Measurement of pressure changes associated with diaphragmatic movement	• Objective evidence • Obviates need for fluoroscopy and additional staff	• Needs a verification studies including larger patient sample • Special blood pressure cuff needed
Venous Waveform	Analyzing changes in femoral venous waveform	• Minimal changes needed to actual procedure • Obviates need for fluoroscopy and additional staff	• Needs verification studies including larger patient sample

Comparison of different strategies for monitoring phrenic nerve palsy during cryoballoon ablation. (Modified with permission from Kowalski M: Prevention of phrenic nerve palsy during cryoballoon ablation for atrial fibrillation. In Ngai-Yin Chan eds: The Practice of Catheter Cryoablation for Cardiac Arrhythmias. Hoboken:Wiley Blackwell, 2014, pp. 67-81)

pulling back enough to observe a slight dye leak, the distortion can be minimized without compromising ablation efficacy.[6] Similarly, a wide area circumferential ablation (WACA) approach can reduce the incidence of PNI in RFA by avoiding proximity to PN.[4]

During the Procedure- Monitoring the Function

At present, pace-mapping of phrenic nerve throughout the 'concerning' part of the ablation remains the only existing method to monitor phrenic nerve function. Currently, there are no practical strategies available to measure phrenic nerve potentials without pacing the phrenic nerve.

Pacing the Phrenic Nerve

PN function is monitored during ablation by advancing a pacing catheter to an optimal site of phrenic nerve capture and pacing at a reasonably high output to ensure capture. It is crucial that this pacing catheter is always placed above the level of ablation, capturing the phrenic nerve at twice the capture threshold. A high current strength can potentially overcome early nerve injury and conceal incipient damage to the nerve. The optimal site for PN capture during ablation of right sided pulmonary veins is the anterolateral portion of the SVC, near the atrial-SVC junction because, at that location, the PN is separated from the SVC wall only by pericardium or near the junction of the SVC. However, Ghosh et al demonstrated that pacing from right subclavian vein may provide better stability and lower threshold values for PN capture.[29] This method can particularly be valuable in cases where catheter stability is an issue. Similarly, left phrenic nerve can be captured from left subclavian vein and monitored if needed. Any catheter can be used to capture PN. In our experience, we found a deflectable decapolar catheter to be most useful. Stability and consistent phrenic nerve capture is extremely important. Lack of good contact and loss of capture due to catheter movement may mimic PNI and cause unwarranted cessation of the procedure. Electroanatomic mapping can be useful to tag the capture site and reposition the catheter in case of movement of the catheter. The pacing should be done at cycle lengths that range from 1500 ms to 1000 ms. A slower rate can delay the detection of PNI, while a rapid rate can prematurely fatigue the diaphragm.[30] It is imperative that paralytics are avoided during ablation. If they have been administered during the induction of general anesthesia, it is important to begin pulmonary vein isolation only after allowing sufficient time to wean off their paralytic effect or using reversal agents such as neostigamine.

Strategies to Monitor Phrenic Nerve Function

Currently, there is no reliable method that predicts PNI prior to the procedure and it can occur despite of the most compulsive monitoring. In addition to standard monitoring methods, recently, novel techniques are reported. (Table 1)

Continuous or intermittent fluoroscopy of the right hemi-diaphragm during PN pacing can accurately diagnose a diminished diaphragmatic excursion; however, it is the least optimal method as it exposes the patient and operator to additional radiation. Palpation of the strength of diaphragmatic excursion during PN pacing, below the costal margin is the most commonly employed method of monitoring PN function. Diaphragmatic contractions during PN pacing are sensed by placing the hand over the right diaphragm and below the costal margin and palpating every excursion. Weakening of the diaphragmatic contraction can indicate PN injury. This method is easily applicable but the subjectivity associated with the measurement and respiratory variations in the diaphragmatic contraction strength can be mistaken as PNI. Although these methods are considered as a gold standard and practiced widely, they are not the earliest to detect PNI.

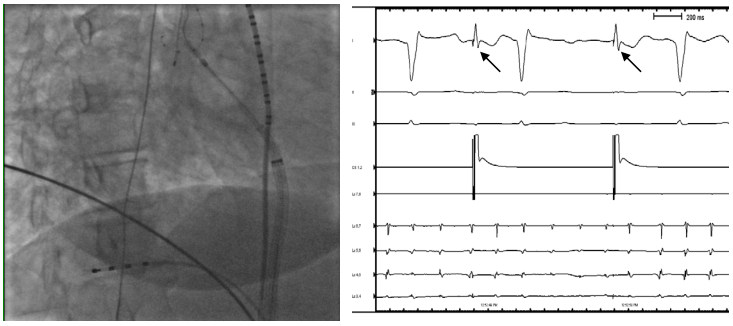

Figure:5 Diaphragmatic compound motor action potential (CMAP). A) Catheter position for phrenic CMAP recording. B) Surface ECG lead V1 and a diaphragmatic CMAP tracing obtained by a quadripolar catheter in the right hepatic vein. The quadripolar catheter is positioned in a hepatic vein to record phrenic CMAP. A multipolar catheter is placed in the SVC to pace the right PN.

Intracardiac echocardiography (ICE) may be utilized to continuously visualize the motion of the liver capsule and indirectly image the contraction of the diaphragm during phrenic nerve pacing.[31] The transducer is positioned at the level of the diaphragm and pointed at the liver (Figure 2). The decrease in intensity of liver movement from the diaphragmatic excursion can be easily observed and can correlate with phrenic nerve palsy. An external fetal heart Doppler monitor placed at the costal margin can also be used to monitor PN function.[10] A decrease in diaphragmatic contraction can be recognized by change in the pitch. The fetal heart monitor can provide an auditory cue to the physician and staff of impending PNI.

The methods of monitoring PN function mentioned above rely on reduction of in the mechanical function of the diaphragm. Novel techniques utilizing diaphragmatic compound motor action potential (CMAP) may provide earlier warning of PN injury.[16-18] CMAPs can be successfully recoded on modified lead I by placing a standard surface right arm EKG electrode 5 cm above the xiphoid and a left arm EKG electrode 16 cm along the right costal margin (Figure 3). The CMAP amplitude is measured from peak to peak with each PN capture. The largest amplitude signal at baseline is compared to the real-time CMAP amplitude during the ablation. Studies have shown that a decrease in CMAP amplitude by 35% from baseline predicted and prevented PNI (Figure 4).[16] The CMAP amplitude can be continuously monitored during ablation by placing a horizontal caliper on the screen of a recording system at the level of 35% below the baseline CMAP amplitude. The average time interval from CMAP amplitude decrease of 35% to palpable PNI was 59 seconds (range 30-110 seconds) in published studies, although transient PNI may occur in less than 10 seconds.

An alternative method to this is advancing a quadripolar catheter in the right hepatic vein and recording phrenic CMAP amplitude during PN pacing (Figure 5).[19,32] The ablation is discontinued if the observed CMAP amplitude decreased by ≥30% from baseline. The study evaluating this method found no reported cases of PNI, including the patients in which ablation was discontinued early, due to decrease in CMAP amplitude. Monitoring PN function using a modified lead I is simple and easily applicable. The surface electrodes may be subject to CMAP amplitude variations with respiratory movements and body habitus. It may be difficult to obtain CMAP recordings in obese patients. Adjusting the electrode to a more superior location may help obtain a better signal in these patients, as the viscera push the diaphragm superiorly when the patient is supine. Monitoring CMAP amplitude by advancing a quadripolar catheter in the hepatic vein is an excellent alternative method especially in patients in whom the recorded CMAP amplitude is less than 0.2 mV. Hence the operator may initially attempt to record CMAP amplitude using modified lead I. If the amplitude is < 0.2 mV or shows significant respiratory variation, a catheter can be advanced into the hepatic vein to record CMAP amplitude. The recorded CMAP amplitude by either method can also be easily displayed directly on the electrophysiology workstation and followed during ablation (Figure 5).

Recently, few other novel methods have been proposed on similar principles. One of them was utilizing diaphragmatic contraction was described by MacVeigh et al.[33] They measured strength of diaphragmatic contractions with the help of modified neonatal blood pressure cuff tied to right coastal margin. In a small group of patients, they demonstrated that change in the pressure measured with the cuff corresponded to changes seen in diaphragmatic contraction strength. Another recently proposed method have used femoral vein pressure waveform to accurately measure phrenic nerve function.[29] With a cut-off of 50% reduction observed in baseline peak to peak venous waveform amplitude to discontinuation of ablation, identification of PNI by this method preceded by a mean of 28s to traditional palpation method. This observation is very similar to other novel methods stressing the point that the commonly employed method of palpation is slower to identify PNI. Although these methods appear promising, they are yet to be confirmed and reproduced in larger sample of patients.

Recently, a series of publications have demonstrated that monitoring with 2 methods (Traditional palpation and a novel method) have decreased the incidence of PNI associated with cryoballoon ablation significantly.[16, 17, 19, 34] This may be partly due to the earliest detection of PNI with novel methods. However, further studies are needed to decide if a novel method can be employed as a stand-alone method.

After the Phrenic Nerve Injury

Early detection of PNI and immediate termination of ablation remains the cornerstone of the prevention of PN palsy. It is imperative to be cautious and continuously monitor the PN function by pacing the phrenic nerve above the level of ablation. Ablation should be interrupted immediately at the first sign of PNI. In cases of cryoballoon ablation, immediate balloon deflation by 'double-tap' the stop button on the console would prevent persistent PNI.[15] Since the decrease in the CMAP amplitude is the earliest sign of detectable injury to the nerve and is simple and easily measurable, it should be used as the primary technique for monitoring in conjunction with one or two other methods. These methods include either palpation of the diaphragmatic excursion or movement of liver visualized on ICE or a fetal heart monitor.

If the phrenic nerve function returns within few minutes, a cautious attempt at ablation can be made again with a more antral position of the balloon. In cases of CBA, the wire/catheter used to engage the vein can be manipulated to select a different branch of the vein so that the balloon-vein angle is modified. If PN function does not return in a reasonable time, then the ablation may be completed using

Table 2: Recommendations to Prevent Phrenic Nerve Injury during cryoballoon ablation for atrial fibrillation

Avoid long-acting paralytics during ablation
Consider performing inhalation and exhalation chest x-ray in patients with previous history of CABG to evaluate for injury to left PN
Inflate the balloon outside the PV and maintain the balloon as antrally as possible to prevent anatomic distortion of the PV orifice. WACA approach is recommended in RFA.
Monitor the rate of temperature changes. A steep descent (colder than -40 degrees at 30 seconds) may indicate distal location of the balloon in CBA.
Rigorously monitor PN function by pacing the phrenic nerve from the SVC above the cryoballoon
The stimulation of the PN should be carried out at twice the pacing threshold and PN function should be monitored for both RSPV and RIPV.
Simultaneously employ diaphragmatic CMAP amplitude and one or two additional techniques to monitor phrenic nerve function
Terminate ablation immediately if there is suspicion of PNI. Immediate deflation of the balloon can be initiated by pressing the emergency deflation button twice on the console
Always maintain the balloon as antral as possible to the PV os.
Utilize the "pull back" method to assess the depth of the balloon inside the PV

Modified with permission Kowalski M: Prevention of phrenic nerve palsy during cryoballoon ablation for atrial fibrillation. In Ngai-Yin Chan eds: The Practice of Catheter Cryoablation for Cardiac Arrhythmias. Hoboken:Wiley Blackwell, 2014, pp. 67-81

radiofrequency with a wide antral circumferential ablation, which is shown to be safer.[4] Additionally, the ablation catheter can be paced at high outputs (10 mA at 2 ms) at putative ablation sites, to discern phrenic capture. Capture of phrenic nerve with high output indicates higher risk of PN injury at that particular site and RF ablation should be performed more antrally. An inhalation and exhalation chest x-ray evaluating the motion of the right diaphragm can assess resolution of PN injury after the procedure.

Clinical Course and Prognosis

The presentation of PNI can range from asymptomatic to cough, dyspnea, and severe respiratory complications. The severity of presentation primarily depends upon the degree of PNI and underlying lung capacity.[2, 35-37] Clinical presentation can vary broadly ranging from asymptomatic to severe respiratory dysfunction, however, majority of them are asymptomatic or mildly symptomatic. Nonetheless, considering potentiality of significant morbidity, PNI should not be discarded as a benign condition and a cautious follow-up is warranted.

Prognosis of PNI is reasonably good. Most of the cases are self-resolving between 3 to 12 months, although, rarely it can be permanent.[2, 35] Most of the PNI recover within a year. The recovery largely depends upon the degree of damage and time needed for nerve to regenerate. Therefore, it is essential to be vigilant and stop the ablation instantaneously on losing phrenic nerve capture.

Conclusions

Phrenic nerve injury is a rare, but a potentially dangerous, complication. PNI is higher with balloon catheter based ablations as compared to radio-frequency ablation. However, novel adjunctive techniques are bridging this gap and making these procedures safer in this regards. Irrespective, it is essential for the EP team to be cognizant of this complication, avoid inadvertent injury and detect it at the earliest.

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Atrial Fibrillation In Athletes: Pathophysiology, Clinical Presentation, Evaluation and Management

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Abstract

Atrial fibrillation (AF) is the most common cardiac arrhythmia in athletes, especially in middle-aged athletes. Studies have demonstrated that athletes who engage in endurance sports such as runners, cyclists and skiers are more prone to AF than other athletes. The effects of exercise on the onset and progression of AF is complex. Triggers of AF in athletes may include atrial ectopy and sports supplements. Substrates for AF in athletes include atrial remodeling, fibrosis, and inflammation. Modulators of AF in athletes include autonomic activation, electrolyte abnormalities, and possibly, gastroesophageal reflux. Management of AF in athletes with rate-controlling agents and antiarrhythmic drugs remains a challenge and can be associated with impaired athletic performance. The value of catheter ablation is emerging and should be considered in suitable athletes with AF.

Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia in athletes, especially in middle-aged athletes.[1] Participation in regular physical exercise has been shown to be beneficial to cardiovascular health and overall well-being.[2-5] However, recent studies have demonstrated that long-term endurance exercise increases the risk of AF, both in athletes training at a competitive level and in individuals who participate in vigorous exercise at a non-competitive level[6-24] (Table 1). The effects of exercise on the onset and progression of AF is complex and remain unclear with some studies also demonstrating no increased risk of AF with exercise.[25-31] This review focuses on the pathogenesis, clinical presentation, evaluation and management of AF in athletes.

Type of Sport and Atrial Fibrillation

Studies have demonstrated that athletes who engage in endurance sports such as runners, cyclists and skiers are more prone to AF than other athletes.[15-18,22,23,32] The exact mechanism involved remains unclear as other athletes who participate in boxing, wrestling, weight-lifting also practice strenuous sport practices, but AF does not appear to be as prevalent in those groups. The question remains – is this related to the type of sport? Unfortunately, little information exists relating to AF risk and sport specificity. Further research is warranted in this area.

Key Words:

Atrial Fibrillation, Athletes, Exercise, Pathophysiology, Evaluation, Management.

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Pathophysiology

The mechanisms by which exercise contributes to AF are not well understood and are presumed to be multifactorial (Figure 1). It is accepted that the initiation and perpetuation of AF requires a trigger, a modulator and a substrate. The mechanism of AF in athletes may be attributable to the interaction among these three factors. A specific trigger (atrial ectopy, sports supplements and illicit drug use) in the presence of a suitable substrate (genetic predisposition, inflammation, fibrosis and cardiac remodeling) and a modulator (autonomic activation, electrolyte abnormalities, acid reflux disease) remains the foundation in onset and maintenance of AF in athletes.

Triggers of AF

Atrial Ectopy

AF is commonly-triggered by focal ectopic discharges within the four pulmonary veins at the left atrial junction.[33] It has been postulated that increased sympathetic activity when participating in vigorous exercise can trigger atrial ectopy. However, this concept lacks convincing evidence.[13,17,34]

A study of 134 professional Swiss athletes and non-athlete controls reported no significant increase in the frequency of isolated atrial ectopic beats (18/62 versus 17/62, p=0.35), despite a significant increase in the frequency AF or atrial flutter (p=0.028) on a 24 hour

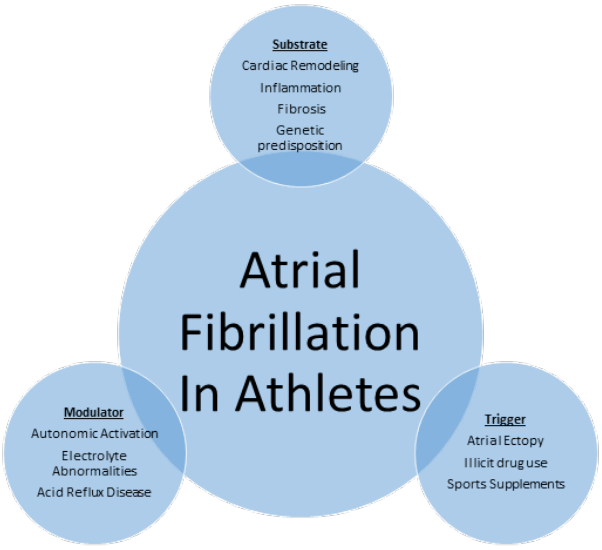

Figure:1 Schematic representation of mechanism of atrial fibrillation in athletes

electrocardiographic monitor.[17]

Sports Supplements

Sports supplements are commonly-consumed by individuals who exercise regularly and indulge in athletic activities, even at a non-competitive level.

Professional athletes occasionally use illicit or performance enhancing drugs, which are not approved by the World Anti-Doping Agency (WADA), to improve performance (Table 2).[35] Anabolic steroids, when associated with competitive sports, has garnered the most attention from media and the public. Increased risk of AF associated with anabolic steroids has been reported in young athletes in isolated case reports.[36,37] There are no systematic data regarding risk of anabolic steroids in the initiation of AF.

Energy drinks have recently gained popularity with young adults participating in competitive and non-competitive sports.[38] Energy drinks contain high levels of caffeine (50 mg to 500mg),[38] stimulants such as taurine, guarana, ginseng, and vitamins such as riboflavin, pantothenic acid and thiamine.[39] Isolated cases of cardiac arrhythmias, including AF with heavy consumption of energy drinks have been recently reported.[38,40] The potential explanation being genetic susceptibility exaggerated by autonomic modulation from high dose caffeine or other ingredients which may trigger AF.

We currently lack objective data on the electrocardiographic effects of energy drinks. One study reported that heavy consumption of energy drinks in healthy individuals can contribute to a transient increase in both blood pressure of 10 mmHg and heart rate of 5-7 beats/minute.[41] However, long-term data concerning the risk of chronic consumption of energy drinks, especially in middle aged individuals who also have other medical comorbidities in triggering AF are lacking.

Substrates for AF

Cardiac Remodeling

There is ample evidence that endurance exercise is associated with both bi-atrial and ventricular enlargement which can occur independent of each other.[8] Left atrial size of >4.0 cm was noted in 20% of athletes who participated in competitive sports.[42] Mont and colleagues reported increased left atrial longitudinal, anteroposterior and transverse diameters and volumes [46.5 ± 17.2 vs 34.6 ± 10.0, p<0.001] with exercise.[19] Atrial enlargement is reported to be related to the lifetime hours of exercise.[43]

Several population studies have demonstrated increased risk of new-onset AF with increased left atrial enlargement.[44,45] However, the role of left atrial remodeling in athletes as a predictor of AF is speculative with no clear evidence. A study of 492-marathon runners with a mean age 42±7 years reported that total higher lifetime hours of training was associated with left atrial enlargement and subsequently higher risk of AF (24% in < 1500 hours, 40% 1500-4500 hours and 83% in > 4500 hours).[13]

Despite increased left atrial size in athletes, one study reported lower left atrial stiffness compared to controls (0.13 ± 0.04 vs. 0.16 ± 0.06, p≤0.01).[46] Another study stratified subjects based on lifetime training as low (<1500 hours), intermediate (1500-4500 hours) and high (>4500 hours). This study reported an increase in left atrial volume (30±5, 33±5 vs. 37±6 ml/m,^{2} p<0.001), but no effect on atrial mechanical function (pump strain -15.0±2.8, -14.7±2.7 vs. -14.9±2.6%, p=0.92 and conduit strain 23.3±3.9, 22.1±5.3 vs. 23.7±5.7%, p=0.455) measured by two-dimensional echocardiographic speckle track imaging.[47]

Fibrosis

The role of fibrosis in exercise induced-AF mostly from animal models. Sixteen weeks of exercise in Wistar rats substantially increased fibrosis marker expression including fibronectin-1, transforming growth factor-β1, matrix metalloproteinase-2, tissue inhibitor of metalloproteinase-1, procollagen-I, and procollagen-III in the atria and ventricles when compared to controls. Furthermore, exercise cessation reversed fibrosis eight weeks after exercise cessation.[48]

Another study in a similar rat model confirmed the above findings concerning the role of cardiac fibrosis with endurance training by noting an increase in protein major profibrotic markers and messenger RNA synthesis. The study also reported that pretreatment with losartan 50 mg/kg/day reduced all markers of fibrosis.[49]

The role of TNFα-dependent activation of both NFκB and p38MAPK with exercise was recently described in rat models as an underlying mechanism of exercise induced atrial remodeling and AF.[50] However, further research is necessary to examine this mechanism.

Another study including 45 veteran elite athletes and controls demonstrated biochemical evidence of myocardial fibrosis.

Table 1: Selected Controlled Studies of the Prevalence of AF in Athletes

Study Type	Number of subjects	Age/Gender	Type of exercise	Prevalence of AF in athletes/ controls (%)
Karjalainen et al[15]	795	35-39 years/ Male	Cross country Running	5.3/0.9
Baldesberger et al[17]	196	~66 years/ Male	Cyclists vs. golfers	10/0
Mont et al[8]	216	<65 years/ Male + Female	Endurance athletes	63/15
Elosua et al[16]	109	41-55 years/ Male	Endurance athletes	32/14
Heidbuchel et al[22]		60 years/83% Male, 17% Female	Cycling, running, or swimming	
Molina et al[18]	557	48 years	Marathon runners vs. sedentary	5/0.7
Grimsmo et al[11]	78	54-62 years- Group I 72-80 years- Group II 87-92 years- Group III	Cross-country runners, skiers	12.8

Markers of collagen turnover including tissue inhibitor of matrix metalloproteinase type I (350 vs. 253 ng/ml, p=0.01); plasma carboxyterminal propeptide of collagen type I (PICP 259 vs. 166 microg/l, p<0.001) and carboxyterminal telopeptide of collagen type I (CITP 5.4 vs. 2.9 microg/l, p<0.001) was demonstrated in veteran athletes when compared to sedentary controls.[51]

In another study including twelve veteran male endurance athletes with a mean age 56±6 years reported that 50% (6/12 athletes) demonstrated evidence of myocardial fibrosis by late gadolinium enhancement (LGE) on cardiac magnetic resonance imaging (CMR). No LGE was demonstrated in sedentary controls. Number of years spent in training (p<0.001) and participation in number of competitive marathons (p<0.001) predicted prevalence of LGE on CMR.[52] Further research is necessary to evaluate the role of cardiac fibrosis with exercise.

Inflammation

The role of inflammation as a substrate in AF is speculative and controversial. Several studies have shown an association between AF and elevated CRP (C-reactive protein).[53,54] Swanson et al hypothesized that excessive training can induce chronic systemic inflammation which may induce high CRP levels that may lead to atrial electrical remodeling and development of AF. Atrial remodeling can be treated with anti-inflammatory drugs.[55] Limited research has demonstrated increased activation of interleukin-6, TNF-α and interleukin beta-1 in induction and maintenance of AF.[56]

Modulators of AF

Autonomic Activation

Several studies have investigated the role of autonomic activation on AF.[12,13,57] AF in athletes is predominantly vagal-mediated.[2] Increased vagal tone initiates AF by creating macro-reentry pathway by increase in the dispersion of the atrial refractory period.[58] Most athletes have a lower resting heart rates which was also a predictor of AF in a study of long-term endurance cross country skiers.[11]

Vagal mediated AF is different from adrenergically-mediated AF which is more commonly seen in the elderly with diseased hearts. Vagal-mediated AF is typically associated with macro-reentry circuits, whereas adrenergically-mediated AF is associated with micro-reentry circuits.[59]

Higher vagal tone was reported in non-elite athletes who participate in regular exercise. A study reported significantly higher vagal tone in non-elite athletes with higher lifetime training hours (>4500 hours versus <1500 hours, 47±16ms vs 34±13ms, p=0.002)].[13]

Mechanistic insight concerning the pathogenesis of AF with exercise comes from animal models. Gausch et al reported that AF duration increased significantly (AF >304 seconds in 64% vs 15%; p < 0.01) in rats who underwent programmed exercise regimen with one hour treadmill training daily for 16 weeks when compared to sedentary controls. Increased vagal tone, atrial dilatation and atrial fibrosis were also reported at 16 weeks in the exercise group. Increased vagal tone was attributed due to messenger ribonucleic acid downregulation of IKACh-inhibiting RGS proteins, was present at 16 weeks in exercising rats. Detraining for 4 weeks normalized vagal tone.[14] The role of IKACh in mediating cardiac response to vagal stimulation was previously described in the genesis of AF from rat models.[60]

Electrolyte Abnormalities

Athletes who are involved in vigorous exercise can have dynamic fluid shifts in the body which can lead to dehydration and alteration in pH and depletion of electrolytes including sodium, potassium and magnesium which may also contribute to AF.

Table 2: World Anti-doping Agency (WADA) List of Prohibited Drugs

Anabolic Agents	1.Anabolic Steroids 2.Other Anabolic Agents (Clenbuterol, selective androgen receptor modulators (SARMs), tibolone, zeranol, zilpaterol) 3.Peptide Hormones, Growth Factors, and related substances.
Beta-2 Agonists	
Hormone and Metabolic Modulators	1.Aromatase inhibitors 2.Selective estrogen receptor modulators (SERMs) 3.Myostatin inhibitors 4.Metabolic Modulators: Insulin, (PPARδ) agonists
Diuretics and other masking agents	1.Diuretics, desmopressin 2.Plasma expanders (e.g. glycerol; intravenous administration of albumin, dextran, hydroxyethyl starch and mannitol)
Stimulants	1.Adrafinil; amfepramone; amfetamine; amfetaminil; amiphenazole; benfluorex; benzylpiperazine; bromantan; clobenzorex; cocaine; cropropamide; crotetamide; fencamine; fenetylline; fenfluramine; fenproporex; fonturacetam [4-phenylpiracetam (carphedon)]; furfenorex; mefenorex; mephentermine; mesocarb; metamfetamine(d-); p-methylamphetamine; modafinil; norfenfluramine; phendimetrazine; phenmetrazine; phentermine; prenylamine; prolintane.
Narcotics	1.Buprenorphine, dextromoramide, diamorphine (heroin), fentanyl and its derivatives, hydromorphone, methadone, morphine, oxycodone, oxymorphone, pentazocine, pethidine.
Cannabanoids	
Glucocorticosteroids	
Alcohol	1.Ethanol
Beta Blockers	1.Acebutolol, alprenolol, atenolol, betaxolol, bisoprolol, bunolol, carteolol, carvedilol, celiprolol, esmolol, labetalol, levobunolol, metipranolol, metoprolol, nadolol, oxprenolol, pindolol, propranolol, sotalol, timolol.

Acid Reflux Disease

Swanson et al postulated that regular exercise can induce gastroesophageal reflux which may induce AF.[57] The association between acid reflux disease, AF and athletes from high vagal tone remains a subject of conjecture.

A study investigated esophageal acidity in healthy athletes and controls after 80 minutes of moderate to hard sprinting. All subjects reported symptoms of acid reflux. Intra-esophageal acidity monitoring was done which showed that in controls pH< 4.0 was noted 4.9% of the time vs. 17.2% of the time for runners fed a light breakfast one hour before the run.[61] Another study reported similar findings of intraesophageal acidity and acid reflux symptoms in 5/11 fasted runners and in 8/9 fed runners during or just after exercise.[62]

Soffer et al, reported a direct correlation between exercise (cycling at a VO2 max of 75% and 90%) and decrease in intra-esophageal pH to below 4.0. In trained cyclists exercising at VO2 max of 75% and 90%, the number of episodes when the pH decreased below 4.0 were 1.2 and 3.7 episodes/hour. In untrained cyclists the number of episodes when the pH decreased was substantially higher at 4.5 and 17.5 episodes/hour respectively.[63,64]

Marathon runners after a 20K race demonstrated evidence of esopghagitis on endoscopy.[65] A large population study including 163,627 patients reported that acid reflux disease increased the risk of AF by 39% [95% confidence interval 1.33-1.45].[66]

Clinical Features and Evaluation

Symptoms such as syncope, palpitations, and dyspnea on exertion reported by athletes should be thoroughly evaluated. A detailed history and a thorough physical examination are warranted. Onset

of symptoms with relation to exercise needs to be established. A history of the use of alcohol, sports supplements and energy drinks is important. AF associated in young athletes is usually paroxysmal.

Persistent AF may occur in middle-aged athletes with comorbid cardiovascular conditions. When an athlete reports palpitations it is important to exclude underlying structural heart disease such as arrhythmogenic right ventricular dysplasia, hypertrophic cardiomyopathy, or underlying conduction abnormalities such as the Brugada Syndrome, the Wolff-Parkinson-White syndrome or concealed atrioventricular bypass tracts.

The natural history of vagal-mediated AF in athletes remains unknown. A study of 30 well-trained athletes with a mean age of 48±7 years followed for nine years reported that paroxysmal AF remained stable in half of the athletes and progressed to persistent or permanent AF in relatively few athletes.[21]

For competitive athletes with recurrent episodes of AF, especially if rates are not controlled, symptoms are present, or exercise tolerance is reduced, activity restrictions must be considered. The need to restrict asymptomatic athletes whose ventricular rates are well-controlled is less compelling, but this may depend on the sport.

All athletes with a diagnosis of AF should undergo standard testing such as basic metabolic panel to access for underlying electrolyte abnormalities, a thyroid panel and a transthoracic echocardiography. Cardiac monitoring devices such as a Holter monitor, a cardiac event monitor or rarely, an implantable loop recorder may be used to determine if symptoms correlate with AF episodes.

Management

Treatment of AF in athletes with either rate or rhythm control medications can be challenging. Identification of overtraining in athletes is important as reduction or temporary cessation of exercise may decrease or even prevent AF recurrence. The initial approach should be to recommend reduction of physical activity.

A study of 1772 athletes with a mean follow up of 62 months reported disappearance of AF with detraining.[9] Similarly, Hoogsteen et al[21] reported that sports abstinence improved symptoms of AF in athletes.

Rate control agents such as beta-blockers or calcium channel blockers may decrease performance and should be avoided, if possible, in professional athletes.

Antiarrhythmic drugs represent a reasonable choice in some athletes with AF. Flecainide may be used regularly or as a "pill in the pocket" for athletes with vagal-mediated paroxysmal AF in the absence of structural heart disease. Caution is recommended with flecainide because of the risk of proarrhythmia due to intense adrenergic hypertonia during professional sports.

Disopyramide, a class IA antiarrhythmic drug, was shown to be effective in vagal-mediated and bradycardia-dependent AF. Early small studies with disopyramide in post-cardioversion patients reported maintenance of sinus rhythm in 67% patients at 6 months and 54% at 1 year.[67,68] Disopyramide is poorly-tolerated due to antimuscarinic properties and proarrhtyhmic effects.

Amiodarone a class III antiarrhythmic agent, is a potent rhythm control medication. Caution is required due to long-term toxic effects. There are no studies on the efficacy of angiotensin converting enzyme inhibitors, aldosterone antagonists and statins in vagal-mediated AF related to endurance sports.

The 36th Bethesda Conference[69] recommended that athletes with asymptomatic AF can safely participate in any competitive sports in the absence of structural heart disease with maintenance of appropriate ventricular rate with no decrease in functional capacity when they were in sinus rhythm.

Risk of stroke from AF is calculated by the CHA2DS2-VASc score which assigns 2 points for age >75 years (A2), 1 point for vascular disease (V), 1 point for age 65-74 years (A), and 1 point for female gender in addition to the standard risk factors.[70]

In low risk athletes such as those with a CHA2DS2-VASc score of 0-1, no antithrombotic therapy is recommended. For CHA2DS2-VASc scores of ≥2, oral anticoagulation is recommended with warfarin or one of the novel oral anticoagulants. There are no data regarding the safety of novel oral anticoagulants in athletes with AF. Any form of oral anticoagulation can be a challenge due to increased risk of bleeding with sports activates.

Direct current cardioversion can be considered in athletes with AF lasting <48 hours or under TEE guidance when the duration remains unknown. Athletes returning to exercise participation after cardioversion have a high likelihood of AF recurrence due to increased autonomic hyper-activation.

The value of catheter ablation in vagal AF is emerging, with recent data supporting its role in management of AF in athletes. A study of 20 athletes (mean age 44.4±13.0 years) reported freedom from AF and antiarrhythmic therapy at 36.1 ± 12.7 months with pulmonary vein isolation. This study also reported a significant increase in exercise capacity (from 183 ± 32 to 218 ± 20 W, $p < 0.02$) and substantial improvement in several quality of life indicators on a self-reported questionnaire.[71] All of the athletes became eligible for competitive sports >6 months after therapy. Another study including 182 subjects undergoing pulmonary vein isolation for AF reported similar arrhythmia-free survival at one year in the lone AF sport group versus controls (59% vs 48%, p=0.44), and similar rates of procedure-related complications (7.1% vs. 4.3%; p=0.45). The frequency of redo pulmonary vein isolation procedures was similar between the lone AF sport group and controls (40.5% vs 37.3%, p=0.5).[72] Koopman et al studied 94 endurance athletes and reported similar AF recurrence after an initial pulmonary vein isolation procedure. However, the recurrence rate was significantly higher in non-endurance controls compared tp endurance athletes (48% vs 34%, p=0.04) after 3 years of follow-up.[73] There was however, similar arrhythmia free survival at 3 years between both groups (87 vs. 85%, p=0.88). The effectiveness of catheter ablation, particularly pulmonary vein isolation, in endurance athletes is partly due to younger age and absence of diseased atria. However, the multifactorial etiology of AF in endurance athletes may be partly responsible for arrhythmia recurrence which may require a repeat procedure. Pulmonary vein isolation should be considered as a first-line therapy in endurance athletes with atrial fibrillation for arrhythmia-free survival, improvement in exercise capacity so that one can resume endurance sports practices. A redo-ablation procedure may be considered with recurrence.

Athletes who are candidates for oral anticoagulation for stroke prevention in AF prior to catheter ablation will likely remain so after the procedure.[74] The issue of cessation of oral anticoagulation in athletes who remain free from AF after catheter ablation is uncertain and requires further study.

Future Directions

There is substantial evidence that endurance training results

in exaggerated vagal tone, cardiac remodeling, inflammation and fibrosis, all of which may contribute to the onset of AF in athletes. AF is a major cardiovascular disorder which increases the risk of stroke by 5-fold, mortality by 2-fold and also impairs quality of life and exercise capacity.[72] This disease should not be trivialized as a mere consequence of overtraining.

It has been recently hypothesized that exercise is associated with a U-shaped effect in terms of cardiovascular benefit. Further studies are necessary to examine the specific effects of endurance exercise on AF risk including sport specificity, duration, type, intensity in specific age groups and gender.

Long-term follow-up data regarding chronic effects of intense endurance exercise investigating training modalities and physiological factors (such as heart rate, blood pressure, VO2 max) may help in better understanding of this condition. Research in animal models examining the specific cardiovascular, cellular and molecular adaptation to intense endurance exercise is necessary.

Genetic studies including identification of specific genomes that may be vulnerable with chronic endurance exercise are required.

Several middle-aged endurance athletes may have brief episodes of atrial arrhythmia which can be triggered both increased resting vagal tone and sympathetic activation during intense physical exertion. The question remains as to whether such athletes can safely continue training. Currently, there are no guidelines on how best to manage such arrhythmias in the aging athlete. Pulmonary vein isolation via catheter ablation may be an effective strategy in these patients.

The decisions by the physician is based on clinical judgment and lack clarity of evidence. Decreasing volume and intensity of exercise is recommended. Further investigation with remote cardiac monitoring device may be warranted.

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Electrophysiological Perspectives on Hybrid Ablation of Atrial Fibrillation

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Abstract

To overcome limitations of minimally invasive surgical ablation as a standalone procedure in eliminating atrial fibrillation (AF), hybrid approaches incorporating adjunctive endovascular catheter ablation have been proposed in recent years. The endovascular component targets residual conduction gaps and identifies additional electrophysiological targets with the goal of minimizing recurrent atrial arrhythmia. We performed a systematic review of published studies of hybrid AF ablation, analyzing 432 pooled patients (19% paroxysmal, 29% persistent, 52% long-standing persistent) treated using three different approaches: A. bilateral thoracoscopy with bipolar radiofrequency (RF) clamp-based approach; B. right thoracoscopic suction monopolar RF catheter-based approach; and C. subxiphoid posterior pericardioscopic ("convergent") approach. Freedom from recurrence off antiarrhythmic medications at 12 months was seen in 88.1% [133/151] for A, 73.4% [47/64] for B, and 59.3% [80/135] for C, with no significant difference between paroxysmal (76.9%) and persistent/long-standing persistent AF (73.4%). Death and major surgical complications were reported in 8.5% with A, 0% with B and 8.6% with C. A critical appraisal of hybrid ablation is presented, drawing from experiences and insights published over the years on catheter ablation of AF, with a discussion of the rationale underlying hybrid ablation, its strengths and limitations, where it may have a unique role in clinical management of patients with AF, which questions remain unanswered and areas for further investigation.

Introduction

The traditional invasive cut-and-sew maze procedure, pioneered by Dr. Cox[1, 2] and with subsequent revisions culminating in the Cox-maze III, has had a durably high success rate in treating atrial fibrillation (AF), with 80-90% of patients having maintained sinus rhythm without antiarrhythmic medications on long-term clinical follow-up.[3, 4] Since the simplification of this procedure using surgical catheter ablation technologies as in the Cox-maze IV,[5] most maze procedures in the USA are facilitated with surgical catheter ablation.[6] Subsequently, minimally-invasive surgical approaches utilizing endoscopically delivered epicardial ablation were developed, parallel to developments in percutaneous catheter-based ablation strategies and technologies,[7-14] obviating the need for cardiopulmonary bypass and curtailing postoperative recovery, whilst maintaining a vantage for adjunctive interventions such as epicardial autonomic modulation and left atrial appendage (LAA) excision.[15-21] These developments were accompanied by increasing number of patients having standalone surgery for AF, constituting 8% of all surgical AF ablations registered in the Society of Thoracic Surgeons Adult Cardiac Surgery Database between 2005 and 2010.[22] However, whereas published outcomes from ablation-facilitated open surgical Cox-maze IV and the traditional cut-and-sew Cox-maze III have been comparable,[4, 23-26] patients treated with minimally-invasive epicardial surgical ablation have fared less well, in particular those with non-paroxysmal AF.[27, 28] On pooled analysis of published results, 75% of paroxysmal, 67% of persistent and only 43% of long-standing persistent AF patients are free of arrhythmia recurrence off antiarrhythmic medications.[27] A recent systematic review estimated a 10-20% higher rate of recurrent atrial arrhythmias after minimally-invasive surgery as compared to open ablation-based surgery, and although there are no adequately controlled trials or registry data comparing the two approaches directly, this likely underestimates the difference as most open surgical AF ablations in published series have been in patients with long-standing persistent AF (56%, with 8% paroxysmal) whilst most minimally-invasive epicardial ablations were in those with paroxysmal AF (59%, with 8% long-standing persistent).[28]

Although the mechanisms underlying this observed difference in outcomes are not fully ascertained, electrophysiological observations during minimally invasive epicardial ablations or at the time of catheter ablation of recurrent atrial arrhythmias following such procedures[29-33] suggest that these paradoxically inferior results

Key Words:
Atrial Fibrillation, Hybrid Ablation, Surgical Ablation, Rotors, Maze.

Disclosures:
None.

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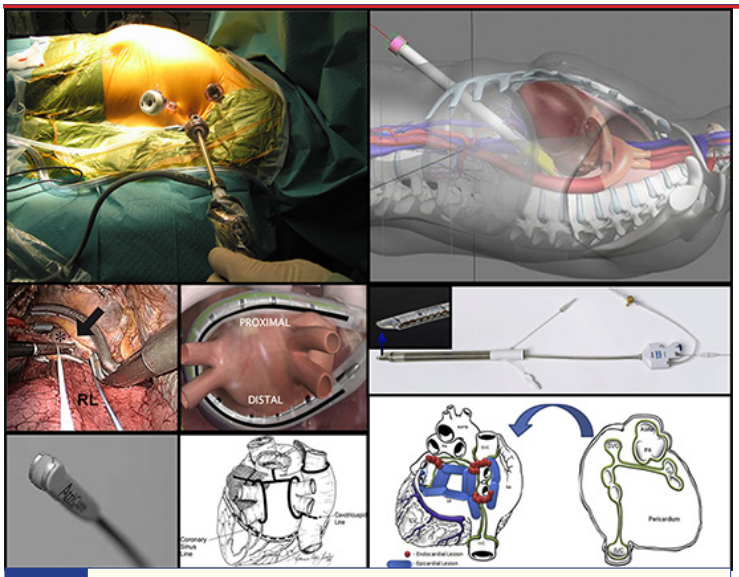

Figure 1: Hybrid ablation: access, tools and lesions sets. Top and middle left: Left thoracoscopic access as part of bilateral clamp-based approach; lesion (large arrow) created by bipolar radiofrequency clamp (Atricure, West Chester, OH) at right pulmonary vein antrum (asterix). RL – right lung. From Pison, J Am Coll Cardiol 2012;60(1):54-61, with permission. Bottom left: Bipolar pen used for linear ablations in bilateral clamp-based approach. From Sakamoto, J Thorac Cardiovasc Surg 2008;136(5):1295–1301, with permission. Bottom middle: Lesion set in bilateral clamp-based approach, from Mahapatra, Ann Thoracic Surg, Volume 91 , Issue 6 , 1890 – 1898, with permission. Central: Suction monopolar radiofrequency catheter (Estech Cobra Adhere XL, Atricure, West Chester, OH) positioned over the posterior left atrium as used in the right-sided thoracoscopic approach. From Muneretto, Innovations (Phila) 2012;7(4):254-8), with permission. Top right: Transabdominal, transdiaphragmatic access used in convergent approach. From Gehi, Heart Rhythm 2013;10(1):22-8, with permission. Middle and bottom right: Vacuum irrigated unipolar radiofrequency device (Numeris Guided Coagulation System with VisiTrax, nContact Surgical, Inc, Morrisville, NC) used in convergent approach; epicardial (blue) and endocardial (red) lesion set in convergent approach. From Gersack, J Thorac Cardiovasc Surg 2014;147(4):1411-6, with permission.

often reflect the demonstrated limitations of current ablation tools in creating transmural lesions sets when applied endoscopically on the epicardium of the beating heart.[34-36] Up to 40% of patients undergoing minimally invasive AF surgery have been reported to develop recurrent atrial flutter, with 50% of isolated pulmonary veins having reconnected at time of repeat ablation,[30] which is significantly higher than rates of 5 to 10% reported following endocardial surgical ablation,[37-39] and is responsive to further catheter ablation.[20] By slowing conduction yet failing to impart conduction block, such lesions are not only ineffective at preventing fibrillatory wave propagation[40] and AF from recurring[41-43] but also establish the tissue substrate required for reentrant atrial tachycardia.[44-54] With multiple, incomplete lines, reentrant atrial tachycardia circuits become complex and increasingly challenging to subsequently map and ablate.[29]

To overcome these limitations of minimally invasive surgical ablation as a standalone procedure in abolishing AF, hybrid ablation was developed, incorporating an adjunctive percutaneous catheter procedure to bridge conduction gaps in the anatomically-based surgical ablation lines as well as additional targets determined electrophysiologically.[55-59] This paired utility of surgical and catheter based approaches has been advocated as providing the combined advantage of both, whilst allowing each to overcome the limitation of the other,[55, 57, 59] Ensuring conduction block at the time of surgery significantly reduces recurrence rates; of 93 patients undergoing either open chest or minimally invasive surgical AF ablation, maintenance of AF off antiarrhythmic medications at 12 months was 87% with confirmation of conduction block vs 48% without.[32]

In this review, we critically appraise the published experience on hybrid ablation, placing it within the context of the experiences and insights attained over the years from catheter ablation of AF. In doing so, we provide a perspective on the rationale underlying hybrid ablation, its strengths and limitations, where it may have a unique role in clinical management of patients with AF, which questions remain unanswered and areas for further investigation.

Systematic Review of Published Literature on Hybrid Ablation of Atrial Fibrillation

Peer-reviewed publications reporting on 5 or more clinical cases undergoing adjunctive minimally invasive epicardial ablation and percutaneous endovascular catheter ablation were identified using Pubmed.gov (US National Library of Medicine, National Institute of Health) using the search term "atrial fibrillation AND (hybrid OR convergent) AND (ablation OR surgery)" (last updated 3/4/2015). This was supplemented by searches on Google Scholar and review of individual studies' references. We identified 11 unique studies reporting on a total of 432 patients who have undergone standalone hybrid ablation at 11 centers (7 European, 3 North American, 1 Asian) and pooled available demographic, procedural and outcome data of 432 (Tables 1 – 3).[33, 56, 57, 59-66] We included 2 publications where we felt that duplication of case ascertainment was minimal on account of a limited data overlap in recruitment of a patient subset[62, 65] and excluded 5 publications with probably significant patient overlap selecting in preference those publications which were more recent with greater patient numbers.[55, 67-70] A further 4 studies (231

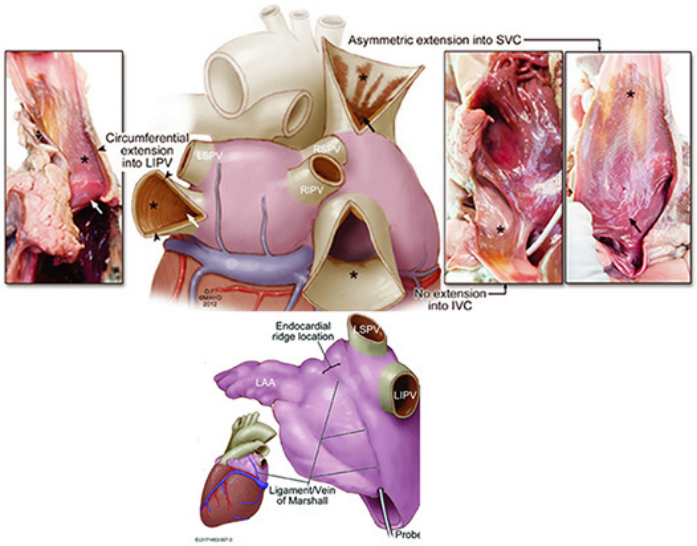

Figure 2: Thoracic venous sources of atrial fibrillation triggers. Top: pulmonary vein and vena cavae. Arrows and asterexis identify myocardium in venous structures adjoining the left and right atria. Bottom: Diagram depicting location of the ligament (or vein) of Marshall, the remnant of the left-sided superior vena cava, which has varying degrees of patency in adult life. From Desimone, J Cardiovasc Electrophysiol 2012;23(12):1304-9, with permission. LAA – left atrial appendage; LIPV/RIPV/RSPV – left/right inferior/superior pulmonary vein; IVC/SVC – inferior/superior vena cava.

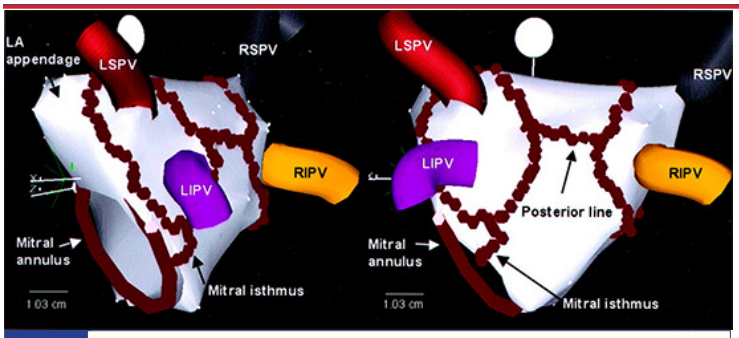

Figure 3: **Ablation lines created during left atrial ablation represented on a 3D electroanatomical mapping system (CartoTM). Individual ablation lesions are represented by red tags. From Oral, Circulation. 2003;108(19):2355-2360, with permission.**

patients) were not included as they were published in journals not indexed by the US National Library of Medicine.[71-74]

The 432 pooled patients had a mean age of 60 years (range, 56 to 63 years), mean CHADS2 scores (reported in 5 studies, n=250, 58%) 1 to 1.6, mean left atrial diameter (reported in all studies) 4.3 to 5.2 cm, mean left ventricular ejection fraction (reported in 11 studies, n=368, 85%) 47 to 62%, and mean AF duration (reported in all studies) 2.8 to 7.0 years (Table 1). AF was categorized in accordance with guidelines75 as paroxysmal (individual episodes lasting ≤7 days) in 19% (83/432), persistent (continuous AF >7 days) in 29% (124/432) and long-standing persistent (continuous AF > 12 months) in 52% (225/432). A history of prior AF ablation was present in 35% (112/319 with reported data). Four studies (n=163, 38%) included only persistent and/or long-standing persistent AF patients. No study reported inclusion of patients with valvular AF (i.e. associated with rheumatic mitral stenosis, prosthetic or bioprosthetic valve, or mitral valve repair 75) or prior cardiac surgery, although these data were not specifically reported in 5 [n=245, 57%] and 4 [n=210, 49%] studies respectively, whilst 2 studies [n=123, 28%] included only lone AF patients.

The published experience encompasses 3 different surgical approaches, each utilizing unique radiofrequency ablation tools (Table 2, Figure 1): bilateral thoracoscopy with circumferential and linear lesions (sometimes referred to as LAMP [La Meir, Ailawadi, Mahapatra, Pison] hybrid ablation) created using bipolar radiofrequency clamps and ablation pens (Atricure, West Chester, OH) respectively (6 studies, n=194, 45%); right-sided thoracoscopy with simultaneous isolation of pulmonary veins and posterior left atrium using a suction monopolar radiofrequency catheter (Estech Cobra Adhere XL, Atricure, West Chester, OH) designed to deliver an encircling linear lesion (2 studies, n=64, 15%); and subxiphoid posterior pericardioscopy (through laparoscopic incision of the central diaphragmatic tendon) with linear ablation using a vacuum irrigated unipolar radiofrequency device (Numeris Guided Coagulation System with VisiTrax, nContact Surgical, Inc, Morrisville, NC, USA) to isolate or debulk the posterior left atrium and partially isolate the pulmonary veins (2 studies, n=174, 40%, referred to as the convergent procedure). Pulmonary vein isolation (PVI) was a common end-point in all studies. One clamp-based study[33] included 5 patients with severe COPD who underwent only right thoracoscopic radiofrequency epicardial ablation with adjunctive endovascular left-sided pulmonary vein cryoablation to avoid bilateral pneumothoraces.

In addition to the differences in epicardial lesions created by these very different strategies and tools, timing of the endovascular catheter component also varied widely, from being performed immediately after surgery in 5 studies ("immediate-staged", n=259, 60%) or after a delay ranging from 4 days to 3 months in 4 studies ("delayed-staged, n=100, 23%), with 1 multicenter study (n=73, 17%) reporting an immediate-staged procedure in 2 centers, delayed at >2 weeks in 1 center, and 50:50 split between immediate and delayed at >2 months in 1 center (Table 2). The endovascular component itself varied significantly between studies, such as whether electroanatomical mapping was utilized, choice of linear ablation lesions and which patients these were performed in, whether physiological targets such as triggers and complex fractionated atrial electrograms (CFAE) were targeted, and selection of end-points including intraprocedural confirmation of conduction block and re-induction protocols. There was variation in ganglion identification and ablation, ligament of Marshall ablation, and LAA ligation or excision (Table 2). There was diversity in approaches to peri-procedural antiarrhythmic and anticoagulant management.

Such diversity in approach is not surprising given the relative infancy of minimally-invasive surgical AF ablation and the novel ablation tools used,[27,76] as well as lack of consensus within the ablation community itself on optimal strategies for persistent and long-standing persistent AF.[77] An appreciation of electrophysiological principles underlying AF mechanisms and ablation approaches is central to understanding the role of these various approaches as therapeutic strategies for AF and their relative shortcomings.

Electrophysiological Perspective 1 – Heterogeneity of Atrial Fibrillation Mechanisms and Implications for Tailored Therapy

The pathogenesis of AF is often multifactorial. Applying the same therapy as a panacea may risk overtreating some and not addressing underlying mechanisms in others. Whilst the success of the maze procedure is consistent with the principle that a critical mass of atrial tissue is required to sustain fibrillatory conduction,[116-118] the cumulative experience from catheter ablation suggests both initiating triggers and arrhythmogenic substrate need to be addressed,[119, 120] particularly in patients with persistent AF,[48, 79, 80, 82-89, 91, 92, 94, 121-129] and underlying risk factors are identified and treated.[104, 105]

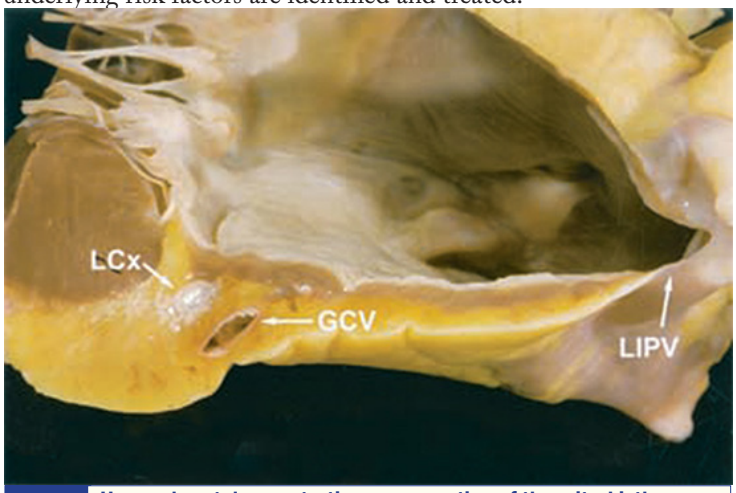

Figure 4: **Human heart demonstrating cross-section of the mitral isthmus. The thickness of the atrial myocardium, epicardial fat and associated vasculature are demonstrated. From Becker, J Cardiovasc Electrophysiol 2004;15(7):809-812, with permission. LCx – left circumflex artery; GCV – great cardiac vein; LIPV – left inferior pulmonary vein.**

Table 1: Systematic Review of Hybrid Ablation Studies – Patient Demographics

First Author	No. patients$	Publication Year	Institution(s)	Procedural Approach	Energy source	Age (mean±SD, years)	PAF	PrAF	LSPrAF	Lone AF only
Mahapatra[57]	15	2011	University of Virginia, Charlottesville, USA	Thoracoscopic Clamp-based	RF	59.5±2.4	0	9	6	No
Lee[56]	7	2011	Northwestern Memorial Hospital, Northwestern University, Chicago, USA	Thoracoscopic Clamp-based	RF	NA	NA	NA	NA	No
La Meir[59]	19	2012	University Hospital Maastricht, Maastricht, The Netherlands	Thoracoscopic Encircling Catheter	RF	60.8±8.6	5	4	10	No
Pison[33]	26	2012	University Hospital Maastricht, Maastricht, The Netherlands	Thoracoscopic Clamp-based	RF±cryoballoon*	57.2±8.6	15	10	1	No
Bisleri[60]	45	2013	University of Brescia Medical School, Brescia, Italy	Thoracoscopic Encircling Catheter	RF	62.3±9.8	0	0	45	Yes
Gehi[61]	101	2013	FirstHealth Arrhythmia Center, Pinehurst and University of North Carolina at Chapel Hill, Chapel Hill, USA	Subxiphoid Pericardioscopic (Convergent)	RF	62.9±9.6	17	37	47	No
La Meir[62]	35	2013	University Hospital Maastricht, Maastricht, The Netherlands	Thoracoscopic Clamp-based	RF	57.1±9.5	16	8	11	No
Kurfirst[63]	30	2014	Hospital Ceske Budejovic, Ceske Budejovice, Czech Republic	Thoracoscopic Clamp-based	RF	61±8	0	0	30	No
Lee[64]	10	2014	Samsung Medical Center, Seoul, South Korea	Thoracoscopic Clamp-based	RF	56.1±7.6	1	0	9	No
Pison[65]	78	2014	University Hospital Maastricht, Maastricht, The Netherlands	Thoracoscopic Clamp-based	RF	60.5±7.5	29	34	15	Yes
Gersak[66]	73	2014	Multicenter¥ (Slovenia, Poland, Germany, France)	Subxiphoid Pericardioscopic (Convergent)	RF	56.3±10.5	0	22	51	No
TOTAL**	432					mean 60.0	83	124	225	

**Excludes 7 patients reported by Lee et al[56] as results pooled with 18 patients undergoing non-hybrid minimally invasive AF surgery; $Additional 8 paroxysmal AF patients not included on account of excluding one study (8 paroxysmal AF and 28 long standing persistent AF)[70] with significant overlap in reported patients with Bisleri et al.[60]; ¥University of Ljubljana Medical Center, Ljubljana, Slovenia; Silesian Center For Heart Diseases, Zabrze, Poland; Herz-und Gefaesszentrum, Bad Bevensen, Germany; L'Institut Mutualiste Montsouris, Paris, France
PAF – Paroxysmal AF, PrAF – persistent AF, LSPrAF – long-standing persistent AF; NA - not available; LVEF - left ventricular ejection fraction; RF - radiofrequency

Electrophysiological Perspective 2 – Insights from Catheter Ablation of Paroxysmal and Persistent Atrial Fibrillation

A major breakthrough in catheter ablation of AF was the finding that myocardial extensions into the pulmonary veins, previously recognized anatomically[132] and present in almost all human hearts (Figure 2),[133] are a dominant and progressive source of AF triggers amenable to ablation.[134,135] The mechanistic cogency of this approach was supported by studies demonstrating that isolating arrhythmogenic veins acutely terminates AF and prevents AF reinduction[140] even when tachycardia persists within the vein,[140, 144-146] and also reduces arrhythmia recurrence compared to focal ablation[147] likely by addressing recurrent triggers from elsewhere in the pulmonary veins[148] or inter-connected veins.[149,150] Once it was realized that atrial myocardium adjacent to the pulmonary ostia, i.e. in the pulmonary vein antra, is a critical source of triggers leading to recurrence after ostial PVI,[151] in keeping with its histological and electrical homogeneity with the venous myocardial sleeves,[152] the approach was further modified to incorporate these areas (antral PVI or wide-area circumferential ablation [WACA]) with a further reduction in arrhythmia recurrence than with ostial PVI.[153-157] In addition to isolating venous[146, 158-160] and antral arrhythmogenic foci,[151, 161-164] proposed mechanisms have included disrupting pulmonary ostial anchors for AF drivers (discussed below)[128, 165, 166] and interrupting neuronal connections.[81, 167,168] A number of randomized clinical trials have demonstrated the efficacy of this approach as a therapeutic strategy for paroxysmal AF,[7, 9, 10, 169-174] and of consecutive patients undergoing radiofrequency PVI, approximately 75% and 90% are rendered arrhythmia-free off antiarrhythmic therapy after 1 and 2 ablation procedures, respectively,[99] and at 10 years, 75% of patients are arrhythmia free, although 40% require repeat ablation and there have been evolving approaches and technologies over this time.[100, 175] In addition to symptomatic benefit and quality of life improvement, there is a significantly lower rate of progression to persistent AF (0.5-0.6% per year)[100,176,177] compared with pharmacological therapy (8.6% per year).[178]

The catheter ablation experience allowed for additional insights into the pathophysiological significance of non-pulmonary thoracic venous myocardium. Atrial myocardium extending into the superior vena cava, seen in 80% of human hearts (Figure 2),[133] has similar electrophysiological characteristics to pulmonary venous extensions and can be a source of AF triggers.[179, 180] It is also present in the coronary sinus, ligament of Marshall and, least commonly, azygous vein (6%).[133] Myocardium within the coronary sinus may be a source of rapid repetitive electrical activity during AF and electrically disconnecting it from the left atrium reduces sustained AF induction, suggesting a role in perpetuating AF.[181] The ligament of Marshall (Figure 2) is an epicardial remnant of the left superior vena cava, which maintains 3-French probe patency in 70% of hearts and consistently overlies the endocardial left lateral ridge between the pulmonary veins and left atrial appendage.[133] It contains both autonomic nerves and muscle fibres, the density of which varies along its length,[182] implicated in triggering or sustaining AF[183] and providing electrical continuity between the coronary sinus and pulmonary veins.[184]

Through experience with ablation, there has also been improved understanding on mechanisms and management of post-ablation atrial arrhythmia. Although early arrhythmia recurrence (<3 months) is a powerful predictor for long-term recurrence,[185]-190 a significant proportion (30%) may go on to be arrhythmia free in the long-term

without repeat ablation,[185, 187] and early restoration of sinus rhythm during this period reduces long-term recurrence rates,[191] although additional antiarrhythmic use does not add incremental value to cardioversion.[192-195] For late recurrence (>3 months), repeat ablation is superior, as demonstrated by one randomized trial of paroxysmal AF patients with recurrence after antral PVI, with reduced AF burden, symptoms and progression to persistent AF (4 vs 23% at 36 months) compared to antiarrhythmic therapy.[196] This is mechanistically consistent with studies demonstrating that recurrence after PVI for paroxysmal AF is usually related to reconnected pulmonary vein conduction,[43, 47, 146, 158, 177, 197-201] likely due to reversible ablation injury with absent circumferential scar on MRI,[202-205] or the presence of extrapulmonary ectopic AF triggers.[151,158,162] Extrapulmonary triggers are noted spontaneously in about 10% of patients undergoing AF ablation, being several fold more frequent with increasing AF burden and duration (3% of paroxysmal, 8% of persistent and 19% of long-standing persistent patients),[99] and in up to 45% following induction with pacing or isoproterenol infusion, most commonly arising from the posterior left atrial wall (20-40%), left atrial appendage (30%), or superior vena cava (30-40%), with a minority from the left atrial roof (8%), ligament of Marshall (8%), crista terminalis (5-10%), coronary sinus (1-10%), and interatrial septum (1-5%).[151, 163, 206-210] It is unknown whether routinely targeting these regions improves outcomes when they are not evident sources of triggers during ablation. For instance, routinely isolating the SVC as a dominant site of extrapulmonary venous triggers has been advocated,[180] whilst randomized trials testing this approach have reported conflicting results.[211-213]

To summarize, in keeping with the predominant trigger-based mechanism underlying paroxysmal AF, catheter ablation studies have demonstrated that an anatomically guided approach to PVI leads to sustained improvement off antiarrhythmic drugs in the majority of patients and offers a definite end point of electrical isolation of the pulmonary vein. Although the extent of atrial fibrosis correlates weakly with clinical phenotype,[78] with some paroxysmal AF patients having high atrial fibrosis burden, systematic substrate modification offers no incremental benefit,[214-222] even with late recurrent paroxysmal AF requiring re-ablation,[223] and may even predispose to macroreentrant atrial tachycardias.[216, 224]

This contrasts with insights gained from catheter ablation of persistent and long-standing persistent AF, where dominant fibrillating frequency shifts away from the pulmonary veins to other left or even right atrial sites[144, 161] with PVI offering limited success on its own[225-228] and additional substrate modification becoming necessary to improve ablation outcomes,[8, 131, 157, 229, 230] all in keeping with the underlying transition from a predominant trigger-based paradigm to one with increasing influence from extrapulmonary drivers and atrial substrate.[128, 209, 231] However, there is mechanistic overlap, such that in persistent AF there is evidence of ongoing dynamic interplay between pulmonary vein triggering and atrial activation144 and PVI may acutely reduce left atrial dominant activation frequency,[232] partially organize AF without necessarily affecting dominant frequency,[233] or acutely terminate AF.[121, 144, 227] Accordingly, atrial substrate modification alone without PVI results in inferior outcomes.[228, 234, 235] Nonetheless, atrial substrate, no matter how defined, is a strong predictor of recurrence after catheter ablation of persistent AF[78, 201, 236-238] and outcomes have been better with more extensive atrial substrate modification.[124, 230] To what extent this reflects current uncertainty over how best to identify pathogenic versus bystander substrate and appropriate end-points for ablation are areas of ongoing investigation.[131]

Electrophysiological Perspective 3 – Successful Substrate Modification and Ablation End Points in Persistent Atrial Fibrillation

An intriguing finding from the PRAGUE-12 randomized trial is that restoration of sinus rhythm was significantly higher with increasingly persistent AF comparing maze to no maze in patients undergoing cardiac surgery (paroxysmal 62 vs. 58%, persistent 72 vs. 50% and long-standing persistent AF 53 vs. 14%, $P < 0.001$).[239] The ability to observe in real time the effects of progressive substrate modification on atrial activation locally, remotely and globally whilst correlating this with structural, functional, and outcome data have allowed for novel insights into mechanism underlying arrhythmia and ablation efficacy in persistent and long-standing persistent AF. Improved catheter ablation outcomes have been reported when additional substrate modification is incorporated in an individualized, stepwise fashion to either reduce AF dominant frequency (>11%)240 or terminate AF,[129, 238] with adjunctive ablation of spontaneous and inducible atrial tachycardias.[127, 241, 242] With this approach, long-term freedom from AF off antiarrhythmic medication has been reported in 65-75% of patients,[129, 238, 240, 242] and though 15-30% of patients with long-standing AF may require 3 or more procedures, recurrences are more likely to be from reentrant atrial tachycardia rather than recurrent AF,[129, 238] albeit the benefits of AF termination decline with longer AF duration (>3 years in one study).[243] There is currently no consensus on what constitutes optimal substrate modification in persistent AF, with reported benefit from an anatomical approach through creating point-by-point ablation lines (linear ablation) following the success of the surgical maze procedure;[46, 51, 229, 232, 244-246] isolating the posterior left atrium in this manner,[247, 248] ablating sites with complex fractionated atrial electrograms (CFAE) during fibrillatory conduction as a strategy to modify electrical substrate;[217, 219, 226, 234, 249-251] identifying and ablating focal drivers;[109, 113, 123, 126, 128, 252, 253] and ablating autonomic ganglia as AF modulators.[82, 84, 86, 88, 91, 92, 254]

The most extensively investigated linear ablation lesions during catheter ablation are the roof line, which connects the superior pulmonary veins (to mitigate risk of atrio-esophageal fistula from ablating over the esophagus posteriorly), and mitral isthmus line connecting the left inferior pulmonary venous antrum to the mitral annulus (Figure 3).[48, 153, 232] When such ablation is successful, it results in dominant activation frequency reduction and cycle length prolongation, which may progress with further ablation to AF termination, often to a macroreentrant atrial tachycardia circuiting around the left atrial roof, mitral isthmus, or cavotricuspid isthmus.[48, 232] Of those still in AF on completion of antral PVI, 60% are left non-inducible for AF after one linear lesion and 95% after two.121 Analyzing frequency-domain transformed activation signaling during linear ablation reveals that acute reductions in dominant activation frequency do not occur until completion of conduction block and coincide with disappearance of discreet lower frequency sources, characteristics of which were consistent with reentrant drivers, an effect not seen after PVI or CFAE ablation in this study.[232] Linear ablation may therefore work by disrupting localized reentrant drivers. Results from whole atrial phase and organization index mapping also suggest this.[128,166,255] In addition, linear ablation may reduce subsequent

Table 2: Systematic Review of Hybrid Ablation Studies – Ablation Details

First Author	No. patients	Ablation Technology	Epicardial Atrial Ablation	Intraprocedural Confirmation of Conduction Block: Epicardial	Ganglion Ablation (identification method)	LOM ablation	LAA Intervention	Endocardial Ablation: Staging	Endocardial Ablation						
									Electroana-tomical Mapping	Confirming Conduction Block	Findings	Intervention	Reinduction	Triggers	Flutters
Thoracoscopic Clamp-based Approach (n=194, 45%)**															
Mahapatra[57]	15	Bipolar clamp, bipolar linear RF pen (Atricure, West Chester, OH)	Bilateral PVI, roof line, anterior line, mitral isthmus line, CS ablation, SVC isolation	PVI: entrance ± exit; linear: none	Yes (HFS)	Yes	Excision (staple)	Delayed staged 4.3±1.3 days	Yes	PV bidirectional block, SVC isolation, bidirectional block across linear lesions, AF inducibility (isoproterenol)	Gaps in 0 PVI and SVC lesions, 27% (4/15) of roof lines and 27% (4/15) of mitral isthmus lines	Consolidation of surgical ablation lines, CTI line, CS ablation, mitral isthmus line and CFAE ablation if AF inducible, ablation of inducible flutters ablated	Isoproterenol	No	Yes
Lee[56]	7	Bipolar RF clamp, monopolar RF pen (Medtronic, Minneapolis, MN)	Bilateral PVI	PVI: entrance ± exit; linear: bidirectional	Yes (HFS)	No	Excision (staple)	Delayed staged >3 months if recurrent AF/flutter	Yes (presumed)	PV bidirectional block, criteria for block across lines not stated	PV reconnections in all 7 patients (mean 2 per patient) at 6±3 months, all with confirmed entrance and/or exit block at time of surgery	Consolidation of surgical ablation lines, roof and mitral isthmus line, CTI line if typical flutter	Unknown	Yes	Yes
Pison[33]	26	Bipolar clamp, bipolar linear RF pen (Atricure, West Chester, OH)	Bilateral PVI, box lesion§, roof line§, mitral isthmus line§, CS ablation, intercaval line§, SVC isolation. Stepwise based on electrophysiological endpoint of non-inducibility of atrial arrhythmia.	PVI: entrance + exit; linear: bidirectional	No	No	Excision (staple)§	Immediate staged	No₮	PV bidirectional block, bidirectional block across linear lesions	Gaps in 0 PVI lesions, 23% (5/22) of box and 100% (3/3) of mitral isthmus lines	Consolidation of surgical ablation lines, CTI line if typical flutter (n=3)	Rapid atrial pacing and isoproterenol	No	Yes
La Meir[62]	35	Bipolar clamp, bipolar linear RF pen (Atricure, West Chester, OH)	Bilateral PVI, box lesion, mitral isthmus line*, CS ablation, intercaval line*, SVC isolation*	PVI: entrance + exit; linear: bidirectional	Yes (HFS)	No	Exclusion (staple or clip)§	Immediate staged	No₮	PV bidirectional block, bidirectional block across linear lesions, AF inducibility (rapid atrial pacing)	Gaps in linear ablation lesions in 14% (5/35)	Consolidation of surgical ablation lines, additional linear ablation if AF inducible, CTI line if typical flutter (n=3)	Rapid atrial pacing and isoproterenol	No	No
Kurfirst[63]	30	Bipolar clamp, bipolar linear RF pen (Atricure, West Chester, OH)	Bilateral PVI, box lesion, additional roof line	PVI: entrance + exit; linear: bidirectional	Yes (HFS)	Yes (ligation + ablation)	Exclusion (clips)§	Delayed staged 3 months	Yes	PV entrance block, unidirectional block across linear lesions, AF inducibility (rapid atrial pacing)	Gaps in PVI lesions in 87% of right PV, 77% of left PV, 67% of roof lines, and 40% of inferior lines	Consolidation of surgical ablation lines, CTI line and mitral isthmus line, ablation of inducible flutters	Rapid atrial pacing	No	Yes
Lee[64]	10	Bipolar clamp, bipolar linear RF pen (Atricure, West Chester, OH)	Bilateral PVI, inferior line	No	Yes (HFS)	Yes	Excision (staple)	Delayed staged 4 days in 8/10	Yes	PV isolation (not detailed)	Gaps in PVI lesions in 12.5% (1/8)	Consolidation of surgical ablation lines, CTI line in 6/8	No	No	No

First Author	No. patients	Ablation Technology	Epicardial Atrial Ablation	Intraprocedural Confirmation of Conduction Block: Epicardial	Ganglion Ablation (identification method)	LOM ablation	LAA Intervention	Endocardial Ablation: Staging	Endocardial Ablation						
									Electroana-tomical Mapping	Confirming Conduction Block	Findings	Intervention	Reinduction	Triggers	Flutters
Pison[65]	78	Bipolar clamp, bipolar linear RF pen (Atricure, West Chester, OH)	Bilateral PVI, box lesion, mitral isthmus line§, CS ablation, intercaval line§, SVC isolation§	PVI: entrance + exit; linear: bidirectional	Yes (unknown)§	No	Exclusion (staple or clip)§	Immediate staged	No₮	PV bidirectional block, bidirectional block across linear lesions, AF inducibility (rapid atrial pacing)	Gaps in 0 PVI lesions and 36% (28/78) of box lesions	Consolidation of surgical ablation lines, CTI line if typical flutter (n=11), mitral isthmus line completion if perimitral flutter (n=10)	Rapid atrial pacing and isoproterenol	No	No
Thoracoscopic Encircling Catheter-based Approach (n=64, 15%)**															
La Meir[59]	19	Encircling suction monopolar RF catheter (Estech Cobra Adhere XL, Atricure, West Chester, OH)	Encircling lesion set - bilateral PVI and box lesion	No	(as part of box lesion)#	No	No	Immediate staged	No₮	Entrance and/or exit block across linear lesions	Gaps in 89% (17/19) of PVI lesions and 100% (19/19) box lesions	Consolidation of surgical ablation lines, mitral isthmus line in persistent AF patients (n=3), CTI line if typical flutter seen (n=3)	No	No	No
Bisleri[60]	45	Encircling suction monopolar RF catheter (Estech Cobra Adhere XL, Atricure, West Chester, OH)	Encircling lesion set - bilateral PVI and box lesion	PVI: entrance ± exit; linear: unidirectional	No	No	No	Delayed staged 30–45 days	Yes	PV bidirectional block, bidirectional block across linear lesions, AF inducibility (rapid atrial pacing)	PV reconnections (7%, 3/45) representing 3/4 with only exit block and 0/41 with bidirectional block immediately after surgical ablation	Consolidation of surgical ablation lines, CFAE if AF inducible (n=20), CTI line if typical flutter (n=11)	Rapid atrial pacing	No	Yes
Subxiphoid Convergent Approach (n=174, 40%)**															
Gehi[61]	101	Vacuum irrigated unipolar RF device (Numeris Guided Coagulation System with VisiTrax, nContact Surgical, Inc, Morrisville, NC, USA)	Non-encircling bilateral antral lesions, box lesion, additional roof line, mitral isthmus line*, CS ablation	PVI: none; linear: unidirectional	No	Yes (undissected)	No	Immediate staged	Yes	PV bidirectional block, unidirectional block across linear lesions, AF inducibility (rapid atrial pacing)	Gaps in PVI lesions in 4% (4/101)	Consolidation of surgical ablation lines, additional roof line (n=90), CS ablation (n=73), mitral isthmus line (n=84), CTI line (n=99), CFAE ablation (n=29). Stepwise based on electrophysiological endpoints of termination to sinus rhythm with no re-inducibility of AF or termination to atrial flutter/ tachycardia	Rapid atrial pacing	No	No

First Author	No. patients	Ablation Technology	Epicardial Atrial Ablation	Intraprocedural Confirmation of Conduction Block: Epicardial	Ganglion Ablation (identification method)	LOM ablation	LAA Intervention	Endocardial Ablation: Staging	Endocardial Ablation						
									Electroanatomical Mapping	Confirming Conduction Block	Findings	Intervention	Reinduction	Triggers	Flutters
Gersak[66]	73	Vacuum irrigated unipolar RF device (Numeris Guided Coagulation System with VisiTrax, nContact Surgical, Inc, Morrisville, NC, USA)	Non-encircling bilateral antral lesions, box lesion	No	No	Yes (undissected)	No	Mixed□	Mixed‖	Entrance and/or exit block across linear lesions and PV	Gaps in all PVI at sites of pericardial reflections - superior margins bilaterally and inferior margin of right inferior pulmonary vein antrum.	Consolidation of surgical ablation lines	No	No	No

**Excludes 7 patients reported by Lee et al56 as results pooled with 18 patients undergoing non-hybrid minimally invasive AF surgery; §Selected patients only; *Persistent and/or long-standing persistent AF patients only; #Dissection of ganglion fat pads prior to box lesion application and HFS confirmation of all except right inferior ganglion; □Immediate staged in 2 centers, delayed at >2 weeks in 1 center, 50% immediate and 50% delayed >2 months in 1 center; ‖Electroanatomical mapping was not utilized in Slovenia; ₹Sites of epicardial ablation identified with fluoroscopic visualization of ablation device in situ. N/A - not applicable - performed as part of box lesion; CS - coronary sinus; CFAE: complex fractionated atrial electrograms

macro-reentrant atrial tachycardia by creating lines of conduction block across critical anatomical isthmi, yet predispose to it when conduction block is not achieved.[51, 54] The major limitation of linear ablation is therefore difficulty in achieving sustained conduction block,[50] particularly at the mitral isthmus (Figure 4) where 40-70% of patients require additional epicardial ablation from within the coronary sinus and 10-35% are left without conduction block,[256-258] especially in areas with anatomical irregularity (such as with a pouch), or interpositioned coronary vessels presumably causing a heat sink.[257-259] Even if successful conduction block is achieved at index procedure, late recovery of mitral isthmus conduction is seen in 75% of instances (much higher than after cavotricuspid isthmus block [25%]) and predisposes to perimitral flutter.[260] The incidence of perimitral flutter is higher after routine mitral isthmus ablation and requires further reablation to achieve lasting freedom from recurrence.[53]

As with antral PVI, gaps in conduction block in linear lesions resulting in reentrant atrial tachycardias is the most common cause for arrhythmia recurrence,[45, 46, 50-52, 245] and may explain why the recently published STAR AF II randomized trial,[261] in which linear ablation resulted in acute conduction block in only 74% of patients and intraprocedural AF termination in 22%, failed to demonstrate benefit of linear ablation over antral PVI, and also why a recent meta-analysis demonstrated a significant reduction of AF recurrence with linear ablation but not with more extensive linear lesion sets.[235] In addition, although patients may manifest with perimitral flutter following persistent AF ablation, they still stand to benefit from confirmation of PVI and ablation of extra-pulmonary triggers, which may by itself result in more patients having reduced arrhythmia recurrence than if the mitral isthmus alone is ablated and blocked, indicating that triggering may underlie some macroreentry post-ablation flutters.[252] As for routinely creating linear lesions in the right atrium, cavotricuspid isthmus ablation during AF ablation does not reduce long-term arrhythmia recurrence[262, 263] unless typical atrial flutter is demonstrated either clinically or during the ablation procedure.[264, 265] These principles also extend to effective surgical lesion sets.[29] Limiting lesion sets also reduces the likelihood of complications, as illustrated by a recent meta-analysis comparing left atrial and biatrial maze which reported equivalent long-term success but with increased pacemaker implantation with biatrial maze.[266]

In a prior study CFAE ablation was reported to significantly improve ablation outcomes as an adjunct to PVI, but as standalone therapy the results were inferior to PVI (1 year arrhythmia-free rates 74 vs. 48 vs. 29% after one procedure in the STAR AF trial).[234] In about 20% of patients, AF terminates whilst ablating a CFAE[267, 268] and an acute decrease in dominant frequency with CFAE ablation predicts reduced recurrence of AF.[269] Certain CFAEs are more likely to terminate AF or reduce its dominant activation frequency than others, such as those with greater duration of continuous activity or complexity,[270-273] whilst other CFAEs may represent bystander activation as suggested by studies demonstrating a reduction in CFAE number and location immediately following PVI or linear ablation.[268, 271, 274] Judicious selection of target sites is therefore needed, whilst identifying appropriate CFAE targets based on grading complexity is somewhat subjective and can be erroneously overestimated at overlapping structures including the interatrial septum. This may explain why, when guided by automated software protocols, CFAE ablation was reported to offer no additional benefit to antral PVI by the STAR AF II trial[261] and, as reported by another randomized trial, have inferior outcome to linear ablation despite more extensive lesions with greater cardiac enzyme release.[275] Further evidence of the importance of strategic CFAE ablation comes from a trial demonstrating no added benefit when right atrial CFAE ablation is routinely added to left atrial CFAE ablation.[114] The three published randomized studies directly comparing linear with CFAE ablation have reported either inferior performance of CFAE ablation, [275] as noted above, or equivalence of the two procedures,[261, 276] though with CFAE ablation resulting in higher rates of intra-procedural AF termination[261] and recurrences which are less likely fibrillation and more likely atrial tachycardia.[276]

The observation that terminating or slowing AF by ablation at discreet

sites modifies atrial substrate in a manner which renders the atrium significantly less likely to fibrillate suggests that the influence of even advanced substrate surrogates in determining recurrence can be overcome by focal ablation.[128, 166, 245, 255, 267-273] Whole atrial activation, phase, frequency and organizational index mapping has identified the presence of rotor-like activity and focal high-frequency sources driving AF.[111-113, 123, 126, 128, 166, 277-283] Ablation of these domains acutely terminates AF,[128, 255] though with longer durations of AF these drivers become more numerous and acute termination is less frequent (75% and 15% of persistent and long-lasting AF terminated, respectively, >6 months cutoff).[128] Though their location varies between individuals,[123, 128, 255, 282] they are predominantly left atrial (70%), with the rest being right atrial (30%),[128, 255] and demonstrate relative spatiotemporal stability with most meandering over 5-10 cm^2 areas around the pulmonary antra, antrally-associated septum and appendage, or left inferior wall/coronary sinus,[128] consistent with earlier data identifying these as sites where ablation is most likely to terminate AF.[245] What determines the observed relationship to these critical areas is unknown[284] and likely involves interplay between individual variation in atrial and pulmonary ostial geometry,[285] fiber orientation and anisotropy,[286-288] fibrosis,[289-291] regional variation in autonomic innervation and tissue response to autonomic input,[83, 85, 86, 292] and geometrically governed variability in exposure to mechanical stress and pressure.[293-295] By imaging fibrosis using MRI, the likelihood of recurrent arrhythmia after ablation has been correlated to the extent of fibrosis left unablated, indicating that substrate modification works best when it targets such fibrotic areas, likely by converting proarrhythmic tissue with heterogenous fibrosis to homogenous inert scar.[230] A stepwise ablation approach also effectively reduces intrinsic scar burden,[296] indicating that both electrophysiologically and anatomically defined targets are likely co-localized. An approach tailored to targeting low voltage (<0.5mV) sites during sinus rhythm as areas representing fibrosis was recently shown to be feasible and associated with comparable outcomes to patients without any atrial scar.[297]

These data provide a mechanistic link between substrate, clinical characterization of AF and the observed responses to ablation. By identifying individual-specific mechanistic targets, providing novel insights into the role of atrial structural changes,[286-288, 291, 297, 298] better understanding why the currently established substrate modification strategies of linear and CFAE ablation sometimes demonstrate greater effect[128, 232, 271, 280, 299, 300] than at other times, [261, 274, 298, 301-303] these approaches raise the possibility that successful persistent AF ablation need not necessarily depend on standardized, extensive atrial compartmentalization or debulking by providing novel patient-specific ablation end-points,[126, 128, 230, 281, 297, 304] though this remains an area of ongoing investigation.

Electrophysiological Perspective 4 – Creating Effective Ablation Lesions: Endocardial vs. Epicardial Approaches

As with the endocardial approach, demonstrating effective conduction block across linear lesions is key to successful epicardial AF ablation.[29, 32] With viable myocardial strands as thin as 1 mm allowing for electrical propagation,[40] creating contiguous transmural lesions is the goal with both approaches and dependent on choice of ablation energy,[305] electrode and catheter design, interplay of biophysical response characteristics of targeted tissue and its related anatomy,[306, 307] including variation in atrial wall thickness regionally (thickest at the roof, mitral isthmus and left lateral ridge[308]) and between individuals (posterior wall 0.9 to 7.4 mm in one study),[309] atrial and pulmonary venous morphology[257, 310, 311] and associated vasculature.[257] The published hybrid ablation experience has thus far exclusively incorporated radiofrequency ablation (Table 2), which relies on current flow alternating at radiofrequency causing resistive tissue heating and depends fundamentally on electrode-tissue contact.[312, 313] Additional variables affecting lesion depth include power and duration of ablation,[314] electrode size and orientation,[315-317] electrode tip cooling to prevent surface char and coagulum allowing for deeper lesions,[318, 319] electrical tissue impedance,[314] and tissue heat sinks.[35, 306, 307, 320] Monitoring electrode contact force, temperature rise, impedance fall, and electrogram diminution allows real-time monitoring of lesion evolution surrogates and safe ablation,[313] though none of these parameters obviate the need for confirming conduction block.[29]

Despite these measures, and documentation of block acutely, conduction may recover and whether this is from tissue regeneration or incomplete ablation and reversible injury is unknown.[284] The latter is supported by data demonstrating that common locations of late recovery after endovascular catheter ablation are sites with known difficulty in maintaining catheter tissue contact (close to the pulmonary veins, left lateral ridge, mitral isthmus, accessory pulmonary veins or a common left pulmonary vein ostium);[50, 311, 321-323] electroanatomical correlation of gaps with measured tissue contact force;[322, 323] echocardiography[324] and contrast MRI showing evidence of reversible injury with edema which resolves on serial scans[205] with recovery over days to weeks, and incomplete scarring at ablation sites with conduction recovery;[203, 204] and histological evidence of non-transmural lesions in pulmonary veins that reconnect late after PVI.[325] In addition, outcomes are better when areas with reversible injury are re-ablated once identified after a 60-90 minute wait period[326] and/or adenosine,[326-328] ablating to unexcitability as a superior tissue endpoint to conduction block,[329] measuring and maintaining tissue contact force to deliver more effective lesions,[322, 330-332] and visually identifying gaps after electroanatomically tagging ablation lesions.[333, 334]

The specific additional challenges with an epicardial approach include constraints from mediastinal anatomy and pericardial reflections[335] in accessing individual-specific arrhythmogenic triggers and substrate; the increased proximity and risk of collateral injury to great vessels, coronary arteries, lungs, mediastinum, esophagus, liver, diaphragmatic vessels, and phrenic nerves;[335] how well suited catheter design is for navigation, maintaining tissue contact over the smooth epicardial convexity of the beating heart and safe delivery of ablation energy; how well matched the selected ablation energy is for the local tissue environment and characteristics;[305, 336] how to overcome endolumenal and intramural arterial heat sinks,[35, 306, 307, 320] the presence of epicardial coronary vessels at key linear lesion sites (mitral and cavotricuspid isthmus), and presence of epicardial fat which limits energy delivery to underlying myocardium[305, 306, 337] as well as independently influencing AF pathophysiology and recurrence after endocardial ablation.[338]

To overcome these challenges, minimally invasive surgical approaches have incorporated versatile access and catheter designs to facilitate controlled tissue manipulation and ablation. The bipolar radiofrequency clamp (Atricure, West Chester, OH) which is utilized for PVI with the bilateral thoracoscopic hybrid approach has favorable preclinical results,[36, 339] though a variable number

Table 3: Systematic Review of Hybrid Ablation Studies – Outcomes

First Author	No. patients	AF type: PAF/ PrAF/LSPrAF	Procedure time (min)	Hospital stay (days)*	Death (N)	Death or Major Complication (N)	Acute non-fatal thromboembolism (N)	Major Surgical Complications (non-embolic, non fatal) (N)	No. with minimum 12-month FU	Confirmation of AF recurrence	12-month AAD-free SR maintanance – All (N)	12-month AAD free FU for PAF (N)	12-month AAD free FU for PrAF/LSPrAF
Thoracoscopic Clamp-based Approach											88.1%	78.3%	88.2%
Mahapatra[57]	15	0/9/6	Both components: mean 450±20	median 5.0 (IQR 5.0–5.5)	0	0	0	None	14	7 day event monitor, AF >30 secs	13/14	-	13/14
Lee[56]	7	NA	NA	median 5 (IQR 4-6)*	0	1	0	1 prolonged ventilation postop*	NA	Continuous ECG monitoring (duration and criteria not stated) or pacemaker/ICD monitoring	(12/23)$	NA	NA
Pison[33]	26	15/10/1	Both components: mean 280±84	mean 7±2	0	2	0	1 pleural effusion requiring drainage, 1 surgical incision pain prolonging hospital stay	24	7-day Holter monitoring, AF/AT >30 secs	20/24	11/15	10/11
La Meir[62]	35	16/8/11	Both components: median 268 (IQR 186–477)	median 3.4 (IQR 2.6–4.1)	0	0	0	None	35	7 day Holter, AF/AT >30 secs	32/35	14/16	16/19
Kurfirst[63]	30	0/0/30	Surgical component: mean 210±30	mean 4.5±3	0	5	0	2 left pulmonary artery bleeding requiring sternotomy, 2 phrenic nerve palsies persistent at 12 months, 1 tamponade postop day 24 with overanticoagulation	0	7 day Holter, AF/AT >30 secs	(27/30 at mean 208±29 days)	-	(27/30 at mean 208±29 days)
Lee[64]	10	1/0/9	Surgical component: mean 221	median 12	0	3	1 stroke	1 reexpansion pulmonary edema and pneumonia, 1 pericardial effusion	0	Holter (duration not specified) AF/AT >30 secs	(10/10 at median 7.6 months [range 6.7 - 11.6]).	NA	NA
Pison[65]	78	29/34/15	NA	median 6 (IQR 5.5-8)	0	6	0	1 reoperation for bleeding, 1 bleeding not requiring reoperation, 2 pneumonia, 2 complete heart block requiring pacemaker implantation	78	7 day Holter, AF/AT >30 secs	68/78	22/29 (76%)	43/49
Thoracoscopic Encircling Catheter - based Approach											73.4%	60.0%	74.6%
La Meir[59]	19	5/4/10	Both components: median 216 (IQR 132–391)	median 3.6 (IQR 2.7–4.3)	0	0	0	None	19	7 day Holter, AF/AT >30 secs	7/19	3/5	4/14
Bisleri[60]	45	0/0/45	Epicardial component: mean 85±9	mean 3.9±1.4	0	0	0	None	45	ILR, AF>5 min or overall AF burden >0.5%	40/45	-	40/45
Subxiphoid Convergent Approach											59.3%	-	51.5%
Gehi[61]	101	17/37/47	NA	mean 4.4	2#	7	1 TIA	2 retroperitoneal bleeding, 2 tamponade	69	24 hour Holter, AF/ AT >30 secs	46/69	NA	NA
Gersak[66]	73	0/22/51	Surgical component: 112±38	NA	0	8	1 stroke	2 bleeding requiring sternotomy, 2 bleeding not requiring reoperation, 1 tamponade, 1 pericardial effusion, 1 pleural effusion	66	ILR (n=48/73) or Holter (24 hours or 7 days), criteria not stated	34/66	-	34/66

First Author	No. patients	AF type: PAF/ PrAF/LSPrAF	Procedure time (min)	Hospital stay (days)*	Death (N)	Death or Major Complication (N)	Acute non-fatal thromboembolism (N)	Major Surgical Complications (non-embolic, non fatal) (N)	No. with minimum 12-month FU	Confirmation of AF recurrence	12-month AAD-free SR maintanance – All (N)	12-month AAD free FU for PAF (N)	12-month AAD free FU for PrAF/LSPrAF
TOTAL**	432	83/124/225			2	32	3	27	350		260	50	160
% of TOTAL					0.5%	7.4%	0.7%	6.3%	81.0%		74.3%	76.9%	73.4%

*Excludes readmissions for delayed staged procedures; **Excludes 7 patients reported by Lee et al56 as results pooled with 18 patients undergoing non-hybrid minimally invasive AF surgery; $Data for all minimally invasive patients including 7 with hybrid and 18 with non-hybrid surgical ablation, with 12 month follow-up; #1 sudden death, 1 death from atrioesophageal fistula
PAF – Paroxysmal AF, PrAF – persistent AF, LSPrAF – long-standing persistent AF; NA - not available

of repeat applications (at least 3 and often more in clinical studies[29, 31]) are required to achieve block and reconnection gaps are increasingly prevalent over time from none when tested immediately[33, 65] to 12.5% after 4 days[64] and 87% of right and 77% of left pulmonary veins at 3 months.[63] Bipolar sources have been reported to create better lesions than monopolar sources with epicardial ablation.[340] Additional linear lesions created with the bipolar radiofrequency pen (Atricure, West Chester, OH), which again has good preclinical efficacy data,[34, 341] resulted in reconnection gaps in 14-36% of box lesions at immediate staged endovascular testing,[62, 65] 27% of roof and mitral isthmus lines at 4.3±1.3 days,[57] and 63% of roof and 40% of inferior lines at 3 months[63] even when bidirectional block was confirmed during epicardial ablation. To overcome limitations in mitral isthmus linear ablation from attempts to avoid coronary arterial injury,[58] some investigators connected the left fibrous trigone to the mitral annulus.[29] However, whether this has similar efficacy and propensity to disrupt focal drivers or reentrant flutters is unknown. Similarly, ablation lines across Bachmann bundle are hard to establish due to atrial thickness and results in inter-atrial dyssynchrony.[63] The bilateral thoracoscopic approach additionally allows visualized access to the epicardial ganglia, ligament of Marshall, and left atrial appendage, can protect or maneuver away from critical anatomical structures, but requires collapsing the lung and opening the pericardium on each side.

The right-sided thoracoscopic approach and convergent (posterior pericardioscopic) approaches utilize specially designed linear ablation monopolar RF catheters incorporating suction to increase tissue contact and optimize catheter stability (Estech Cobra Adhere XL, Atricure, West Chester, OH, and Numeris Guided Coagulation System with VisiTrax, nContact Surgical, Inc, Morrisville, NC, USA, respectively), allowing for less invasive access than the bilateral thoracoscopic approach. Both of these catheters performed less well than the bipolar clamp in preclinical studies.[34] However, with the encircling suction catheter (Estech Cobra Adhere XL), when applications were repeated until entrance and/or exit block in conduction to/from the posterior left atrium, block was maintained after 1 month at endovascular in all with bidirectional block and 25% with unidirectional block at epicardial ablation.[60] In contrast, when block is not tested for during epicardial application, almost all had conduction gaps during immediate-staged endovascular study.[59] The ablation line also abolished standardized ganglionic responses except at the right inferior ganglion, which was located outside the box lesion.[59] A limitation with the unilateral right-sided approach is lack of access to the left atrial appendage. The convergent approach avoids thoracoscopy altogether, utilizing laparoscopy to guide subdiaphragmatic posterior pericardioscopy.[55, 68] Space constraints limits placement of additional catheters for simultaneous electrophysiological monitoring and, although inferior and posterior left atrial surfaces are well visualized, the superior and anterior lesions need to be made without direct visualization and rely on knowing catheter angulation and orientation. Pericardial reflections lead to discontinuous lesions at both superior and right inferior pulmonary veins, necessitating routine endocardial touch-up lesions at these sites, whilst access to the ligament of Marshall, appendage and ganglia is limited and the esophagus is left more vulnerable than with the bilateral thoracoscopic approach.[55, 68] Although the other hybrid approaches have isolated the posterior left atrium, the convergent approach has focused on debulking this region. There are no data comparing the two approaches directly.

When electroanatomical mapping was not utilized to register lesions during epicardial ablation, techniques to correlate with the endovascular component during immediate staging involved leaving the epicardial ablation catheter in situ to correlate fluoroscopically or gently prodding epicardially at the ablation line whilst correlating endocardial catheter position with intravascular ultrasound.

Electrophysiological Perspective 5 – Cardiac Autonomic Ganglia as Targets during Atrial Fibrillation Ablation

An autonomic etiology for AF was first recognized with description of vagally-induced AF in 1978.[342] Pulmonary vein isolation has reduced efficacy in treating paroxysmal vagotonic AF,[80] whereas atrial vagal denervation can abolish it.[88] The importance of autonomic influences on AF is also evident from a reduction in AF recurrence following antral PVI when vagal responses (bradycardia, atrioventricular block, hypotension) are fortuitously elicited during radiofrequency ablation and abolished,[81] the increase in late AF recurrence in those with high serum titres of autoantibodies against the beta-1 adrenoceptor and M2 muscarinic receptor at the time of cryoballoon PVI,[96] and in the post cardiac transplantation population, whose denervated recipient hearts are relatively resistant to AF with 70% lower AF incidence than matched patients undergoing cardiac surgery with left atrial maze.[90]

The atria are richly innervated by autonomic nerves[343] and between 700-1500 epicardial ganglionated autonomic neuronal plexi are associated with the heart, though numbers decline by up to 50% with age, with complex circuits involving both parasympathetic and sympathetic components.[344] The atrial ganglia are primarily clustered at the superior right atrium, superior left atrium, posterior right atrium, posteromedial left atrium, and the inferolateral aspect of the posterior left atrium.[344] Following the demonstration in dogs that ganglionic stimulation induces calcium-mediated pulmonary vein triggers[345] and enhances trigger-induction of AF, with the opposite effects with ganglionic block,[292] studies began to focus on modifying local autonomic atrial input by targeting epicardial ganglia to improve outcomes of

catheter AF ablation[82] and surgical maze.[346] After validation of the technique in dog experiments, eliciting bradycardic responses and atrioventricular block at sites of high frequency atrial burst pacing has been used to map ganglionic cluster sites from the endocardium[82] with descriptions of five common left atrial sites (superior left, inferior left, ligament of Marshall, anterior right, inferior right).[86] Although some ganglionic sites may not elicit such a response yet still exert modulatory influence,[84] whilst surgical approaches are able to directly visualize these ganglia, elimination of the high frequency stimulation response may serve as a useful ablation end-point. Such ganglionic responses were shown to be present in 86% of 216 patients after antral PVI and predicted arrhythmia recurrence in patients with paroxysmal AF (51 vs 8% at >6 months) but not persistent AF (40 vs 39%), even though a higher proportion of persistent AF patients had positive ganglionic responses.[94] Ganglia may also co-localize with CFAE although the mechanism is not fully explained.[83, 85, 86]

There is currently no consensus on whether to routinely perform ganglion ablation during catheter ablation of AF.[347] A meta-analysis of six randomized trials (342 patients) concluded that ganglion ablation improves the results of catheter PVI or surgical maze in reducing freedom from AF recurrence, but as standalone therapy the outcome is inferior to PVI,[348] with similar results in a recent trial of 242 patients with paroxysmal AF (at 2 years, freedom from recurrence 74 vs 56 vs 46%, respectively).[92] In persistent AF, even though retained ganglionic responses after antral PVI may not predict AF recurrence,[94] trials of ganglionic ablation during both catheter ablation[91] and surgical maze[346] have reported positively on efficacy. Long-term outcomes are unknown, with dog data demonstrating the reappearance of ganglionic responses with time,[349] presumably due to axonal regrowth, whilst isolated ganglionic ablation (i.e. without PVI) may be paradoxically proarrhythmic.[350]

Electrophysiological Perspective 6 – Stroke Prevention and Left Atrial Appendage Closure

Stroke mechanisms in AF are complex and demonstrating a role for fibrillation independent to atrial myopathy and vascular disease is challenging as both not only predispose to AF but also to stroke risk with AF.[351] There are at present no randomized data demonstrating that AF ablation, whether surgical or catheter-based, reduces stroke risk. Although Cox et al reported a low incidence of stroke (0.7%) after the cut-and-sew maze procedure in 265 patients followed for 11.5 years,[352] the majority had low stroke risk at baseline and the study was non-randomized. The PRAGUE-12 trial randomized 224 patients undergoing cardiac surgery to concomitant maze or no maze, and reported 1-year stroke rates of 2.7 vs. 4.3% (p=0.319).[239] Overly aggressive atrial compartmentalization and debulking may paradoxically increase stroke risk by rendering the atrium without contractile activity despite restoration of sinus rhythm, mitigating any benefit.[353] In a large, unselected catheter ablation cohort, 2% developed stroke after 1,347 patient-years follow-up, with no significant difference when sinus rhythm was maintained, though the study was probably underpowered as most patients had low baseline stroke risk.[175] A study of 4,212 patients who underwent AF ablation reported reduced risk of stroke, death and dementia compared to 16,848 age-gender matched controls with AF but no ablation, with similar rates to 16,848 age-gender matched controls without AF.[354] The results of the CABANA trial (clinicaltrials.gov/ NCT00911508), which aims to study the effects of catheter ablation on mortality, stroke and bleeding as compared to drug therapy, are awaited.

Recent advances in cardiac imaging have allowed an appreciation that morphological complexity of the LAA significantly influences thromboembolic risk, supporting a structural approach to thromboprophylaxis.[355] The efficacy of this approach was demonstrated by the WATCHMAN trial of percutaneous LAA occlusion.[356] A meta-analysis of 7 studies including 3,653 patients undergoing appendage closure (n = 1716) versus not (n = 1937) at the time of cardiac surgery reported a significantly reduced stroke incidence with closure (0.95 vs 1.9% at 30 days, 1.4 vs 4.1% at last follow-up) and reduced mortality (1.9 vs 5%).357 Surgical approaches, however, have been limited by incomplete closure, with surgical amputation and oversewing yielding highest maintained closure rates.[351] Results of the LAAOS III trial (clinicaltrials.gov/ NCT01561651), which plans to randomize 4,700 patients undergoing cardiac surgery to LAA occlusion or no occlusion, are awaited. A number of minimally invasive approaches have been developed, using either suture or clip exclusion or staple excision, though none have yet been proven to reduce stroke.[351] In addition, LAA exclusion may not be regarded as a panacea for stroke reduction in AF, as vascular mechanisms may coexist and thrombi are more likely to be extra-appendicular in valvular AF patients.[358] There are also hemodynamic sequelae which are in keeping with loss of its compliance and atrial booster function.[359, 360] In addition to modulating stroke risk, appendage ligation or excision results may serve as a form of substrate modification[361] by reducing atrial mass[118] and eliminating appendage triggers and drivers,[362, 363] whereas electrical isolation without mechanical closure may paradoxically increase stroke risk through appendage blood stagnation.[364]

Electrophysiological Perspective 7 – Hemodynamic Impact of Atrial Fibrillation Ablation

In the majority of individuals, restoration of sinus rhythm with ablation leads to significant improvement in left ventricular function, effects that extend beyond rate control,[11, 365, 366] even when baseline ejection fraction is normal,[367] with improvements also reported after surgical maze.[368] Restoration and maintenance of sinus rhythm results in reverse atrial remodeling[8, 369, 370] and similar effects are seen after surgical maze,[371] although with time these effects can subsequently reverse[372] and it is unclear whether this is due to the maze procedure itself or persistent risk factors leading to progressive atrial myopathy. Without the expected benefits of reverse atrial remodeling from immediate restoration of sinus rhythm, such as those with paroxysmal AF and low arrhythmia burden, a reduction in atrial contractile function is seen after maze, more so with more extensive ablation (new left atrial dysfunction 8.5% after PVI compared to 30% after additional linear ablation).[373] Surgical maze may result in reduced atrial compliance which can cause severe, symptomatic pulmonary hypertension ("stiff left atrial syndrome").[374] This has also been reported after catheter ablation in 1.4% of 1,380 patients, predisposing factors being smaller pre-procedural left atrial size (≤45mm), preexisting left atrial hypertension, increased baseline left atrial fibrosis, diabetes mellitus and obstructive sleep apnea.[375]

Electrophysiological Perspective 8 – Critical Appraisal of the Role of Hybrid Ablation in Improving Outcomes from Atrial Fibrillation Ablation

Outcome from Hybrid Ablation of Atrial Fibrillation: Results of

Systematic Review

Published success rates from hybrid ablation (Table 3), defined as maintained sinus rhythm off antiarrhythmic medications at 12 months, are 74.3% overall (data available for 81% [350/432]), 76.9% for paroxysmal (data available for 76% [65/83]) and 73.4% for persistent / long-standing persistent AF patients (data available for 62% [218/349]). Methods used to detect recurrence varied from a 24-hour Holter monitoring at prespecified follow-up intervals to continuous ECG monitoring using implantable loop recorders or pacemakers and defibrillators (Table 3). Success rates differed significantly among the three approaches (Table 3}, with highest rates reported with the bilateral thoracoscopic clamp-based approach (88.1% [133/151]), intermediate with the unilateral thoracoscopic suction encircling catheter-based approach (73.4% [47/64]) and lowest with the convergent approach (59.3% [80/135]), p<0.001). The difference in the proportion of patients with long-standing persistent AF (37% [72/205]), 86% [55/64] and 56% [98/174] respectively, p<0.001) may partly account for some of this difference in outcome (Table 3). However, when data were available, success rates in patients with persistent and long-standing persistent AF were similar to overall success rates (88.2% [82/93], 74.6% [44/59] and 51.5% [34/66] respectively, p<0.001). There was limited separately reported 12-month data for paroxysmal AF patients (78.2% [47/60], 60.0% [3/5], no data for convergent procedure, p=0.325).

Major complications (Table 3) were death (n=2, both with convergent approach), thromboembolic (n=3, of which 2 were with convergent approach, none fatal) and non-thromboembolic complications (n=27), consisting of 10 thoracic or retroperitoneal bleeds with or without rescue sternotomy, 6 tamponade/pericardial effusion, 2 complete heart block requiring pacemaker implantation, 2 phrenic nerve palsy, 2 pleural effusion, 4 respiratory complications and 1 with incisional pain delaying hospital discharge. Rate of death or non-fatal major complications were 7.4% overall, 8.5% with the bilateral thoracoscopic clamp-based approach, 0% with the thoracoscopic suction encircling catheter-based approach and 8.6% with the convergent approach (Table 3). Average length of hospital stay, when reported, was between 3.6 and 7 days (average for the three different approaches 5.6 vs. 3.8 vs. 4.4 days respectively, Table 3).

Hybrid Ablation vs. Sequential Catheter Ablation

For endovascular catheter ablation of paroxysmal AF, 18-month freedom from arrhythmia recurrence and antiarrhythmics was reported in 75% of 9,590 patients in a worldwide survey of 182 centers from 24 countries treated between 2004-6.376 Results at 5 years are 47-78% after the first procedure[99, 176, 177] and 75-92% after repeat procedures.[99, 100, 176, 177] In most cases, recurrence is due to recovered conduction at a prior ablation site.[99, 177] A 12- to 24-month success rate of 73-92% has been reported from contemporary catheter ablation techniques to prevent late reconnection of pulmonary veins, which include using a force-sensing catheter (SmartTouch, Biosense Webster, Inc., Diamond Bar, CA) to ensure adequate contact force during ablation, a second generation cryoballoon catheter designed for better contact and surface temperature distribution (Arctic Front Advance, Medtronic, Minneapolis, MN), using failure to capture as an ablation endpoint, and incorporating a wait period and adenosine to identify reversible injury and unmask latent conduction.[326, 329, 331, 377-379] It is unknown whether these strategies will be subject to similar rates of late attrition in success seen with earlier approaches.[177]

With persistent and long-standing persistent AF, endovascular catheter ablation yield sinus rhythm maintenance off antiarrhythmic medication in 35-77% at 12 months after a single procedure[122, 129, 238, 240, 242] and 64-79% at 18-24 months after repeat procedures.[129, 242, 243, 376] Patients with persistent and long-standing persistent AF have a higher rate of late attrition than with paroxysmal AF,[380] with reported 5 year success rates of 45-81%.[99, 129, 381, 382]

Complications of endovascular catheter AF ablation were seen in 6.3% of an estimated 93,801 procedures performed between 2000-10 in the National Inpatient Sample database.[383] Complications were cardiac in 2.5%, including 1.5% pericardial and 0.3% requiring rescue cardiac surgery, respiratory in 1.3%, postoperative hemorrhage in 3.4%, vascular complications in 1.5%, and neurological (thromboembolic) in 1%. In-hospital mortality was 0.5%. In the California State Inpatient Database, complications after first AF ablation between 2005-8 were seen in 5% of 4,156 patients, most commonly vascular.[384] The world-wide survey reported major complications in 4.5% of 20,825 catheter ablation procedures on 16,309 patients between 2003-6.376 Complication rates were low in other large cohorts with patients undergoing multiple procedures (3.3% of 1,404 patients, 20% had repeat ablation;[99] 5.2% of 1,220 patients, 27% had repeat ablation176). Rates of pulmonary vein stenosis are 0.3-1.3% and atrio-esophageal fistula are 0-0.04%.[99, 176, 376] Studies reporting on the second generation cryoballoon ablation have reported higher rates of right phrenic nerve palsy (3.5-5.6%) than catheter radiofrequency ablation.[378, 379] Cost-effectiveness analyses of endovascular catheter ablation in various developed countries' healthcare models have demonstrated reasonable cost-effectiveness in patients who have paroxysmal AF, with improved quality of life and avoidance of future health care costs,[385,386] including when utilized as a first-line approach in younger patients,[387] although are sensitive to AF recurrence rates and impact on stroke risk.[388-393]

The FAST trial compared bilateral thoracoscopic epicardial ablation to endovascular catheter ablation, randomizing 124 patients with drug-refractory non-valvular AF (67% paroxysmal, 33% persistent, CHADS2 of 0 or 1 in 90%) to either surgical PVI using a bipolar radiofrequency clamp with intraoperative confirmation of block, LAA staple excision, ganglionated plexi ablation, ligament of Marshall transection and optional additional linear ablation (31%), or endovascular antral radiofrequency PVI with optional additional linear ablation (50%).[394] More patients in the surgical group were free from recurrent atrial arrhythmia off antiarrhythmics at 12 months (overall: 66 vs 37%, p=0.002; paroxysmal AF: 69 vs 35%, p=0.005; persistent AF: 56 vs 36%, p=0.341). It is unclear whether the difference in success was due to more durable lesions or the more diverse ablation targets with surgical ablation, but the results should be interpreted in light of the higher proportion with persistent AF in the endovascular catheter ablation group (41 vs 21%) and lower success rate of catheter ablation in comparison to the published contemporary data above, particularly with paroxysmal AF. There were more frequent procedural complications (23 vs 3.2%) and fewer thromboembolic events at 12 months (0/61 vs 2/63), with surgical ablation preventing an arrhythmia recurrence for every 3.4 and causing an additional complication for every 5.1 procedures.[394] The procedural complication rate was higher than that of the published hybrid ablation literature summarized above (7.4%).

To compare hybrid ablation with repeat catheter ablation, Mahapatra et al[57] matched their hybrid ablation group of 15

persistent and long-standing persistent AF patients to a control group of 30 long-standing persistent AF patients undergoing repeat catheter ablation, matching for left atrial size, duration and type of AF, lack of prior cardiac surgery, left ventricular ejection fraction and use of antiarrhythmic medications. The hybrid group had bilateral thoracoscopic clamp-based approach with delayed staged endovascular ablation at 4.3±1.3 days, multiple linear ablation sets, ganglion ablation, ligament of Marshall ablation, LAA excision, coronary sinus ablation and CFAE ablation. The catheter ablation group all had antral isolation, roof line, cavotricuspid isthmus line and optional mitral isthmus line (17 cases), coronary sinus ablation (9 cases), SVC isolation (11 cases) and CFAE ablation (12 cases). After a mean follow-up of 21 months, 87% (13/15) of hybrid ablation and 53% (16/30) of catheter-alone patients were free of atrial arrhythmia off antiarrhythmics. Repeat ablation was performed in 0/15 hybrid ablation and 3/30 catheter-alone patients.

In summary, the fundamental principle underlying hybrid ablation in assessing the eletrophysiological effects of lesions and ensuring that targets are ablated to specific endpoints to improve outcomes is incontrovertible. However, there is limited evidence supporting the concept that a multidimensional intervention targeting all possible arrhythmia mechanisms for all patients in the same sitting will result in superior results, even when these lesions are reinforced from both epicardial and endocardial sides to maximize the chances of sustained conduction block. Hybrid ablation procedures are associated with increased complications and longer post-procedural hospital stay, whilst cost-effectiveness studies have been limited by the lack of long-term outcome data. [395] Studies directly comparing hybrid with endovascular catheter ablation have had small numbers, differences in patient characteristics and ablation targets, variable periprocedural antiarrhythmic and anticoagulant management, different methods for identifying recurrence arrhythmia, and have not incorporated recent advances in endovascular ablation practice offering more durable lesions or better identifying individual-specific mechanistic targets, an understanding of which has implications on long-term tailored approaches. Outcome data from contemporary endovascular catheter approaches suggest similar success rates to hybrid ablation, both for paroxysmal and persistent patient groups, particular when repeat catheter ablations are accounted for. When considering the hybrid approach, matching intervention to mechanism is key for identifying targets, ablation endpoints, and the specific advantage over the endovascular approach for the patient at hand, balanced against the increased procedural complexity, more complications some of which are life-threatening, and longer hospital stay.

Hybrid Ablation vs. Cut-and-Sew Maze

Since the first description of the ablation-assisted open surgical maze yielding similar short-term outcomes to the traditional cut-and-sew technique, 5 others have reported that the traditional approach yields superior long-term outcomes, with hazard ratio for recurrent arrhythmia of 0.40 up to 5 years and 0.23 beyond 5 years.[396] In a meta-analysis of 16 randomized trials, the cut-and-sew approach was associated with higher sinus rhythm prevalence and lower stroke rates outcome compared to ablation-assisted approaches.[397] Lee et al compared 25 hybrid ablation patients (bilateral thoracoscopic clamp-based) to 38 cut-and-sew maze patients and reported 1 year freedom from AF and antiarrhythmic medication in 52% and 87.5%, respectively (p=0.004), even though the cut-and-sew group had more with long-standing persistent AF (40 vs 16%).56 However, in their hybrid group, only 7 patients followed through with the endovascular catheter ablation component. There were more frequent complications in the cut-and-sew group (18 vs 4%). A systematic review comparing minimally invasive endocardial Cox-maze, minimally invasive epicardial ablation and hybrid ablation reported operative mortality at 0%, 0.5% and 0.9%; perioperative permanent pacemaker implantation in 3.5%, 2.7% and 1.5%, rescue median sternotomy in 0%, 2.4% and 2.5%, reoperation for bleeding in 1.0%, 1.5% and 2.2%, mean length of stay of 5.4, 6.0 and 4.6 days, and 12-month maintenance of sinus rhythm off antiarrhythmics in 87%, 72% and 71%, respectively.[28]

Immediate vs. Delayed Staged Hybrid Ablation

There is limited published data allowing direct comparison of immediate to delayed staging of the endovascular component of hybrid ablation. Immediate staging requires a laboratory hosting both surgical and electrophysiological setups, careful management of intraprocedural anticoagulation with transeptal and endoscopic accesses, and the available time and resources to complete both interventions in the same sitting. Delayed staging, where endovascular testing and ablation has been performed days to months after minimally invasive epicardial ablation, allows healing of the surgical wounds and time for reversible injury from ablation to abate and reconnections to establish, and has been shown to increase the likelihood of discovering PV reconnection during endocardial mapping versus a same day procedure (48% vs 14%).[398] It can be performed in separate surgical and electrophysiological laboratory setups. Patients may prefer a procedure where both components are completed in the same sitting or during the same hospitalization.

Future Directions

Atrial fibrillation ablation offers considerable benefits to patients towards symptom control and quality of life improvement.[75] The multiplicity and progressive nature of AF mechanisms and recovery of conduction may account for progressive attrition in maintaining sinus rhythm with long-term follow-up.[129, 380] The pioneering developments that have led to the various hybrid ablation approaches are an opportunity in properly selected patients without having to recourse to open heart surgery. The choice of procedural approach utilized for hybrid ablation is important, given the difference in possible lesion sets, success rates, complications, adjunctive LAA closure and access to adjunctive ablation targets. However, randomized trial data are lacking and long-term efficacy is unproven. The PRHACA (Prospective, Randomized Comparison of Hybrid Ablation vs. Catheter Ablation) trial (clinicaltrials.gov/NCT02344394) is an investigator sponsored trial which is currently recruiting patients with persistent AF to test the nContact system (convergent approach). The CONVERGE (Epi/Endo Ablation For Treatment of Persistent Atrial Fibrillation) trial (clinicaltrials.gov/NCT01984346) is an industry sponsored trial which is also recruiting persistent AF patients to test the nContact system. The SCALAF trial (clinicaltrials.gov/NCT00703157), which aims to compare efficacy of minimally invasive surgical and catheter-based PVI, is underway. Another active trial (clinicaltrials.gov/NCT02392338) is comparing hybrid ablation with minimally invasive thoracoscopic ablation alone in persistent AF.

A promise of progress comes from an improved understanding of how anatomical substrate relates to electrophysiological observations, better catheters and mapping technologies, novel energy sources, adequate management of recurrences, and identifying and treating

underlying clinical risk factors. Whether hybrid ablation will add to this remains to be seen. In the absence of robust efficacy data, and given the increased risk of complications, associated morbidity and length of hospital stay as compared to catheter ablation, caution should be exercised in adopting this approach universally. The present data suggest that, perhaps, with appropriate patient selection, accurate identification of patient-specific mechanisms and targets, and selection of optimal access to maximize anatomical vantage to these targets, this novel approach may have a role in specific situations. It may be better suited as a concomitant procedure during cardiac surgery for other reasons, for example patients requiring thrombectomy or LAA closure. Alternatively, it may help translate novel therapeutic pathways to practice, such as controlled delivery of genetic vectors influencing arrhythmia mechanisms[399-401] or humeral mediators governing response to injury.[402-404]

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Atrial Fibrillation in Cardiac Sarcoidosis

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Abstract

Sarcoidosis is a systemic granulomatous disease that affects the myocardium. Although ventricular arrhythmias are well known manifestations of cardiac involvement, there is increasing evidence that a significant proportion of patients with cardiac sarcoidosis (CS) also have atrial arrhythmias, atrial fibrillation being the most frequent. The incidence and mechanism of atrial fibrillation in CS is not precisely known. The management of atrial fibrillation in patients with CS is currently done according to the general guidelines for management of atrial fibrillation. Evidence is emerging regarding the additional role of immunosuppression for the treatment of atrial arrhythmias in CS. This paper reviews the incidence, possible mechanisms and treatment strategies of atrial fibrillation in patients with CS.

Incidence and Diagnosis

Sarcoidosis is a granulomatous disease that affects predominantly the lungs of young adults aged 25-45 years and to a lesser extent other organs, including the heart. The annual incidence of sarcoidosis in the United States has been estimated to be 10.9 per 100,000 in whites and 35.5 per 100,000 in African Americans.[1] The prevalence of CS varies significantly depending on the population studied and methodology used for detection. In a series of 40 patients with systemic sarcoidosis, 17 out of 31 asymptomatic patients (54.8%) had subclinical cardiac MRI abnormalities,[2] while in another series from the Netherlands, only 3 of 82 (3.7%) asymptomatic patients with pulmonary sarcoidosis had CS.[3]

Therefore the screening and diagnosis of CS represent a challenge for the clinician. A definite diagnosis of CS is made through the presence of non-caseating granulomas on histological examination of myocardial tissue with no alternative cause (negative organismal stains). A myocardial biopsy is not often performed. For most cases the diagnosis of CS is "probable" using the expert consensus criteria which consist of the pesence of a histological diagnosis of extracardiac sarcoidosis in addition to one or more of the following: steroid +/- immunosuppressant-responsive cardiomyopathy or heart block, unexplained reduced LVEF (<40%), unexplained sustained (spontaneous or induced) VT, Mobitz type II 2nd degree or 3rd degree heart block, or a pattern consistent with cardiac sarcoidosis on cardiac PET, cardiovascular magnetic resonance (CMR) or gallium uptake study.[4] The three major manifestations of CS are

1. conduction abnormalities,
2. ventricular arrhythmias, and
3. heart failure, yet supraventricular arrhythmias are frequently seen in patients with CS.

The exact incidence of atrial fibrillation in CS is difficult to know, as a proportion is undetected due to lack of symptoms. Cain et al., in a recent study, examined 192 consecutive patients who underwent CMR. Atrial arrhythmias were documented more frequently than ventricular arrhythmias in patients with sarcoidosis with cardiac involvement and were 3 times more prevalent than in patients with sarcoidosis without cardiac involvement.[5] In a series of 100 patients with confirmed CS reported by Viles-Gonzalez et al., the prevalence of supraventricular arrhythmias was 32%.[6] Atrial fibrillation was the most common arrhythmia (18%), followed by atrial tachycardia (7%), atrial flutter (5%), and other supraventricular tachycardias (2%).[6] In study reported by Betensky at al., of 45 patients with CS and an implantable cardioverter-defibrillator (ICD), 6 patients (13.3%) received inappropriate ICD therapies mostly representing atrial fibrillation.[7] However, it is likely that not all episodes of atrial fibrillation led to defibrillator shocks, so the true prevalence may be higher.

Mechanism

The cause of atrial fibrillation in patients with CS is likely due to granulomatous involvement of the atrium leading to inflammation and scarring, and raised end-diastolic pressures from sarcoid involvement of the lung and left ventricle. In a landmark study

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Atrial Fibrillation, Outcomes, Arrhythmia Control, Cardiac Sarcoidosis, Sarcoidosis.

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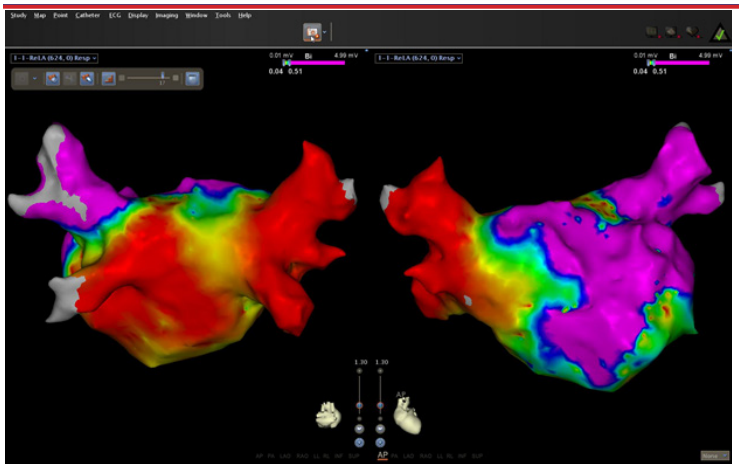

Figure: 1 **Postero-anterior and anterior-posterior views of electro-anatomical voltage map of the left atrium (CARTO) in a 45 year old patient with paroxysmal atrial fibrillation prior to ablation. Left atrial appendage is not included. There is extensive atrial scar represented by areas of low voltage. Purple areas had voltage above 0.5 V rest of the left atrium had voltage <0.5V, red areas <0.05 V and thus represent atrial scar**

examining the clinical and autopsy findings of 113 hearts with CS, granulomas were detected in the left ventricle in 97% and in the atria in 22% of patients with symptomatic CS. Of note, 15 out of 89 patients (17%) in this study had atrial arrhythmias.[8]

While it is plausible that granulomas in the left atrium lead to scarring and the development of atrial fibrillation, there are other factors that contribute to the development of atrial arrhythmia. Left atrial enlargement (LAE) secondary to LV dysfunction is believed to be a contributing factor. In data from our center reported by Viles-Gonzalez et al, the incidence of supraventricular arrhythmias among patients with and without LAE was 267.8 and 38.3 per 1,000 person-years, respectively (RR, 6.99; 95% CI, 3.31-14.77).[6] Among the variables studied in a multivariate analysis, LAE was the only variable associated with atrial arrhythmias. Age, race, gender, systolic and diastolic ventricular dysfunction, presence of pulmonary sarcoidosis, right atrial enlargement, mitral valve disease, systemic and pulmonary hypertension or use of steroids/immunosuppressant were not significant. In a recent report using speckle tracking echocardiography, left and right atrial reservoir functions were significantly lower in CS patients compared to controls.[9] This report suggests that atrial mechanical function is impaired early in patients with CS before left ventricular dysfunction is seen on conventional echocardiography. The role of inflammation in the genesis of AF in these patients has been supported by a number of case series, in which glucocorticoids significiantly reduced patients' arrhythmic burden.[10] Data from our laboratory has suggested that pulmonary vein triggers may also play a causal role:4 out of 5 (80%) CS patients with AF who underwent pulmonary vein isolation were free from recurrent AF at a median follow up of 18 months.[11]

Treatment

As discussed above CS is thought to cause atrial arrhythmias through two primary mechanisms:

1. sarcoid infiltration of the lungs and ventricles, leading to elevated end-diastolic pressure and atrial remodeling, and

2. direct granulomatous infiltration of the atria themselves, resulting in inflammation and fibrosis.[12,13] Treatment of elevated filling pressures centers on the use of cardiac-specific drugs for the management of systolic and diastolic dysfunction, and anti-arrhythmic drugs for control of symptomatic arrhythmia. While no single anti-arrhythmic drug strategy is favored, it is recommended that class IC agents generally be avoided due to the high incidence of myocardial scar in this population.[4] Management of myocardial sarcoid infiltration has largely employed the use of immunosuppressive therapy, though such treatment has never been assessed in a clinical trial format. As a result, choice of immunosuppressive agent, dose and duration remains widely variable in the treatment of CS.

Immunosuppression

In the Delphi Study, which sought to establish an expert consensus on the diagnosis and treatment of CS, it was found that clinical management varies widely among physicians. More than three-quarters, however, agreed that immunomodulatory therapy should be instituted on the basis of ventricular dysfunction or arrhythmia, or a positive FDG-PET scan. The majority indicated that they would treat CS in the presence of conduction abnormalities or a positive MRI. Prednisone was widely the treatment of choice, though there was no particular agreement on strength or duration of therapy.[14]

Data on the use of corticosteroids for the treatment of CS has centered predominantly on the amelioration of ventricular arrhythmia, conduction block, and LV dysfunction; its use for treatment of atrial arrhythmia is largely extrapolated from such studies.[15-19] A systematic review by Sadek, et al., identified 10 retrospective studies examining the utility of steroids in CS.[20] All studies included had involved at least three patients with at minimum three months of follow up. Of those patients presenting with CS-related conduction disease, 47% showed improvement in conduction after initiation of steroids. None of the 16 patients with conduction disorders who did not received steroids improved.[15,17,19,21-23] Four studies have examined the effect of steroids on LV dysfunction, noting preservation or improvement in patients with normal or mild-to-moderate LV dysfunction, respectively.[15,17,19,24] Those subjects with severe LV dysfunction failed to derive any benefit, perhaps a reflection of the degree of disease progression. Data on the use of corticosteroids in ventricular arrhythmia has been similarly encouraging, though its use in both studies was confounded by the concomitant administration of anti-arrhythmic drugs.[19,25]

Dose and duration of corticosteroid therapy remains poorly established. Most studies have recommended initiation of prednisone at 1 mg/kg per day. However, retrospective review of CS patients managed on high dose (>30 mg/day) versus low dose (<30 mg/day) prednisone showed no difference in outcome, raising the possibility that CS flares can be effectively managed on lower doses of corticosteroids, thus mitigating the many side-effects of intensive steroid therapy.[18] Most experts at this time favor an early period of intensive prednisone therapy (approximately 0.5 mg/kg), followed by slow titration to a minimum suppressive dose (typically 5-10 mg/day).[14] This dose is maintained indefinitely, as there are several worrisome reports of sudden death following complete cessation of steroid therapy.[26]

Steroid-sparing immunosuppressants, including methotrexate, hydroxychloroquine, cyclophosphamide, and azathioprine, have been employed with varying degrees of success.[27,28] Though their use in pulmonary sarcoidosis has become well established, data regarding their efficacy in the treatment of CS remains scarce. They are typically employed when steroid therapy becomes limited by side effects, or as an adjunct to low-dose steroid therapy.

Studies directly examining the role of corticosteroids in CS-related atrial arrhythmia are limited to case reports and small series.[10,29-31] In each case, steroids either eliminated or significantly reduced the burden of atrial arrhythmia in patients refractory to anti-arrhythmic therapy and, in one case, catheter ablation. It may stand to reason that reduction of myocardial inflammation and improvement in left ventricular function would have a moderating role on arrhythmic burden in the atrium in much the same way it does in the ventricle, though this hypothesis requires further validation in larger studies.

Catheter Ablation

Research on the role of catheter ablation in the treatment of CS has focused primarily on ventricular tachycardia, in which the majority of arrhythmia is caused by macro-reentry around areas of granulomatous scar. Studies have consistently shown reasonably high procedural non-inducibility with somewhat more measured long-term success rates.[32-34]

While more limited, data regarding the treatment of atrial arrhythmia using catheter ablation has also shown some promise. Abnormal automaticity, triggered activity, and macro-reentry have all been described in non-AF atrial arrhythmia.[11,35] In our group's published experience, 9 patients with CS underwent catheter ablation—2 for paroxysmal AF, 3 for persistent AF, 1 for cavotricuspid isthmus-dependent flutter, 2 for atypical flutters, and 1 for both CTI-dependent flutter and paroxysmal AF. Mean follow up was 1.8 ± 1.9 years. In the patients with paroxysmal AF, programmed stimulation with and without isoproterenol infusion failed to identify atrial triggers. Both underwent circumferential pulmonary vein isolation (PVI), and remained free from recurrence at follow up. In the patients with persistent AF, bipolar voltage mapping revealed a small area of low voltage in the septal area in one patient and diffuse, extensive left atrial scar in another (figure). Both underwent PVI and complex fractionated atrial electrogram (CFAE) ablation. The remaining patient with persistent AF had minimal atrial scar and had PVI alone. One patient had subsequent recurrence and was started on anti-arrhythmic drug therapy with good response. Microreentrant circuits were seen originating from the septum and left atrial anterior wall in the patients with atypical flutters and were successfully ablated.[11]

The success of PVI in those patients with AF suggests a causal role of the pulmonary veins despite the diffuse nature of CS. However, not all patients underwent electro-anatomical mapping to define the extent of left and right atrial scar; further study of atrial scar burden in these patients would help better define the nature of atrial arrhythmia in CS patients.

Anticoagulation

Patients with sarcoidosis may be at increased risk of venous thromboembolism, suggesting a hypercoagulable state.[36] It remains unknown whether CS patients with AF are at increased risk of LA thrombosis beyond traditional risk factors. Further, the efficacy of novel oral anti-coagulants (NOACs) in CS patients with AF has not been studied. At present the use of anti-coagulation, including NOACS, for CS patients with AF is suggested on the basis of the CHA2DS2-VASC score as is done for non-valvular AF, in keeping with current guidelines.[4]

Treatment Recommendations

Given the prevalence of atrial fibrillation in the general population, the diagnosis of CS cannot be made on the basis of the presence of atrial arrhythmias alone. Further, identifying the presence of inflammation or scar within the atria is limited using current imaging modalities, though progress in this area is ongoing.[37] The routine use of immunosuppression for the treatment of atrial arrhythmias as the sole manifestation of cardiac sarcoidosis is therefore not recommended. Rather, we recommend that a trial of immunosuppression may be considered in the presence of a confirmed or probable diagnosis of CS as defined by the 2014 HRS Consensus Statement.[4]

At this time, data on catheter ablation in CS remains too limited to recommend a distinct ablation strategy in these patients. It is encouraging, however, that routine PVI offered high rates of freedom from recurrent arrhythmia at medium-term follow up. It is thus our recommendation that catheter ablation employing PVI (with or without the addition of ancillary therapies) be offered to patients with symptomatic AF despite medical therapy.

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Routine Implant of Biventricular Devices Guided by an Electroanatomic Mapping System - Ready for Prime-Time?

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Abstract

Biventricular devices play an important adjunctive role in the treatment of heart failure. However, biventricular device implantation is associated with significant radiation exposure and a high proportion of non-response to cardiac resynchronization therapy (CRT). The use of electroanatomic mapping (EAM) during biventricular device implantation may help overcome these issues. This article will review the literature on the role of EAM in biventricular device implantation.

Introduction

Cardiac resynchronization therapy (CRT) with an implantable cardioverter-defibrillator (ICD) plays an important role in reducing heart failure morbidity and improving survival in patients with severe left ventricular (LV) dysfunction, intraventricular conduction delay, and heart failure symptoms despite optimal medical therapy. However, there are still significant limitations to this therapy. For one, biventricular device implantation may be associated with significant radiation and contrast exposure. In addition, approximately 30% of patients do not experience improvements in heart failure symptoms or LV function with CRT.[1] Optimizing the degree of response to CRT is complex as multiple factors influence the result, and not all are completely understood.

Electroanatomic mapping (EAM) is a method most commonly employed in the electrophysiology laboratory for the assessment and ablation of tachyarrhythmias. However, in recent years, there has been increasing use of this technology for the implantation of cardiac resynchronization devices. One use of this technology has focused on defining relevant anatomy to aid in the implant, in order to potentially reduce the delivery of radiation and contrast. Another usage is to potentially improve the selection of left ventricular pacing targets. One possible explanation for the nonuniform response rates is suboptimal lead placement with current anatomically based methods. Mapping has demonstrated the heterogeneous ventricular activation patterns amongst patients,[2, 3] and EAM has been explored as a means of defining the site of optimal LV lead positioning. This article reviews the uses of EAM in biventricular device implantation.

Key Words:

Sleep Apnea, Atrial Fibrillation, CPAP, Outcomes, Arrhythmia Control.

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Uses of Electroanatomic Mapping and Potential Benefits

The clinical utility of the 3-dimensional EAM system was first reported nearly two decades ago.[4] The advantages of the use of EAM over conventional mapping during electrophysiology studies and complex arrhythmia ablation procedures include its non-fluoroscopic capability and high spatial resolution, thereby leading to reduced procedural time and radiation exposure, as well as improved outcomes. Based on these advantages, it is therefore intuitive that EAM may also aid in device implantation, and more particularly in cardiac resynchronization therapy.

Use of Electroanatomic Mapping in Reducing Radiation Exposure

Reduction in radiation exposure during device implantation is beneficial not only to the patient, but also to the operator and support staff. Despite the widespread use of EAM systems as an adjunctive tool in electrophysiology procedures, its use during device implantation has remained more limited. Pacemaker implantation and atrioventricular node ablation without fluoroscopy was first reported by Ruiz-Granell et al. using the EAM (EnSite NavX) system.[5] This was subsequently followed by a case series involving 15 consecutive patients who underwent single chamber pacemaker implantation using the EAM system.[6] These patients were compared to retrospective data from 15 patients who underwent pacemaker implantation by conventional (fluoroscopic) means, acting as a

Table 1: Summary of studies on device implantation using electroanatomic mapping to reduce radiation exposure

Study	Device type	Details	Results
Ruiz-Granell et al.[6]	Single chamber pacemaker	15 consecutive patients vs. retrospective series of 15 control patients. Only passive leads were used.	Total implant time was 59.3±15.6 mins in the EAM group vs. 51.5±12.3 mins for control group (p = 0.14). In EAM group, 14/15 patients had no fluoroscopic exposure, 1 had lead dislodgement.
Del Greco et al.[7]	CRT-defibrillator	Cases series involving 4 patients. No control group.	Learning curve evident, with procedural times decreasing from 168 to 124 mins, and fluoroscopy times decreasing from 16.8 to 4.2 mins. Fluoroscopy also used for coronary sinus venogram.
Mina et al.[8]	CRT	10 consecutive patients vs. retrospective series of 10 control patients. EAM group used printed venous phase of prior coronary angiograms to help identify target veins, and decapolar catheter via the right internal jugular vein to obtain anatomy.	EAM group had markedly reduced fluoroscopic times (13.6 vs. 1.5 mins, p < 0.001), reduced use of contrast (54.9 vs. 0.3 cc, p < 0.001), but similar procedural times (178 vs. 162 mins, p = 0.53).

CRT = cardiac resynchronization therapy; EAM = electroanatomic mapping.

control group The total implant time was 59.3±15.6 mins in the EAM group compared to 51.5±12.3 mins in the control group (p = 0.14). All patients except one in the EAM group had no fluoroscopic exposure during their device implantation. One patient in the EAM group experienced a lead dislodgement that required re-operation the following day. In this study, only passive leads were used in the EAM group.

However, radiation exposure in single and dual chamber device implantation remains acceptably low, especially in experienced hands. Of particular relevance is the use of EAM in biventricular device implantation, whereby radiation exposure can be substantially higher compared to single and dual chamber device implantations. The use of EAM in biventricular device implantation was first reported by Del Greco et al., who described a series of 4 patients who underwent CRT-defibrillator implantation using the EnSite NavX EAM system and minimal fluoroscopy.[7] In this series, there appeared to be a learning curve in using EAM in biventricular device implantation, with procedural times decreasing in a step-wise fashion from 168 to 124 mins, and fluoroscopy times decreasing from 16.8 to 4.2 mins. Fluoroscopy was also used to perform a coronary sinus venogram. These patients were not compared to those who underwent biventricular device implantation using conventional (fluoroscopic) means.

More recently, EAM-guided biventricular device implantation was reported in a series of 10 patients, which were compared to a retrospective series of 10 (control) patients who underwent biventricular device implantation using conventional (fluoroscopic) means.8 In this study, implantation using EAM was aided by use of the printed venous phase of prior coronary angiograms to help identify target veins, and the use of a decapolar electrophysiology catheter via the right internal jugular vein to obtain anatomy. The authors found that, compared with control patients, those who underwent EAM-guided biventricular device implantation had markedly reduced fluoroscopic times (13.6 vs. 1.5 mins, p < 0.001), reduced use of contrast (54.9 vs. 0.3 cc, p < 0.001), and similar procedural times (178 vs. 162 mins, p = 0.53). One patient with endstage renal disease also avoided use of contrast with the EAM-guided biventricular device implantation. Improvements in functional class and cardiac function post biventricular device implantation were similar between the 2 groups of patients. The above mentioned studies are summarized in Table 1.

Use of Electroanatomic Mapping in Determining Optimal LV Pacing Site

Despite careful selection of patients, a substantial proportion of patients fail to respond to CRT. The traditional strategy is placement of the LV lead along the posterolateral LV wall, which is presumed to be the site of latest activation in patients with left bundle branch block (LBBB). Indeed, several studies have reported that leads placed at sites of prolonged LV lead electrical delay during native rhythm (i.e. the interval between QRS onset on the surface electrocardiogram to the peak of sensed electrogram on LV lead, corrected for QRS width, corresponding to sites of latest activation) were associated with improved hemodynamic response, LV reverse remodelling and clinical outcomes (heart failure hospitalisation and/or mortality).[9-12] However, significant variability in intrinsic LV activation patterns

Table 2: Summary of studies on use of electroanatomic mapping to obtain optimal LV pacing site

Study	Details	Results
Del Greco et al.[7]	Case series involving 4 patients. No control group.	Site of latest LV activation chosen as optimal site. All patients improved by one NYHA class. See also Table 1 for details.
Mina et al.[8]	10 consecutive patients vs. retrospective series of 10 control patients. EAM group used printed venous phase of prior coronary angiograms to help identify target veins, and decapolar catheter via the right internal jugular vein to obtain anatomy.	In some patients, EAM was used to identify site of latest LV activation and optimal LV pacing site (no further details were available from the manuscript). In both groups, patients improved on average by one NYHA class and ejection fraction improved by 13-14%. See also Table 1 for details.
Niazi et al.[13]	32 patients enrolled (17 with LBBB – Group A, 15 with RV-pacing induced LBBB – Group B).	Complex and variable LV activation patterns. The lateral or posterolateral branches were the sites of latest activation in 47 % of group A and 73 % of group B. Sites of LV lead positioned conventionally were concordant with the site of latest LV activation only in small number of patients (18% of Group A patients, none of Group B patients). Clinical outcomes not assessed.
Rad et al.[14]	25 consecutive patients enrolled.	Site of latest LV activation variable, being located anterolaterally in 18 patients and inferolaterally in 6 patients (1 patient had limited coronary venous anatomy which precluded assessment). Clinical outcomes not assessed.
Ryu et al.[18]	N/A	Description of novel technique combining both intraoperative assessment of mechanical (using custom software) and electrical activation (using EnSite NavX EAM system) of the coronary sinus for guidance of LV pacing site optimization during CRT implantation
Spragg et al.[19]	Examined detailed endocardial LV EAM and maps of LV dP/dT in 11 patients with ischemic cardiomyopathy.	In the majority of patients, pacing at traditionally accepted LV pacing sites (mid-lateral LV) yielded suboptimal results. Interestingly, in 8/11 patients, optimal pacing sites were located at regions other that the latest activated sites.

CRT = cardiac resynchronization therapy; EAM = electroanatomic mapping; LBBB = left bundle branch block; LV = left ventricle; NYHA = New York Heart Association; RV = right ventricle

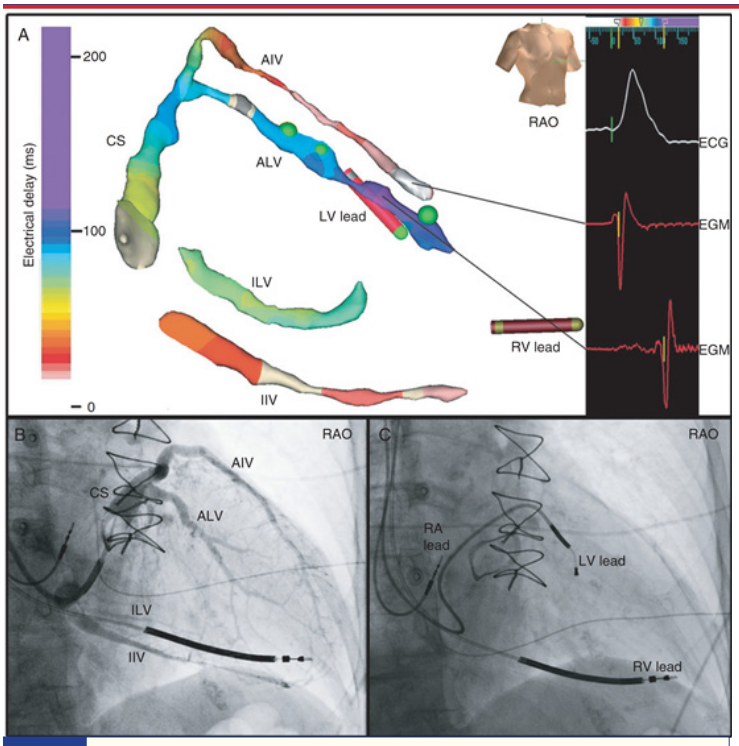

Figure:1 **(A) EAM of the coronary venous system, with the site of latest activation in purple, with corresponding electrograms (EGMs) shown; (B) corresponding coronary sinus venogram; (C) LV lead placement at site of latest activation.**
AIV, anterior inter-ventricular vein; ALV, anterolateral vein; CS, coronary sinus; IIV, inferior inter-ventricular vein; ILV, inferolateral vein; RV, right ventricular; RA, right atrial; Red dot, phrenic nerve stimulation (PNS); Green dot, no PNS.
Reproduced with permission.[14]

due to heterogeneity in the location of conduction block have been observed in patients with LBBB,[2,3] and this may account for the lack of response to CRT in some patients.

Therefore, a relevant issue is whether the use of EAM can help identify the site of latest activation and optimal site for LV pacing and lead position. The feasibility of such an approach has been explored by a number of studies.[7,8,13,14] Consistent with the earlier reports, the study by Niazi et al. involving 32 patients found that sites of latest LV activation were variable, and that the LV lead which was positioned conventionally by a physician blinded to the mapping data was concordant with the latest activated segment in only a small proportion of patients.[13] In a more recent study involving 25 patients, Rad et al., using EAM of the coronary sinus venous system (figure), also found considerable variability in site of latest LV activation, being located anterolaterally in 18 patients and inferolaterally in 6 patients (1 patient had limited coronary venous anatomy which precluded assessment).[14] In this study, a quarter of the patients had phrenic nerve stimulation at the optimal site, which might have been overcome in the current day by the use of multipolar LV leads (which were not available at time of study) or perhaps LV endocardial pacing. In another recent study, Ginks et al., utilizing noncontact EAM, reported that in patients with myocardial scar or absence of functional block, endocardial or multisite pacing appeared to be required to achieve CRT response.[15]

Apart from site of latest LV activation, LV lead placement at the site of latest mechanical activation has been shown to improve clinical outcomes in 2 recent randomized trials.[16,17] Ryu et al. recently described a novel technique combining both intraoperative assessment of mechanical (using custom software) and electrical activation (using EnSite NavX EAM system) of the coronary sinus for guidance of LV pacing site optimization during CRT implantation.[18]

Spragg et al. examined detailed LV endocardial EAM in patients with ischemic cardiomyopathy, creating maps of LV dP/dt with biventricular pacing, in addition to activation maps of native rhythm in eleven patients.[19] They found that in the majority of patients, pacing at traditionally accepted LV pacing sites (mid-lateral LV) yielded suboptimal results. In most patients, pacing immediately below the mitral valve ring in the anterolateral or lateral wall was the most reproducible spot for optimizing LV function, though significant interpatient variability was seen, and often multiple noncontiguous sites could produce similar optimal results. Interestingly, in 8 of 11 patients, optimal pacing sites were located at regions other that the latest activated sites. A study by Derval et al. also suggested that pacing at the optimal site was superior in terms of LV dP/dt when compared to the coronary sinus, lateral wall or latest activated LV wall.[20] The studies exploring the use of EAM for optimal LV pacing site are summarized in Table 2.

Unanswered Questions and Future Directions

Although EAM-guided biventricular device implantation show potential in reducing radiation exposure and guiding optimal site of LV lead placement, larger, randomized studies are required to see whether such an approach will result in improved clinical outcomes. Most of the current data is derived from small, single center trials with varying methodology. Often, it is unclear how control patients were chosen. The use of EAM technology also adds an additional significant cost per study,[8] and therefore a cost-effectiveness analysis is also required before its widespread use can be recommended. Concerns regarding adequacy of lead deployment and risk of lead perforation without use of fluoroscopy may be overcome with 3D mapping leads with lead body sensors, allowing assessment of slack and helix deployment without the use of fluoroscopy. Currently, although widespread routine use of this technology may not yet be appropriate, it appears reasonable to consider its use in certain groups of patients, such as children, fertile women, and in particular, pregnant women requiring device implantation.

Although there may be promise in the use of EAM for selection of optimal pacing targets, for the time being, further investigation is needed. Many variables affect the ability to place an LV pacing lead by the usual transvenous/coronary sinus route. The pacing site chosen is affected not only by identification of an optimal pacing site, but also by coronary venous anatomy, including vein caliber and tortuosity, accessibility of the site with current leads, capture thresholds, and phrenic nerve stimulation. In addition, there is mixed data and no clear consensus on defining the optimal pacing site. Further clarification is also needed on whether endocardial or epicardial approaches produce results superior to traditional techniques. The value of EAM in improving CRT responder rates in patients with non-left bundle branch block conduction delays also remains to be elucidated. The use of EAM will likely be a useful tool in answering these questions. At that time, it will become more clear whether routine use of EAM systems in device implantation can be recommended.

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Subclinical Atrial Tachyarrhythmias:Implantable Devices and Remote Monitoring

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Abstract

Atrial fibrillation (AF) and Atrial Tachyarrhythmias (AT) are the most common clinical arrhythmias and their worst issue is a well-recognized correlation with ischemic stroke. High incidence of "subclinical" AF/ATs has been demonstrated in several trials (TRENDS, ASSERT, CRYSTAL AF, EMBRACE) in patients with both cardiac implantable electronic devices (CIEDS) and external loop recorders. Moreover, a relationship between device-detected AF/ATs and stroke risk has been observed in the same studies. However, while the net clinical benefit of the antithrombotic treatment is well established in patients with "clinical" atrial fibrillation, there may be a lower benefit in patients with device-detected arrhythmias. Subclinical AF/ATs may be considered as a marker of stroke risk rather than the proximate cause and their burden may be used in combination with CHA2DS2-VASC and HAS-BLED scores to identify high-risk population who deserves anticoagulation.

Today the remote monitoring associated with the CIEDs is effective in the early detecting of AF/ATs by avoiding delays in the therapy evaluation, as demonstrated by several trials (TRUST, CONNECT, COMPAS). However clinical evidence for stroke risk reduction by remote monitoring is still awaited; the recent trial IMPACT failed to demonstrate that the handling of the anticoagulation therapy guided by device-detected ATs and remote monitoring improves the patients' outcome.

The challenges for clinicians are to deal with the huge data entry, to define new organizational models, to improve device patient management and to continuously update AF guidelines in according to the great amount of data offered by the new technology.

Introduction

Atrial fibrillation (AF) and Atrial Tachyarrhythmias (AT) are the most common clinical arrhythmias.[1] They have been associated with compromised hemodynamics, heart rate irregularity, uncontrolled ventricular rate and lower exercise capacity.[2] However their worst issue is a well-recognized correlation with ischemic stroke.[3,4] These adverse events due to AF or ATs are common and frequently devastating. AF is known to increase the risk of stroke up to 5-fold and the risk of mortality up to 2-fold; 15% of all strokes are caused by AF.[5] Anticoagulant therapy can reduce the risk of stroke by 60-70%.[4,6] Therefore the focus has to be moved on the detection of subclinical AF episodes and, possibly, on their correct quantification, especially in patient at high thromboembolic risk. However, this task results difficult due to the often paroxysmal and asymptomatic nature of these arrhythmias.[7] AF/ATs may go undetected with the use of traditional monitoring techniques (table 1) and the patients often do not report any symptoms. AF can be asymptomatic in up to 30-40% of cases.[2,4] Consequently many patients with subclinical AF/ATs may suffer ischemic strokes which are defined as "cryptogenic": it is known that embolic risk in AF is independent of symptoms.[8] Subclinical atrial arrhythmias may be unmasked only with a more aggressive monitoring technique. Recently, an high incidence of subclinical AF and ATs has been demonstrated thanks to the cardiac implantable electronic devices (CIEDs).[9,10] Pacemakers (PMs) and implantable cardioverter defibrillators (ICDs) should be seen not only as therapeutic devices but also as diagnostic tools which can prevent serious adverse events, especially thromboembolic ones. In addition implantable subcutaneous cardiac monitor (ICM) can be used to allow continuous monitoring over extended periods of time. This may lead to a more patient-centered approach: the anticoagulant therapy can be adjusted for each individual by considering both the presence and the duration of specific arrhythmic episodes as well as clinical risk scores.

Key Words:
Atrial Fibrillation, Atrial Tachyarrhytmias, Cryptogenic Stroke, Remote Monitoring, Cardiac Implantable Electronic Devices.

Disclosures:
None.

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Relation Between Subclinical Device-Detected Atrial Tachyarrhythmias And Cryptogenic Stroke

Cryptogenic strokes account for about 20% of all ischemic strokes.[2] Patients with cryptogenic strokes are usually treated with antiplatelet

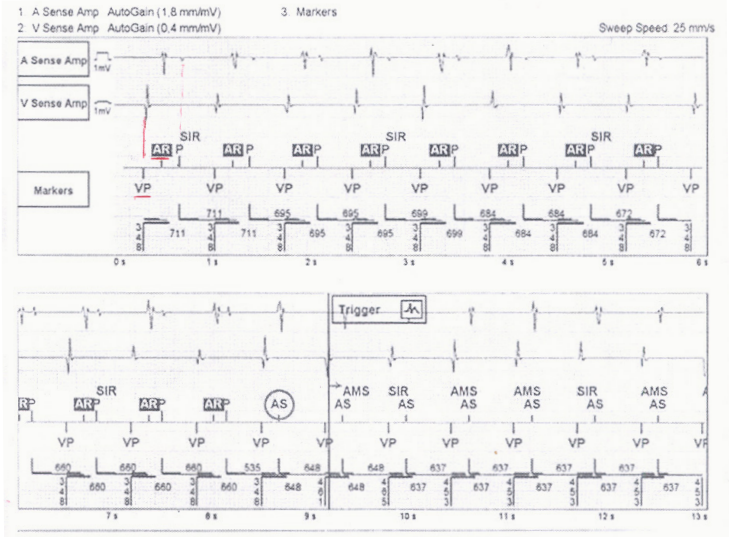

Figure:1 Episode of inappropriate mode switch due to repetitive non-reentrant ventriculoatrial synchrony (RNRVAS). See text for detailed description of the phenomenon

therapy, but they have an high recurrence rate of cerebral ischemic events. Moreover, the etiology of a subsequent stroke episode can be different from the first: for example 10-15% of patients with a first atherothrombotic event suffer a recurrent cardioembolic stroke (mainly caused by AF).[8] This background underlies the importance of a comprehensive approach involving the screening for subclinical AF/ATs since they are a possible cause of "idiopathic" cerebral ischemic events.

Recent studies have observed the relationship between device-detected AF/ATs and stroke risk. The TRENDS[9] trial was a prospective, multicenter observational study that enrolled 2486 patients after CIED implantation (pacemakers or defibrillators with an implanted atrial lead), all aged >65 years and with >1 risk factor for stroke (mean CHADS2 was 2.2). Patients with and without prior AF were also included. Device-detected AF/AT was defined as any Atrial High Rate Episode (AHRE) >175 bpm lasting at least 20 seconds, further refined by device-specific algorithms. Subclinical AHREs were diagnosed in 45% of 1988 patients without a documented history of prior AF. A daily AF/AT burden >5.5 hours (defined "high burden") appeared to double the thromboembolic risk in the following 30 days with an annualized thromboembolic event rate of 2.4%. The risk remained increased even after the adjustment for other risk factors. The rate of thromboembolic events observed in "high burden" AF/AT group of TRENDS was, anyway, far below from the 4-4.5% annual rate expected from AF patients with average CHADS2 score ≥2.[2,3,4] The annualized thromboembolic event rate was 1.1% for either subsets with "zero" or "low" AF/AT burden. However the difference in hazard ratio (HR) between "low" and "high" burden AHRE groups was not statistically different.

The ASSERT trial[10] was a prospective, multicenter, observational study designed to evaluate if subclinical episodes of AHREs can be associated with an increased risk of ischemic stroke, in patients without previous evidence of AF. 2580 patients with an implanted pacemaker (n=2451) or defibrillator (n=129), and an implanted atrial lead, were enrolled and monitored for 3 months to detect subclinical atrial tachyarrhythmias and for a mean of 2.5 years for the primary outcome of ischemic stroke or systemic embolism. There was a substantial incidence of subclinical (asymptomatic) AF/ATs. These arrhythmias were detected in 10.1% of patients within the first 3 months after implantation and at least once in 34.7% of the patients during a mean follow-up period of 2.5 years. The second major finding of the study was that subclinical ATs were independently associated with an increase, by a factor of 2.5, in the risk of ischemic stroke or systemic embolism and this risk was independent of other risk factors. The annualized thromboembolic event rate has been found equal to 2.1% in the subgroup with CHADS2 score >2 (similar to TRENDS). The risk of ischemic stroke or systemic embolism associated with ATs before 3 months was 13%, which is similar to the one associated with clinical atrial fibrillation reported by previous studies. The study also suggested that the risk of stroke was higher when episodes of subclinical ATs were of longer duration (AHRE >190 bpm lasting >6 minutes), but the study was underpowered for this analysis. Anyway the incremental stroke risk has been observed for longer and more numerous subclinical episodes. Subclinical AHREs have been reported 8 times more common than clinical (symptomatic) AF.

Data from TRENDS and ASSERT are also supported by several smaller prospective trials which evaluated the relationship between AHREs and embolic events in patients with PMs and ICDs. Capucci et al.[11] found that in 725 patients with dual-chamber PMs AHRE lasting>5 minutes did not significantly increase embolic risk, whereas episodes>24 hours did (odds ratio 3.1). Botto et al.[12] analyzed embolic risk by combining duration and burden of AHREs with CHADS2 score. 568 patients with a dual-chamber pacemaker were followed for the first year after implantation and stratified by using a combination of AHRE burden and CHADS2 score. Separate populations with different stroke risk emerged: in patients with CHADS2 score >1 and cumulative AHRE>24 hours and in those with CHADS2 score ≥2 and AHRE>5 minutes the annualized thromboembolic event rate was found as high as 5%.

Subclinical atrial tachyarrhythmias can also be detected by using implantable subcutaneous cardiac monitors (ICMs) or external loop recorders. The CRYSTAL AF study[13] was a prospective, multicenter, international, randomized study to determine the incidence of AF among patients randomized to ICM vs standard monitoring. Eligible patients (n=441) were older than 40 years and had a stroke within the last 90 days defined as cryptogenic after to have undergone 12-lead ECG, 24-hour ECG monitoring, transesophageal echocardiography (TEE), computed tomographic angiography or magnetic resonance angiography of the head and neck to rule out an arterial source, and screening for hypercoagulable states in patients younger than 55 years. Standard monitoring was left to the discretion of the attending physician and therefore represents daily practice. AF was detected

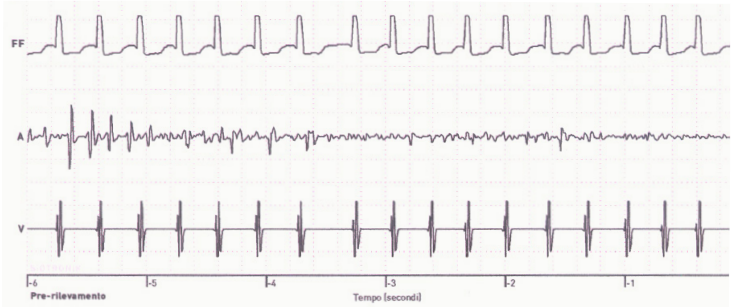

Figure:2 Example of atrial fibrillation detected in a single-lead defibrillator with atrial floating sensing dipole

at a rate of 8.9%, 12.4%, and 30% in the ICM arm and 1.4%, 2%, and 3% in the standard monitoring arm at 6, 12 and 36 months, respectively. At 12 months, the median time from randomization to AF detection in the ICM arm was 84 days, and 79% of these episodes were asymptomatic. More than 92% of patients in the ICM arm with AF detected at 12 months had a day with >6 minutes of AF, a threshold found in the ASSERT study to confer an increased risk of subsequent ischemic stroke. At 36 months, AF was detected at a rate of 30% among ICM patients compared to 3 % among control patients (HR 8.8, P<0001). Oral anticoagulant therapy (OAC) was prescribed for 96.6 % of ICM patients in whom AF was detected, by suggesting that physicians found the amount of AF detected clinically relevant. This study demonstrates that long-term continuous monitoring with an ICM is significantly more effective than standard arrhythmia monitoring for the identification of subclinical AF in patients who suffered a cryptogenic stroke.

Similar findings could be demonstrated by using an external loop recorder. The recent EMBRACE study[14] randomly assigned 572 patients (age ≥ 55 years) with cryptogenic stroke to 30-day event triggered external loop recorder vs conventional 24-hour Holter monitoring. Unlike CRYSTAL AF, TEE or intracranial vascular imaging was not required as part of the stroke workup. The primary end-point (detection of AF ≥ 30 seconds within 90 days) was met in 16.1% and 3.2% of patients in the event recorder and control arms, respectively. The secondary end-point (detection of AF ≥ 2.5 minutes within 90 days) was met in 9.9% and 2.5% of patients in the event recorder and control arms, respectively. OAC was prescribed in 18.6% of patients in the event recorder arm vs 11.1% of patients in the control arm, presumably because of the higher rates of AF detection. Compliance with the protocol in the intervention arm was reasonably high at 82% completing ≥3 weeks of monitoring, which may not be easily replicated in clinical practice. This study demonstrated that 30-day event-triggered recorder was significantly more effective than conventional 24-hour Holter monitoring for identification of AF in patients who suffered a cryptogenic stroke. Prolonged monitoring nearly doubled the proportion of patients who subsequently received anticoagulant therapy for secondary prevention of stroke. At 90-days follow up 87% of patients with AF episodes in the study group were receiving OAC. This finding is a clinically meaningful change in treatment that has the potential to avoid recurrent strokes. The common practice of relying on 24 to 48 hours monitoring for AF after either a stroke or a TIA of undetermined cause is insufficient and should be considered only as an initial screening.

Oral Anticoagulation for Device-Detected Atrial Tachyarrhythmias

The benefits of OAC in patients with AF/AT are clear, leading to a substantial reduction of not only stroke risk, but also of stroke severity and mortality.[8] Underused of OAC in AF patients is a well described phenomenon with multiple causes and multifaceted aspects in a general AF population. The increasing prevalence of patients with CIEDs in combination with AHREs and their associated increased risk of stroke/embolism pose new clinical challenges to clinicians.[9, 10, 11, 12] At present the management of patients with device-detected AF/AT remains controversial, and uncertainties exist about the duration of the longest episode, the cumulative duration and the individual stroke risk.[8] To date the only prospective randomized trial to address this question was the IMPACT study,[15] which was stopped early and was unable to demonstrate that daily remote monitoring for ATs with a predefined plan for anticoagulation is superior to a conventional strategy for identification of patients deserving OAC.[16] The incidence of AF/AT detected by PMs or ICDs can reach 50% but only <25% of these patients are treated with OAC.[8] On the other side, and inexplicably, when AF is detected with an ICM or an external loop recorder (like in CRYSTAL and EMBRACE) many more patients are anticoagulated.[13, 14] There are several potential explanations for this trend. First of all, although Guidelines recognize the role of cardiac devices in detecting AHREs (a surrogate for AF/AT), there is no specific recommendation regarding their use for diagnosis and management in these patients.[1, 6] Few evidences exist about a critical threshold for duration/number of AHRE burden, even if many short episodes could result in the same AF burden as single long-lasting episode.[8] Moreover while the net clinical benefit of antithrombotic treatment is well established in patients with "clinical" atrial fibrillation, there may be a lower benefit in patients with device-detected AF/AT: in patients with CHADS2 score >2, the annualized thromboembolic event rate associated with subclinical AHREs was 2.4% in TRENDS and 2.1% in ASSERT,[9, 10] far below from the 4-4.5% annual rate expected in "clinical" AF patients with similar risk profile. So patients with device-detected AHREs (although having a higher risk compared to patients without AHREs) appear to be at lower risk for stroke compared to a "general" AF population: as a result the net clinical benefit of OAC may be reduced.[17] Another issue to consider is the lack of a temporal relationship between subclinical AF and stroke in studies of patients with CIEDs: in ASSERT study 73% of patients with thromboembolism did not show a temporal relationship between AHRE and embolic events.[8, 10] Given the lack of temporal association between device-detected ATs and stroke, a clinician could consider AF only as a marker of stroke risk rather than the proximate cause; so monitoring atrial activity with a CIED could promote a "wait-and-see" approach.

Even if the overall stroke rate in patients with AHREs appears to be less than that in clinically recognized AF, it is crucial to identify a certain high-risk population who deserve anticoagulation, provided that embolic risk exceeds the risk of serious bleeding. By combining AF/AT burden with CHADS2 or CHA2DS2-VASC score and HAS-BLED score we can individualize OAC for appropriate patients at high risk for stroke.[12] It has been suggested that with a CHADS2 or CHA2DS2-VASC score of 1-2 the anticoagulation could be appropriate if a single AHRE episode exceeds 24 hours; with a score >2 the anticoagulation could be started for AHRE lasting > 6 minutes (the higher is the score the shorter is the AHRE duration threshold to start OAC).[12, 17]

CIEDS and ATs Detection: Potentials, Technical Issues, Pitfalls, Clinical Implications

CIEDs are sensitive and specific for diagnosis of AF/ATs. The presence of an implanted atrial lead allows a continuous monitoring of atrial activity and the recording of the episodes in which the sensed atrial rate exceeds a predefined cutoff or deviates from a running average.[17] However, when a CIED is used for the detection of atrial arrhythmias all cardiac rhythm recordings must be adjudicated and reviewed by a qualified clinician to verify their diagnostic accuracy.[8] There are some factors that limit the diagnostic performance of a CIED: oversensing, undersensing, far-field sensing, cross talk, interference, inappropriate programmed detection

Table 1: Methods for cardiac rhythm monitoring

	PRO	CONS
NON INVASIVE		
Hospital Telemetry	Accurate, also for asymptomatic events	Only hospitalized patients
Holter ECG	Easy to use, continuous recording, also for asymptomatic events	Short monitoring
Event Recorder	Longer monitoring Rhythm-symptoms correlation	Not for asymptomatic events Requires patient's trigger
INVASIVE		
Implantable Loop Recorder	Long periods of monitoring Remote monitoring Asymptomatic events	Expensive and invasive False negative and positive Does not offer therapy
Pacemakers and Defibrillators	Asymptomatic events Also therapeutic	Only if therapeutic indication Expensive and invasive Complications

criteria, differences between manufacturers in diagnostic algorithms for AHRE detection.[18,19] Moreover the ATs detection rate and the duration of the post-ventricular atrial blanking interval can influence the number of automatic mode-switching episodes.[8] The storing of electrograms (EGM) in the device memory improved the diagnostic accuracy by allowing to detect and document appropriate versus inappropriate sensing or detections. Several studies showed that the data retrieved from diagnostic counters may sometimes be misleading and, although AHRE are used as a surrogate for AF, the data must be interpreted with caution.[8,18,19] For example in the ASSERT study 17% of AHREs (>190 bpm lasting >6 minutes) were found to be false positives because of atrial oversensing, runs of premature atrial complexes, far-field R wave detection, repetitive non-re-entrant ventriculoatrial synchrony (RNRVAS). RNRVAS, in particular, was the single most common cause of false positive detection in the ASSERT study; it is triggered by a retrograde ventriculoatrial conduction with functional atrial undersensing and results from retrograde atrial activation during the post-ventricular atrial refractory period and functional atrial non-capture due to stimulation during the absolute refractory period, with the potential to trigger inappropriate mode switching (fig. 1).[8] On the other hand false AF negatives have been observed when episodes were very brief or atrial sensing was unreliable.[8, 17, 18, 19]

The need to insert an atrial electrode to detect ATs carries in itself a significant associated risk for complications and higher costs[20] which could be solved by using an atrial floating VDD lead if there is no need of atrial pacing. However, an acknowledged issue with VDD system is the dissatisfaction and the instability of the atrial sensing amplitude over time.[21] This may easily cause underestimation of atrial arrhythmic burden and the loss of synchronized ventricular pacing. Recently a single-lead ICD with atrial sensor (DX ICD Biotronik SE & Co. KG, Berlin, Germany), has been developed in order to maintain the crucial atrial information without implanting an atrial lead. The DX ICD system relies on an atrial floating dipole with enhanced sensing capabilities and has demonstrated to provide reliable atrial sensing in the medium to long term (fig. 2).[22]

Regarding ICMs, three new devices with dedicated AF algorithms are on the market (Medtronic Reveal XT, model 9529, Medtronic Inc., Minneapolis, Minnesota; SJM Confirm ICM model DM2102, St Jude Medical Inc., Sunnyvale California and Biotronik BioMonitor, Biotronik SE & Co. KG, Berlin). The Medtronic Reveal XT reported to have an overall accuracy of 98.5% in AF detection.[23] These monitors usually detect AF by analyzing the irregularity and the incoherence of successive R-R intervals with high sensitivity and good specificity.[24] However also ICM are affected by to false AF detection due to oversensing or missed AF due to undersensing: so clinical evaluation of recorded episode is always fundamental.

Early Detection Of Atrial Arrhythmias With Daily Remote Monitoring

It is now clear that diagnostics of last-generation devices allow us to have a detailed and complete monitoring of the atrial arrhythmic episodes. These data become meaningful if they are early available for the physician to prevent arrhythmia-related severe adverse events.[25] Without remote monitoring any information is available only during in-hospital follow-up, usually scheduled every 6 or 12 months. This represents a great limitation, mainly for asymptomatic patients and for those with mild symptoms. The main potential advantage of daily remote control application in AF management is represented by early detection and early reaction to the arrhythmia occurrence.[26] A pilot Italian single-centre study involving 166 patients (73% pacemakers; Biotronik Home Monitoring [HM] system) demonstrated that 20% of patients had alerts for AF. The median reaction time to AF was reduced of 148 days compared with scheduled follow-up.[27] The HM-guided unscheduled follow-ups led to clinically significant reactions to AF such as antiarrhythmic drug therapy introduction or modification (48%), anticoagulation starting (45%), or external cardioversion (21%).

In the TRUST trial, (ICDs; Biotronik HM system), AF detection was 34.5 days earlier with remote monitoring vs standard follow-up (5.5 vs 40 days).[28]

In the CONNECT trial (ICDs; Medtronic CareLink system) the interval between an AF event longer than 12 h and the clinical reaction was eight times shorter with remote monitoring when compared with standard follow-up (3 vs 24 days).[29]

In the COMPAS trial (PMs; Biotronik HM system), although the study was not powered to make these comparisons, significant differences were observed between the two study groups (remote monitoring vs standard in-hospital follow-up) in the rates of hospitalizations for the management of atrial arrhythmias and strokes.[30] Several follow-ups prompted by remote monitoring, which enabled the early detection and management of atrial arrhythmias in the active group, may have prevented the development of more serious adverse events.

The potential benefit of remote continuous monitoring on 2-year incidence of stroke was modeled by running repeated Monte Carlo simulations based on a real population of 166 patients prospectively followed daily.[31] The results suggested that daily monitoring may reduce the 2-year stroke risk by 9 to 18% with an absolute reduction of 0.2 to 0.6%, compared with conventional inter-visit intervals of 6–12 months. Although this result was derived from a clinical experience performed using a particular paradigm for remote control (Biotronik HM system), it may apply to any remote monitoring system, provided that this is based on wireless automatic daily transmissions with immediate (within 24 hours) notification of AF episodes.

However, the clinical evidence for stroke risk reduction by remote monitoring is still awaited. As outlined before, the prospective randomized IMPACT trial[15] was stopped early. The study hypothesis was that daily remote monitoring for ATs with a predefined plan for

anticoagulation would have been proved superior to a conventional strategy for the identification of patients deserving OAC. 2718 patients, with a dual-chamber or biventricular ICD, were enrolled and randomized 1:1 to either office visits or remote monitoring for AHRE detection (>200 bpm for 36 of 48 beats). When ATs were detected an anticoagulation prespecified protocol was started in the intervention group on the basis of CHADS2 score. Discontinuation of OAC was contemplated for patients without ATs recurrences over time and with low CHADS2 scores. Previous stroke, transient ischemic attack, systemic embolism and clinically documented atrial arrhythmias were Exclusion criteria. No significant differences existed in baseline demographics between the 2 groups. The incidence of ATs was similar for the 2 groups (33% control, 36% interventional group). The adjudication of device-based atrial EGM verified 60.5% of events as AF, 30% as atrial flutter, 9.5% as false positive episodes (with no significant differences between the 2 groups). After 5 years follow-up the Data Monitoring Committee recommended the trial termination, because of the failure to demonstrate any significant differences in the outcome between the two groups. No statistically significant difference was found in the primary outcome, which was a composite of ischemic stroke, systemic embolism, major bleeding and all-cause mortality. However, in the interventional group the OAC was started earlier (3 vs 54 days; $p<0.001$) by indicating that remote monitoring facilitated earlier reactions for ATs.[16] No clear explanations for these results are available; the compliance with the OAC in the interventional group was suboptimal, but the overall primary event rate was low nevertheless. Moreover, like in the previous studies[8, 10] no temporal relationship was found between device-detected ATs and thromboembolic events. The investigators concluded that the beginning and the discontinuation of the anticoagulation therapy based on the presence of device-detected ATs available from the home monitoring did not improve clinical outcome in this specific population.[8]

The first experiences of AF home monitoring with ICMs have been carried out showing promising results.[32, 33] A single center pilot study involving 186 patients suffering of AF and implanted with ICM equipped with daily remote monitoring (Biotronik HM system) demonstrated that 26% of the patients had a clinical interventions triggered by remote transmissions with a mean follow up of 6 months. All the clinical interventions were performed within 24 hours after the remote alert. The main frequent reaction was a therapy change.[33]

The Organization Model for Remote Monitoring of AF Patients

The HomeGuide Registry (Biotronik HM system) is a large registry which investigated the impact of remote monitoring of CIEDs on the patient management in daily practice.[34] The main result of the study showed that, by applying a structured organizational model, remote monitoring of CIEDs may be effectively introduced in standard clinical practice combining high effectiveness in clinical and device-related cardiovascular events detection, with a very low manpower and resource consumption. This is crucial for AF management, where early reaction from the remote notification is fundamental. The HomeGuide model is essentially based on a cooperative interaction between the roles of an expert reference nurse and a responsible physician, with an agreed list of respective tasks and responsibilities. Home Monitoring transmissions were reviewed by the nurse within two working days. In the case of critical alerts, such as AF episode detected, the responsible physician was contacted for the clinical decision.

The HomeGuide Registry showed that the applied organizational model may lead to an overall manpower for remote follow-ups which is less than one hour/month every 100 patients.[35] Such result was obtained in centers with different activity volumes recruited in different regions of Italy, by underlining the success of the applied workflow model and the used technology.

Conclusions

Patients with CIEDs represent a special population with multiple comorbidities predisposing to atrial arrhythmias, especially AF, which are often paroxysmal, intermittent and asymptomatic. "Subclinical" atrial tachyarrythmias are associated with a significant increase in the risk of stroke and systemic embolism and may be unmasked only with more aggressive monitoring techniques. Patients with dual-chamber pacemakers and implantable cardioverter defibrillators, as far as with implantable cardiac monitor, represent a unique opportunity to screen for and unmask silent AF episodes. Until further studies will be carried out, anticoagulation therapy should be individualized according to stroke risk scores in combination with the burden of AF/AT detected by the device. At the meantime, the recently designed ARTESIA study will evaluate if the treatment with Apixaban, compared to aspirin, could reduce the risk of ischemic stroke and systemic thromboembolism in pacemaker patients with subclinical AF ad additional risk factors for stroke.[35]

All these data become meaningful if they are early available and today this is possible thanks to the daily remote monitoring of the devices. The challenges for clinicians are to deal with the huge data entry, to define new organizational models, to improve device patient management and to continuously update AF guidelines according to the great amount of data offered by new technologies. Future AF guidelines should consider this peculiar scenario and, hopefully, make more specific recommendations, in particular regarding anticoagulation therapy.

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Periprocedural Management of Non-Vitamin K Oral Anticoagulants in Chronic Kidney Disease: A Review of Existing Heterogeneity and Contemporary Evidence

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Abstract

Non vitamin-K oral anticoagulants (NOAC) have considerably enhanced anticoagulation practice for non-valvular atrial fibrillation with specific advantages of fixed dosing, non-fluctuant therapeutic levels and obviation of therapeutic level monitoring. NOAC pharmacology is remarkable for considerable renal excretion. Heterogeneity in the precise time cut-offs for discontinuation of NOACs prior to elective surgical or percutaneous procedures arise from the non-linear variations of drug excretion with different levels of creatinine clearances as in chronic kidney disease. Multiple authors have suggested cut-offs leading to ambiguity among practicing clinicians. Recent data pertaining to systemic thromboembolism, stroke and major bleeding derived from randomized controlled clinical trials have simplified the periprocedural management of NOACs. This review focusses on heterogeneity in the management of NOACs in patients with CKD in this peculiar scenario and highlights the contemporary evidence to support a unified approach towards perioperative management of NOACs. Multiple antidotes targeted towards binding of specific NOACs have been developed and are in the testing phase, thereby offering immense potential for rapid and complete reversal of NOAC activity in emergent procedures and major bleeding episodes. Targeted research on thromboembolism, stroke and major bleeding following temporary periprocedural interruption of NOACs using multicentric registries could further expand the clinical utility of these agents.

Introduction

With the advent of non-vitamin K oral anticoagulants (NOACs), there has been a paradigm shift in anticoagulation for stroke prevention in non-valvular atrial fibrillation (NVAF). Distinct advantages of NOACs include fixed dosing, non-fluctuant therapeutic levels, elimination of the need for therapeutic level monitoring, lack of dietary restrictions and minimal drug interactions in comparison to warfarin.[1] However, there is minimal objective data to support the optimal time at which NOACs need to be withheld and restarted for elective procedures in patients with chronic kidney disease. The timing is dependent on the creatinine clearance (CrCl) and bleeding risk associated with the surgical procedure.[2] The clinical relevance of this timing is underscored by the fact that approximately 10% of patients receiving anticoagulation undergo surgical or invasive procedures mandating temporary interruption (TI) of these medications.[3] There is a discrepancy between the recommendations from the manufacturers and the cut-offs suggested by multiple authors, thereby indicating a lack of consensus for the management of this often encountered clinical scenario.[2,4-8] Earlier withholding of NOACs for elective procedures might predispose to suboptimal anticoagulation while withholding it later might predispose to higher intraprocedural bleeding risk. A similar dilemma is noted during resumption of NOACs after procedures. This article focusses on the pharmacokinetic profiles of the four commercially available NOACs and an approach to their management in the periprocedural setting.

Key Words:

Non-Vitamin K Oral Anticoagulants, Chronic Kidney Disease, Bleeding Risk, Thromboembolism, Periprocedural.

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Pharmacokinetics of Dabigatran and Discrepancies in its Usage in the Periprocedural Setting

Dabigatran is a potent oral direct thrombin inhibitor with a half-life of 12-17 hours which has shown to have lower rates of stroke and thromboembolism as compared to warfarin when used at a dose of 150 mg twice daily with similar rates of major hemorrhage in the Randomized Evaluation of Long-Term Anticoagulation Therapy

Table 1: Discrepancies in the time of stoppage (in hours) of Dabigatran prior to elective surgeries*

Author	Creatinine Clearance (CrCl) (ml/min)							
	> 80		50-80		30-50		<30	
	Low-Risk	High Risk	Low-Risk	High Risk	Low-Risk	High Risk	Low-Risk	High Risk
Heidbuchel et al.	≥ 24	≥48	≥36`	≥72	≥48	≥96	-	-
Fawole et al.	-	-	24	48	48	96	96	144
Schulman et al.	24	48	24	48	48	96	96	144
Lai et al.	≥24	≥48	≥36	≥72	≥48	≥96	≥48	≥96
Hankey et al.	24	48-96	24	48-96	≥48	96	48-120	>120
Levy et al.	24	48-96	24	48-96	≥48	≥96	48-120	>120

*Package insert recommends discontinuing dabigatran 1-2 days (CrCl ≥ 50 mL/min) or 3 to 5 days (CrCl <50 mL/min) prior to elective surgical procedures. Longer but unspecified times are recommended for major surgery, spinal puncture, or placement of a spinal or epidural catheter or port.

(RE-LY) trial which evaluated 18,113 patients with NVAF.[4,9] In contrast, a dosage of 110 mg twice daily resulted in similar rates of stroke and thromboembolism as warfarin but lesser rates of major hemorrhage. Evidence from this trial is limited to patients with a CrCl of >30ml/min, thereby restricting the use of this agent to those above this CrCl cut off. The paucity of pharamacokinetic, safety and efficacy data in patients with CKD translates into considerable heterogeneity in the time cut-offs at which dabigatran needs to be withheld in patients with CrCls in the 50-80 ml/min and <30ml/min range (Table 1).[2,8,10-13]

The non-linear variations in NOAC concentrations with different grades of CrCls complicates the process of arriving at precise cut-offs. Most of the studies with respect to dabigatran listed in table 1 present data which is fairly consistent across most grades of CrCls except in the 50-80 ml/min and <30ml/min range, where discrepancies of approximately 12-48 hours are evident. Wysokinski et al. have recommended a conservative approach to withholding dabigatran (7 days) prior to elective surgery carrying high risk of bleeding in patients with CrCls <50 ml/min and ≥50 ml/min, respectively.[2] In contrast, this is significantly different from multiple studies which recommend holding of NOACs 2-4 days prior to surgery at CrCls ≥50 ml/min and <50 ml/min respectively (Table 1).[8,10-14] The European Heart Rhythm Association (EHRA) has also recommended stoppage of dabigatran at ≥96 hours prior to elective surgery carrying high risk for bleeding for the same CrCl cohort.[12]

A comprehensive analysis of the pharmacokinetic profiles of dabigatran at various levels of CrCl has shown that the area under the curve, maximum plasma concentration and the half-life of dabigatran increased by 3.2-, 1.7- and 1.4-fold, respectively in patients with a CrCl of 30-50 ml/min as compared with those having normal renal function.[15] A 1.4-fold increase would extend its half-life to 21 hours (15 hours for normal CrCl x 1.4). Assuming the clearance of dabigatran from the system takes approximately 4.5 half-lives, one would expect complete clearance only at the end of approximately 4 days (21 hours x 4.5) which is closely congruent with the cut-offs from table 1. However, the small sample size of this study with 6 patients from each CrCl subgroup poses significant limitations to the extrapolation of this data to the general population. Moreover, recommendations for stopping NOACs in the lower surgical bleeding risk cohort at approximately 2-3 half-lives prior to surgery as opposed to 4.5 half-lives are less evidence based (Table 1).

Table 2: Recommended Timing of Pre-Procedural stoppage of Dabigatran in Relation to Creatinine Clearance Values Evaluated in the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial

	Timing of Dabigatran Stoppage Before the Procedure	
Creatinine clearance (ml/min)	High Bleeding Risk	Standard Bleeding Risk
≥ 50 to <80	2-3 days	24 hours
≥ 30 to <50	4 days	2 days
< 30	> 5 days	2-4 days

Low bleeding risk procedures: coronary angiography or pacemaker implantation; High risk of bleeding: cardiac, abdominal, and neurosurgery or procedures requiring spinal anesthesia.

Evidence-Based Approach to Temporary Interruption of Dabigatran in the Periprocedural Setting

The incidence of thromboembolic and bleeding complications in 4591 patients who underwent 7631 surgical procedures over a mean follow-up period of 2 years following periprocedural TI of dabigatran in the RE-LY trial has been published.[16] This subgroup of patients comprised of different stages of CKD and a specific protocol was used to decipher the time at which dabigatran was withheld in the periprocedural setting (Table 2). Results from this study highlight the non-inferiority of dabigatran at either doses to warfarin in terms of 30-day post procedural thromboembolic events [Ischemic or hemorrhagic stroke: Dabigatran (D) 110mg vs. warfarin: relative risk (RR) 0.73, 95% confidence interval (CI) (0.28–1.92; P=0.53) and D150mg vs. warfarin, RR 0.71 95% CI, (0.27–1.85; P=0.48)] as well as bleeding of any magnitude in both elective and urgent surgeries [Major bleeding: D110 mg vs. warfarin: RR 0.83; 95% CI, 0.59-1.17; P=0.28; D150 mg vs. warfarin: RR 1.09; 95% CI, 0.80-1.49; P=0.58). Moreover, patients anticoagulated with dabigatran demonstrated a 4-fold higher likelihood of completing the procedure within 48 hours of TI. Periprocedural bridging with heparin products was significantly lower with dabigatran [D110mg 15.3% vs D150mg 17% vs warfarin 28.5%, P<0.001]. Event rates were comparable to the randomized trial and moreover, this study offers the maximal sample size for assessment of thromboembolic and bleeding complications associated with anticoagulants in this scenario.

A prudent approach to clinicians would be to follow the protocol in table 2 for management of dabigatran considering the well-validated nature of outcomes with this strategy. Additionally, a uniform interruption of dabigatran for 24 hours prior to the surgical procedure showed no difference in the aforementioned outcomes in comparison to warfarin. However, when this strategy was adopted, there were a disproportionately higher number of patients noted to have a standard and not a high surgical bleeding risk profile, thereby underwhelming in terms of statistical power for the latter scenario. In patients undergoing high bleeding risk procedures and having severely impaired renal function, a normal activated partial thromboplastin time (aPTT) or thrombin time (TT) essentially excludes drug levels and could be considered to confirm systemic drug elimination.[1] Dilute TT and ecarin-based assays offer the best interrelationship with therapeutic drug levels but the lack of standardization across laboratories and limited availability restrict their usage.[1]

Pharmacokinetics of Rivaroxaban and the Variations in Its Use in the Periprocedural Scenario

Rivaroxaban is a direct oral factor Xa inhibitor with a half-life of 5-9 hours in healthy individuals of age 20-45 years and 11-13 hours in the elderly subgroup.[5] Evidence substantiating the use of rivaroxaban emerges from the Rivaroxaban Once Daily Oral Direct Factor Xa

Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET-AF) involving 14,264 patients with NVAF.[17] These results demonstrate non-inferiority to warfarin for stroke, thromboembolism and major bleeding along with lower incidence of intracranial and fatal bleeding in the rivaroxaban group.[17] The rivaroxaban arm in this study comprised of patients with CrCl ≥50 ml/min or 30-49 ml/min who received 20 mg once daily or 15 mg once daily doses, respectively. Though a bulk of the safety and efficacy data has been derived from patients with compromised renal function in this study, patients with a lower CrCl of 15-30 ml/min have been approved to receive rivaroxaban 15 mg once daily despite paucity of randomized evidence to support it.

Evidence and Recommendations for Periprocedural Management of Rivaroxaban

The manufacturers recommend stoppage of rivaroxaban at least 24 hours before any invasive procedure, irrespective of the bleeding risk associated with the procedure or the CrCl level.[5] Table 3 summarizes the variations among different authors for the time at which rivaroxaban needs to be stopped prior to the procedure. Considering the increase in factor Xa inhibition and prothrombin time by 10-20% with reduction in CrCl below 50 ml/min, there is potential for excessive bleeding complications with this unified approach.

Robust evidence from a subset of 4692 patients with varying levels of CrCls above 15ml/min who underwent 7555 TIs ranging between 3-30 days from the ROCKET – AF trial elicited no difference between rivaroxaban and warfarin in terms of major bleeding [Rivaroxaban 0.99% vs warfarin 0.79% per 30 days; hazard ratio (HR) 1.26; P=0.32], minor bleeding, strokes and thromboembolic episodes [Rivaroxaban 0.30% vs warfarin 0.41% per 30 days; hazard ratio (HR) 0.74, P=0.40] over a mean follow-up period of 24 months.[18] Of these patients, 90% of TIs were initiated ≥3 days prior to invasive procedures. However, only 13% of these were surgical procedures with high bleeding risk. A total of 9% of patients with >2 risk factors for stroke underwent bridging therapy and there were no statistical differences between the rivaroxaban and warfarin groups among these patients.

For practical purposes, a unified approach of stopping rivaroxaban ≥3 days prior to invasive procedures of any bleeding risk in patients with CrCl≥15ml/min is recommended. An exception would be those undergoing procedures with a high bleeding risk such as cardiac or neurosurgery and having CrCl<50ml/min, where withholding of rivaroxaban at least 5 days prior to the procedure is recommended. Normal prothrombin time, international normalized ratio or anti-factor Xa activity essentially excludes clinically significant blood levels and could be used to confirm clearance of rivaroxaban in high bleeding risk situations.[1] Anti-factor Xa assays calibrated to the respective NOACs provide the best correlation to therapeutic levels of all oral Xa inhibitors but the assay availability is often limited.[1]

Pharmacokinetic Profile of Apixaban in Normal and Compromised Renal Function

Apixaban is an oral direct factor Xa inhibitor with a half-life of 12 hours and 25% renal clearance.[6] It has been evaluated for anticoagulation in NVAF in the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) randomized controlled trial with 18,201 patients.[19] Patients with CrCl<25 ml/min were excluded from the study and those with a serum creatinine of >1.5mg/dL received a reduced dose of 2.5 mg twice daily as opposed to those with better CrCls who received a 5mg two times daily dosing. Results from this trial showed superiority to warfarin in terms of stroke and thromboembolism prevention, incidence of major bleeding and more importantly, mortality benefit. Present recommendations from the package insert recommend dose reduction to 2.5 mg twice daily if two of either criterion is met: body weight ≤60 kg, serum creatinine ≥1.5 mg/dL or age≥80 years. However, no dose reduction in individuals with isolated renal impairment, including those with end-stage renal disease on hemodialysis. However, there is lack of evidence to support lack of dose reduction in those with CrCl<25 ml/min.

Evidence-Based Management Strategy for Apixaban in the Periprocedural Setting

Table 4 summarizes the variations in the time cut-offs for withholding apixaban prior to elective procedures as suggested by different authors. The most substantial data on the periprocedural management of apixaban is derived from the sub-study of the ARISTOTLE trial comprising of 5924 patients with a total of 9260 analyzed procedures necessitating TI.[20] 37.9% of patients who were on apixaban continued through the procedure without any interruption. Results from this study indicated no significant differences between apixaban (either doses) and warfarin in terms of 30-day post-procedural outcomes of major bleeding [Apixaban 1.62% vs warfarin 1.93% of procedures], minor bleeding and stroke or systemic embolism [Apixaban 0.35% vs warfarin 0.57% of procedures (odds ratio [OR] 0.601; 95% CI, 0.322-1.120] irrespective of the CKD stage. A total of 11.7% of patients in both groups underwent periprocedural bridging anticoagulation. However, this study comprised of only 13.1% major procedures defined as those requiring general anesthesia. Extrapolation of this data to those undergoing high bleeding risk procedures in the real world must be exercised with caution. The heterogeneity in the time at which apixaban was stopped prior to the procedure is to be noted (on the day of the procedure or anytime up to 7 days prior to it).

For practicing clinicians, this data offers substantial evidence for either non-interruption or holding of apixaban ≥24 hours for low bleeding risk procedures irrespective of the CKD stage and is therefore recommended. Until more comprehensive data is available, procedures involving a high risk of bleeding would mandate holding of apixaban, at least 48 hours prior to the procedure. Normal anti-factor Xa excludes systemic drug levels in high risk situations.[1]

Pharmacokinetic Profile, Safety and Efficacy of Edoxaban in Non-Valvular Atrial Fibrillation

Edoxaban is an oral direct factor Xa inhibitor with a half-life of

Table 3: Discrepancies in the time cut-off for stoppage (in hours) of Rivaroxaban prior to elective surgeries*

Author	Creatinine Clearance (ml/min)	Low-Risk	High Risk
Schulman et al./Fawole et al.	>30	24	48
	≤30	48	96
Heidbuchel et al.	≥30	≥24	≥48
	15-30	≥36	≥48
	<15		Not indicated
Wysonkinski et al. (irrespective of surgical bleeding risk)	≥50		72
	<50		120

*Package insert recommends holding of rivaroxaban at least 24 hours prior to surgery irrespective of CrCl and magnitude of surgical bleeding risk.

Table 4: Discrepancies in the time cut-offs for holding (in hours) Apixaban prior to elective surgical interventions*

Author	Creatinine Clearance	Low-Risk	High Risk
Heidbuchel et al.	≥30	≥24	≥48
	15-30	≥36	≥48
Fawole et al.	<15	No data	
	>30	24	48
	≤30	48	96

*Package insert recommends holding of Apixaban at least 24 and 48 hours prior to low and high bleeding risk procedures respectively (irrespective of creatinine clearance)

10-14 hours with a 50% renal clearance which has a targeted patient population of those with pre-existent renal dysfunction.[7] Notably, edoxaban use is contraindicated in those with CrCl> 95 ml/min due to a higher incidence of ischemic strokes in patients taking the 60 mg once daily dose. Results from the Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation –Thrombolysis in Myocardial Infarction 48 (ENGAGE AF TIMI-48) trial demonstrated non-inferiority of edoxaban to warfarin in terms of stroke prevention and thromboembolism (systemic embolism: edoxaban 5mg twice daily 1.18% vs. warfarin 1.5%, HR 0.79, 95% CI, 0.63-0.99, P<0.001; edoxaban 2.5 mg twice daily 1.61% vs warfarin 1.5%, HR 1.07, 95% CI, 0.87-1.31, P=0.05) and in addition, lower incidence of major bleeding (Edoxaban 5mg twice daily 2.75% vs. warfarin 3.43%, HR 0.80, 95% CI, 0.71-0.91, P<0.001; edoxaban 2.5 mg twice daily 1.61% vs warfarin 3.43%, HR 0.47, 95% CI, 0.41-0.55, P<0.001) and cardiac mortality.[21] In this prospective trial, a significant portion of patients with CrCl 30-50 ml/min received a reduced dose of 30mg twice daily as opposed to the 60mg twice daily dosing for those with a higher CrCl value. Primary endpoints and bleeding risks as mentioned above were unaffected by dose reduction. Though the manufacturer recommends use of edoxaban at a reduced dose in patients with CrCl 15-50 ml/min, there is less evidence in terms of safety and efficacy in this range.

Recommendations for Periprocedural Management of Edoxaban

Presently, there is no randomized controlled trial evidence for bleeding and thromboembolic complications from TI of edoxaban in the periprocedural setting. In the absence of concrete evidence, stoppage of edoxaban at least 24 hours prior to the procedure is recommended in accordance with the package insert.[7] aPTT and anti-factor Xa activity are sensitive indicators of therapeutic edoxaban levels.[1] A unified approach derived from randomized controlled trials to the time at which NOACs need to be discontinued prior to the procedure is outlined in table 5.

Resumption of NOACs Following Temporary Interruption for Procedures and Indications for Bridging Therapy

Discrepancies have been noted in the optimal time at which NOACs should be restarted following elective surgery. In contrast to Wysokinski at al. who recommend re-initiation of NOACs ≥48 hours post-surgery, the EHRA recommends earlier reinstitution of NOACs 6-8 hours post-hemostasis or even bridging with heparin products until 48 hours after surgery when NOACs would be safe to use.[2,12] Early post-operative reinstitution of NOACs might increase the risk of bleeding which could prove deleterious, particularly in the absence of well-validated reversal agents.

Ideally, NOACs should be initiated a time point after the procedure when hemostasis is complete. The decision to use periprocedural bridging therapy with short acting heparin products is a clinical decision which needs to account for 3 different factors:

1. The risk of thrombosis objectively derived from the CHADS2 Vasc scores;
2. The risk of bleeding associated with the procedure by itself;
3. And the adequacy of hemostasis.

It is highly recommended that clinicians assess adequacy of hemostasis in conjunction with the primary procedure operator before resumption of NOACs. Due to the fast onset of action of NOACs, bridging is not recommended except in cases of high CHADS2 vasc scores or in instances where the risk of re-bleeding is high (to facilitate reversal if indicated), wherein bridging with short acting heparin products may be considered until one reaches a point where NOAC resumption is considered safe. A rule of thumb is to initiate bridging therapy in those with high risk of thrombosis at 24-48 hours after the procedure until NOACs can be safely resumed.

Emergent Surgeries and Major Bleeding: Role of Antidotes Targeted Towards Specific NOACs

Enhancements in the understanding of NOAC pharmacology has paved way for the development of specific fast-acting antidotes which are presently being evaluated. Idarucizumab is a monoclonal antibody fragment targeted to bind dabigatran which has demonstrated complete reversal of anticoagulant activity within minutes of administration in a prospective cohort of 90 patients in the Reversal Effects of Idarucizumab on Active Dabigatran (REVERSE AD) trial.[22] Andexanet Alfa, a recombinant engineered variant of human factor Xa has been recently evaluated in a phase III trial with 33 patients for up to 90% reduction of apixaban anticoagulant activity within 2-5 minutes of administration. Preliminary results from the Andexanet Alfa a Novel Antidote to the Anticoagulant Effects of fXA Inhibitors – Apixaban (ANNEXA-A) trial have shown no serious adverse prothrombotic effects.[23] Similar results for rivaroxaban (ANNEXA-R) reversal are currently being evaluated. PER977 (Perosphere), has demonstrated near-complete reversal of edoxaban activity within 10-30 minutes of administration without prothrombotic effects.[24] Notably, this agent is a non-specific antidote which has been shown to provide effective and rapid reversal of anticoagulant effects of both direct thrombin inhibitors and all commercially available oral factor Xa inhibitors.[24] With the advent of multiple antidotes which provide rapid reversal of NOAC effects, one could expect further minimization of TIs of NOACs in the periprocedural setting.

Often, reversal agents such as fresh frozen plasma or prothrombin complex concentrates (PCC) have counterproductive prothrombotic effects such as systemic thromboembolism, myocardial infarction and stroke. A meta-analysis comprising of 27 studies evaluating use of PCC in vitamin K antagonist reversal for emergent surgeries

Table 5: Unified Recommended Timing (in hours) for Discontinuation of Non-Vitamin K Oral Anticoagulants Prior to the Procedure

Agent	Bleeding Risk Associated With the Procedure	
	Low Risk	High Risk
Rivaroxaban*	≥72	≥96
Apixaban†	≥24	≥48
Edoxaban‡	≥24	unclear

Procedures with high risk of bleeding include cardiac surgery, vascular surgery (excluding endovascular procedures) and neurosurgery where bleeding could be deleterious; Most other procedures are considered low risk for bleeding.
*Data derived from ROCKET-AF trial. †Data derived from ARISTOTLE trial. ‡Data derived from ENGAGE TIMI-48 trial.

or for severe bleeding showed a significant incidence of systemic thromboembolism (0.7-1.8%) and a mortality rate of 10.6%.[25] These results further reinforce the need for specific NOAC reversal agents.

Conclusion

In conclusion, patients with CKD present a diverse population in whom considerable heterogeneity exists in the timing of stoppage of NOACs prior to the procedure. Data emerging from landmark prospective trials such as RE-LY, ROCKET-AF and ARISTOTLE have simplified the approach to this specific clinical scenario and considerably reduced the heterogeneity noted in in this timing.[9,17,19,21] Lesser emphasis is being placed on the level of renal compromise (except for Dabigatran) and more on the bleeding risk associated with the procedure. With the emergence and ongoing development of rapid-acting and effective antidotes for NOACs, there is immense potential to reduce duration of TIs, costs of bridging therapy and minimize risk of bleeding and thromboembolic complications in the perioperative setting. Important clinical decisions such as when to withhold and resume NOACs in relation to procedures, as well as the need for bridging therapy should be individualized based upon the patient profiles which account for risk of thromboembolism and the risk of bleeding associated with the patient profile and the procedure per se. Multicentric registry data could further enhance our understanding of this peculiar clinical scenario.

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Mapping Atrial Fibrillation: 2015 Update

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Abstract

Atrial fibrillation requires a trigger that initiates the arrhythmia and substrate that favors perpetuation. Cardiac mapping is necessary to locate triggers and substrate so that an ablation strategy can be optimized. The most commonly used cardiac mapping approach is isochronal or activation mapping, which aims to create a spatial model of electrical wavefront propagation. Historically, activation mapping has been successful for mapping point source and single or double wave reentrant arrhythmias, while mapping multiple wavelets or driving sources that underlie most episodes of atrial fibrillation remains challenging. In the multiple wavelet model of AF there is no particular area critical to sustain atrial fibrillation, and a "critical mass" of atrium is required to maintain AF. Recent studies suggest endocardial and epicardial dissociation may play an important role. Investigation of driving sources that sustain AF has focused on the presence of rotors. Rotors in human AF have now been observed using multiple imaging modalities, however ablation strategies targeting rotors remain of unproven benefit. In addition, substrate mapping of AF is now feasible. Increasing degrees of atrial fibrosis on delayed enhancement magnetic resonance imaging (DE-MRI) has been shown to correlate with poor procedural outcomes for AF ablation, which suggests the increased burden of scar promotes more complex and extensive arrhythmia substrate. Atrial fibrosis is also identifiable using electrogram voltage tagging in an electro-anatomic mapping system. Patient-specific ablation strategies targeting areas of fibrosis are currently under investigation. Recent technological advances have facilitated greater understanding of the potential role for AF mapping and has allowed initiation of clinical studies to evaluate the effectiveness of mapping-based intervention. Multi-modality mapping is likely to play an increasingly important role in AF ablation, but is currently limited by the inability to simultaneously record and interpret electrical signals from both atria and from both the epicardium and endocardium.

Introduction

Atrial fibrillation requires a trigger that initiates the arrhythmia and substrate that favors its perpetuation. The majority of ectopic discharges initiating atrial fibrillation (AF) emerge from the pulmonary vein sleeves.[1] Rapid activity from the PVs may be due to new impulses generated due to automaticity, triggered activity or from micro-reentry due to abnormalities in PV tissue.[2] These impulses propagate into the posterior LA wall where highly heterogeneous and anisotropic fiber bundle arrangements and abrupt changes in thickness provide an ideal substrate for sink-to-source mismatch, wave-break, and reentry formation.[3,4] Theoretically, catheter ablation for AF may be aimed at destroying the trigger mechanism or altering the perpetuating substrate or both.

Subjects with AF represent a spectrum of patients with arrhythmia episodes varying in duration, frequency, pattern of onset, triggers and mode of termination. Persistent and permanent forms of AF incorporate more complex electrical and structural remodeling forming the necessary substrate for AF maintenance. In these patients, persistence of AF depends on an "arrhythmogenic substrate."

Structural changes are part of the progression of atrial disease and contribute to AF being permanent.[5] In many cases, AF may progress from paroxysmal to persistent forms through the influence of atrial remodeling caused by the arrhythmia itself and/or progression of underlying structural heart disease.[6] Progressively longer duration AF is observed after repeated AF induction (either via burst stimulation or rapid atrial pacing) in both the goat and canine models of AF, a concept referred to as "AF begets AF".[7,8] The increased AF stability is associated with a decrease in atrial effective refractory periods (ERPs), increased spatial heterogeneity of ERP and loss of normal ERP rate adaptation.[7] Until recently there has been relatively limited data characterizing wavefront patterns in human persistent AF due to the spatial-temporal complexities and technical challenges. Improved understanding of the underlying mechanism of AF is critical for developing treatment modalities for AF.

Key Words:
Atrial Fibrillation, Catheter Ablation, Mapping.

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Theoretically, catheter ablation for AF may be aimed at destroying the trigger mechanism or altering the perpetuating substrate or both. However, a selective ablation approach requires knowledge of the underlying mechanism. The success of PVI in eliminating AF episodes can be attributed to a number of factors such as:

1. Isolation of the trigger(s),
2. Modification of the arrhythmogenic substrate located in the pulmonary veins and left atrial posterior wall,
3. Interruption of crucial pathways of conduction,
4. Atrial debulking or
5. Atrial denervation. Reported success rates for AF ablation vary widely in the published literature ranging from 40% to 70% and suggest a need for better patient selection criteria.[9] Cardiac mapping may be a suitable tool to acquire knowledge of the arrhythmogenic substrate necessary for selection of the optimal ablation strategy.

Activation Mapping

The most commonly used cardiac mapping approach is isochronal or activation mapping, which creates a spatial model of the wavefront excitation sequence. The crucial element in cardiac activation mapping is correct interpretation of the electrogram morphology and timing consistent with local activation. Mapping of AF is particularly challenging as there is a considerable beat-to-beat variability in the morphology, timing and duration of fibrillation potentials; as AF persists for longer duration a greater number of prolonged and fractionated potentials are seen. These complex and variable recordings hamper appropriate determination of the local activation times. There is no question that AF is disorganized, but whether that disorganization results from organized sources or whether it is the primary driver of AF has been debated for years.[10] Decades of simulation, animal, and human studies have lead to the development of two schools of mechanistic thought: multiple wavelets vs. small number of driving sources.

Multiple Wavelets

Factors such as shortened ERP, ERP heterogeneity, slowed conduction, increased tissue mass increase the stability of AF in the multiple wavelet model in which no particular area is critical to sustain AF.[2] Multiple studies have provided evidence that suggest that AF requires a 'critical mass' of tissue.[11,12] Perpetuation of AF is determined by the number of simultaneously wandering wavelets.[13] Thus, a larger atrial mass can accommodate more wavelets, thereby stabilizing AF and reduction of atrial mass may therefore be anti-fibrillatory. Although, one may sometimes observe fibrillatory conduction confined within PVs isolated in a wide circumferential fashion, it rarely persists (figure). It is thought that PVI efficacy may be in part related to diminishing atrial mass as a significant amount of atrial myocardium may be replaced by scar tissue.[11,12]

Evidence is accumulating that persistent AF in patients with structural heart disease is a complex 3-dimensional problem.[14-17] A recent study of high-density, segmental, biatrial mapping of acute and persistent AF during cardiac surgery has provided evidence for a variation of the multiple wavelet concept in which the substrate of persistent AF is the result of progressive endo-epicardial dissociation, transforming the atria into an electrical double layer of dissociated waves that constantly 'feed' each other.[15] In patients with long-standing AF, endo-epicardial breakthroughs were found to generate >400 fibrillation waves per second,[15] and 35% of the fibrillation waves have been shown to arise from a focal point on the epicardium, distributed over the entire atrial surface.[16] Progressive uncoupling of cardiac myocytes and muscle bundles was identified as the main mechanism of enhanced AF stability ("longitudinal dissociation"). Epicardial breakthrough was enhanced in persistent AF patients, hypothesized to be due to more electrical dissociation between the epicardial layer and endocardial bundle network.[15] In a goat model, progressively longer duration of AF was associated with pronounced dissociation of electrical activity between the epicardial layer and the endocardial bundle network owing to progressive electrical uncoupling between these layers, leading to increasing stability and complexity of the AF substrate.[17] Additional studies with simultaneous bi-atrial mapping and simultaneous endo-epicardial mapping are required to better characterize the role of endo-epicardial dissociation in the maintenance of AF and to understand any possible implications for the interventional management of AF. Clearly, our current ablation procedures routinely map the endocardium alone, which limits our field of view. Perhaps body surface mapping techniques or pericardial access may be necessary to get a complete picture as mapping techniques are refined.

Driving Sources

Specific sources that have been hypothesized to drive AF include stable reentry circuits known as "mother waves", which are unstable re-entry circuits which can sustain AF as long as at least one is always present, and rotors that can be fixed or wandering through the atria.[2] Studies postulate that these rotational waves are the major organizing centers of AF with a hierarchical distribution of local excitation frequencies, mostly originating from the left atrium (LA), in particular the posterior LA.[18-21]

Identification of driving sources remains a clinical challenge. Complex fractionated atrial electrograms (CFAE) sites may represent critical areas responsible for the maintenance of AF.[22,23] When used in combination with pulmonary vein isolation (PVI), CFAE site ablation has been shown to result in acute AF slowing and termination and long-term freedom from AF recurrence.[24,25] Although CFAE sites are purported to represent critical sites crucial to AF perpetuation, some CFAE may represent sites of passive wavefront collision, which are not important to the maintenance of AF.[26] Recent studies have shown increased incidence of AT following CFAE site ablation without improvement in overall arrhythmia-free survival,[27] and thus the role of CFAE mapping and ablation in AF ablation remains unclear.

An important property of the bipolar EGM is the direct relationship between wavefront direction and EGM amplitude.[28,29] Changing wavefront direction near the rotor pivot has been hypothesized to lead to changes in EGM morphology and information content, while bipoles located at the periphery of rotating waves should have relatively stable EGM morphology because of consistency of wavefront direction approaching these locations. Shannon entropy is a statistical measure based on the distribution of amplitude values within the signal histogram that may identify areas of wavefront pivot that correspond with rotors. Increased Shannon entropy was noted at wavefront pivot points in a study of multiple models of AF, however, in the same study there was no association between CFAE regions and wavefront pivot points.[30]

Clinical evidence supporting the presence of localized sources of AF includes the presence of stable frequency gradients between and within the atria,[31] the presence of consistent and reproducible

directions of propagation in AF within the atria in many patients,[32] and the ability of ablation to modulate AF before trigger sites are isolated or lines are complete.[33]

Dominant frequency (DF) mapping is aimed at identifying localized sites of maximal DF (DFmax) during AF.[34,35] Retrospective analyses have shown that radiofrequency (RF) ablation at such DFmax sites results in slowing and termination in a significant proportion of paroxysmal AF patients, indicating their role in AF maintenance.[35] Furthermore, RF ablation leading to elimination of LA-to-RA dominant frequency gradients has been reported to predict long-term SR maintenance in AF patients,[31] although these findings have not been confirmed in all studies.[36] Recently, frequency gradients have been shown to persist as AF progresses from paroxysmal to persistent using a chronic RA tachy-pacing model of persistent AF in sheep,[37] suggesting that the location of driving sources are likely stable over time. A growing body of evidence suggests that rotors may be a key driving source of AF.

Rotors have been defined using three key characteristics:

1. Extreme wavefront curvature at the core in which head meets tail,
2. An excitable and precessing core,
3. A highly variable reentrant wavelength, with an often-undetectable excitable gap.[38,39] These criteria distinguish rotors from other rotational arrhythmia mechanisms such as classical reentry, in which electrical activity around a fixed obstacle occurs with a fixed wavelength and an excitable gap, and leading circle reentry, in which reentrant circuits surround a functionally inexcitable core that remains in a stable position. Investigators have proposed that these differences, particularly the precessing core, made rotors undetectable in-vivo until novel mapping approaches were developed to allow a greater field of view of atrial electrical activity.[38]

Rotors were first demonstrated in human AF using a system in which filtering and digital processing of intracavitary signals obtained using 64-pole atrial basket catheters (eight splines of eight electrodes; Constellation, Boston Scientific, Natick, MA, USA)[40-42] and analyzed using a proprietary algorithm (Topera Inc.) that produces a video of the computed activation processes of the right and left atria during AF. A mapping and ablation strategy, targeting Focal Impulse and Rotor Modulation (FIRM), successfully identified an electrical rotor somewhere in the right or left atrium in 98 of 101 patients with sustained AF[40] and RF energy delivered at the center of the rotor terminated AF in 31 of 36 patients (86%). Rotor ablation, in addition to conventional ablation, resulted in an almost doubling of the long-term success rate. After a median of 273 days, 82.4% vs. 44.9% of patients were reported to be free from AF,[40] although some of these patients had AT as a recurrent arrhythmia or required multiple procedures and antiarrhythmic drugs to maintain SR. Importantly, AF sources were analyzed to be coincidentally ablated in 45% of conventional cases (e.g., at the LA roof or near the PVs).[41] This coincidental ablation of driving sources might help explain why wide area PVI is more effective than more ostial PVI, and especially, why patients might remain free of AF recurrences despite PV re-connection. These data, however, are to be interpreted with caution given that treatment assignment was not randomized and conventional ablation did not necessarily include currently accepted means of improving PVI efficacy such as monitoring of impedance during ablation,[43] assessing dormant PV conduction using adenosine, using contact-force sensing ablation catheters, or assessing pace-capture of the ablation lesion set.[44]

A recent multi-center registry of patients who underwent rotor ablation followed by PVI showed a single-procedure freedom from AF at 1 year of 80.5% in a cohort that included patients with paroxysmal AF, persistent AF, and long-standing persistent AF.[45] This promising and novel technique may be improved with the use of catheters with more electrodes than the currently available 64 electrode basket catheter and improved catheter design to achieve more uniform electrode distribution and stable electrode contact to the atrial wall.

A novel technique of mapping persistent AF is the reconstruction of atrial activation to identify drivers of AF by body surface mapping. In this technique a computed tomography scan is used to obtain the biatrial geometry and relative positions of the 252 body surface electrodes after which a specific signal analysis process, combining filtering, wavelet transform, and phase mapping, is applied to transform the signals from the thorax into a movie of atrial activation (CardioInsight Inc., Cleveland, OH, USA).[46] One patient with paroxysmal AF and one patient with persistent AF were mapped a few hours before the ablation procedure was started. In the patient with persistent AF, a drifting rotor was identified in the LA wall that was not stationary for more than two rotations. Ablation at the rotor locations abruptly converted AF into atrial tachycardia after 10 min of RF application. Thus, noninvasive AF mapping may identify active sources like (stable or unstable) rotors and may help identify a patient-specific ablation strategy. As AF persists for longer durations, driving sources were found more frequently and AF termination with ablation was more rare. Most importantly, validation studies are needed to compare clinical outcomes from ablation of rotors detected by each technique.

The ongoing debate regarding the underlying activation pattern of AF may largely reflect differences in approaches to mapping AF. A clear and important discrepancy exists between the results of direct high-resolution mapping of AF,[14-16] and computed maps based on lower resolution intracavitary or body surface recordings.[40-42,46] Whereas a larger field of view appears to exhibit a large rotor that drives the rest of the atria in an irregular way, high-resolution mapping suggests a higher degree of complexity, with rotors happening only transiently or not at all. An important question is whether higher complexity during AF is missed by lower-density mapping and observed rotors are inappropriate extrapolations of insufficient data, or perhaps higher density mapping may miss rotors because it is too focused on the details at the expense of the "big picture." High density, simultaneous mapping of the entirety of both atria during surgery has recently been shown to be feasible and may provide both the large field of view and high electrode density required to address this question.[47] Given that multiple groups now report rotors in AF using different techniques, the debate regarding rotors is shifting towards clinical trials that will define the best approach toward identification and ablation of rotor sites using various novel technologies and whether this substrate approach improves the success of ablation compared with conventional anatomically based ablation. The reproducibility of individual patient maps over time, the duration of AF mapping required to capture all potential sources, the role of epi-endocardial dissociation, and necessary spatial mapping resolution all require further investigation.

Substrate Mapping

Studies have demonstrated that AF is associated with electric,

contractile, and structural remodeling in the LA that contributes to the persistence and sustainability of the arrhythmia.[48] Atrial structural remodeling promotes atrial tissue fibrosis, which perturbs the continuous cable-like arrangement of atrial cardiomyocytes and slows atrial conduction.[49] In contrast to electrical remodeling, which reverses after resumption of sinus rhythm, the structural changes seen in the atria take longer to recover and recovery is incomplete.[50,51] The degree of voltage reduction may help grade the severity of tissue pathology underlying AF, and preliminary results suggest that the success of pulmonary vein isolation is reduced when substantial low-voltage tissue or preexisting scar is present.[52] Whether fibrotic transformation of atrial myocardium is a cause or consequence of AF in patients with cardiovascular disease remains unclear.

There is now increasing evidence that even in patients with "lone" or idiopathic AF, the AF is an arrhythmic manifestation of a structural atrial disease which has recently been defined and described as fibrotic atrial cardiomyopathy (FACM).[53,54] This may explain AF recurrence following a period of stable sinus rhythm after ablation with durable PVI. Such progression is seen with other substrate-based arrhythmias (e.g., ventricular tachycardia in ischemic or nonischemic ventricular cardiomyopathy), in which remodeling of the substrate after an initially successful ablation may lead to new arrhythmias.

Electroanatomic bipolar voltage mapping has been described to define the relationship between anatomic and electrophysiological abnormalities in an experimental model[55] and is now used in clinical electrophysiological studies for substrate description in atrial arrhythmias. Low bipolar endocardial voltage can be identified and localized using an electroanatomic mapping system. It is unclear at this time if this information is beneficial for guiding catheter ablation. Investigators have reported anecdotal success with a new patient-tailored ablation strategy – box isolation of fibrotic areas,[56] however these findings require further evaluation.

Alternatively, delayed-enhancement magnetic resonance imaging (DE-MRI) is an established method for visualizing tissue necrosis and scarring in cardiac disease processes, including myocardial infarction and myocarditis.[57,58] Contrast enhancement occurs as a result of altered washout kinetics of gadolinium relative to normal surrounding tissue, which may reflect increased fibrosis or tissue remodeling of the myocardium.[57] Using DE-MRI, atrial fibrosis has been categorized into four stages (Utah I – IV) with higher grades corresponding to greater fibrosis.[59,60] The feasibility of DE-MRI to provide a noninvasive means of assessing left atrial myocardial tissue in AF patients has recently been demonstrated, and patients with a greater extent of delayed enhancement in the LA wall have been shown to suffer much higher recurrence rates after PVI for AF.[59,60,61] The role of targeting areas of DE-MRI identified atrial fibrosis during catheter ablation remains unclear and is currently under investigation.

The relationship between fibrosis on substrate maps and drivers on activation maps has yet to be defined. Of note, a recent study demonstrated that extensive MRI-based atrial fibrosis was associated with a lower prevalence of fractionated electrograms.[62] These findings suggest that drivers of AF may localize independently of substrate for AF, however.

Conclusions

After decades of investigation and debate, recent technological advancements have brought the field of AF mapping to an inflection point, and understanding of the fundamental nature of AF now seems within reach. While greater understanding of AF activation patterns and AF substrate have occurred in parallel, the relationship, if any, between activation patterns and substrate remain unknown. Future studies will be aimed at development of tailored ablation strategies based on integration of anatomical and electrophysiological characteristics. After over 50 years of investigation, AF mapping is just beginning to move into the realm of clinical practice.

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Syncope And Atrial Fibrillation: Which Is The Chicken And Which Is The Egg?

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Abstract

Syncope and atrial fibrillation are both common entities and frequently occur together in an acute clinical scenario. Treatment of each in this presentation requires acquiring a good history and understanding the presentation of the patient. In this manuscript, there are 5 case studies that demonstrate common misperceptions when attempting to treat syncope when it presents with the arrhythmia atrial fibrillation. Rarely, does atrial fibrillation cause syncope. However, when a patient presents in atrial fibrillation, it becomes the focus of therapy rather than trying to define the etiology of the syncopal episode. It may be that well thought out algorithms to treat atrial fibrillation in an acute setting are replacing deductive thinking particularly when it comes to diagnosing the cause of a syncopal spell.

Introduction

Both syncope and atrial fibrillation are common disease entities, frequent contributors to the economic footprint of the healthcare system, both leading to frequent admissions and to significant morbidity. Both are often associated with other syndromes such as sinus node dysfunction and stroke. Both are multifactorial in etiology. As most electrophysiologist, and indeed most healthcare workers in fact, are aware: they can both be challenging to treat.

Both Are Common Clinical Entities

Syncope

Syncope is defined as a transient loss of consciousness, with unresponsiveness, loss of postural tone and spontaneous recovery. By definition, with spontaneous termination, specific attempts at resuscitation are not required. It is thought to occur in 40% of the population. It is a symptom frequently seen in 12%-48% of young healthy adults, most of whom do not seek evaluation. Nearly 60% with a syncopal episode who seek attention and have some evaluation will not have a recurrence. But it is a disease that affects all ages: the elderly in long-term residence care may have a 6% annual incidence of syncope. Falls occur in 20% of those over age 65 years and 10% of falls in this population are caused by syncope. Approximately, 1% to 3% of emergency department/ urgent care visits are related to syncope. Nearly, 35% of these individuals with an emergency department diagnosis of syncope are admitted. In 2000, there were over 200,000 hospital admissions with a diagnosis of syncope. The estimated cost was 2.5 billion dollars. In those hospitalized with an unclear etiology for their syncopal spell, the actual diagnosis remains a mystery in the vast majority (~ 90%).

Atrial Fibrillation

This is the commonness cardiac tachycardia. In the space of 30 years it has gone from a topic of clinical nuisance to now a disorder of major clinical importance. In the early 1990's, the prevalence of atrial fibrillation was at the 1%-2% level of adults in the United States. Twenty years later, the prevalence ranges from 1% to 6% but is generally quoted to be in the 5% neighborhood. This is best explained by the overall increase in life expectancy in this country. The average female will live to be 81 years old and the average male will reach 76 years old. The prevalence of atrial fibrillation is both age and sex related. At age equivalents, more men have atrial fibrillation than women. Those individuals below age 50 years have an incidence that is less than 1% but it is greater than 8% in those over age 80 years. The incidence increases significantly after age 65 years where the incidence shifts from 1% to the 2% - 4% range. The trend has been for the total number of individuals with atrial fibrillation to increase in accordance with the aging population increase. The number of individuals with atrial fibrillation in 1980 was 1.3 million and in 1995 a little over 2 million. Naccarelli et al.[2] estimated that

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None.

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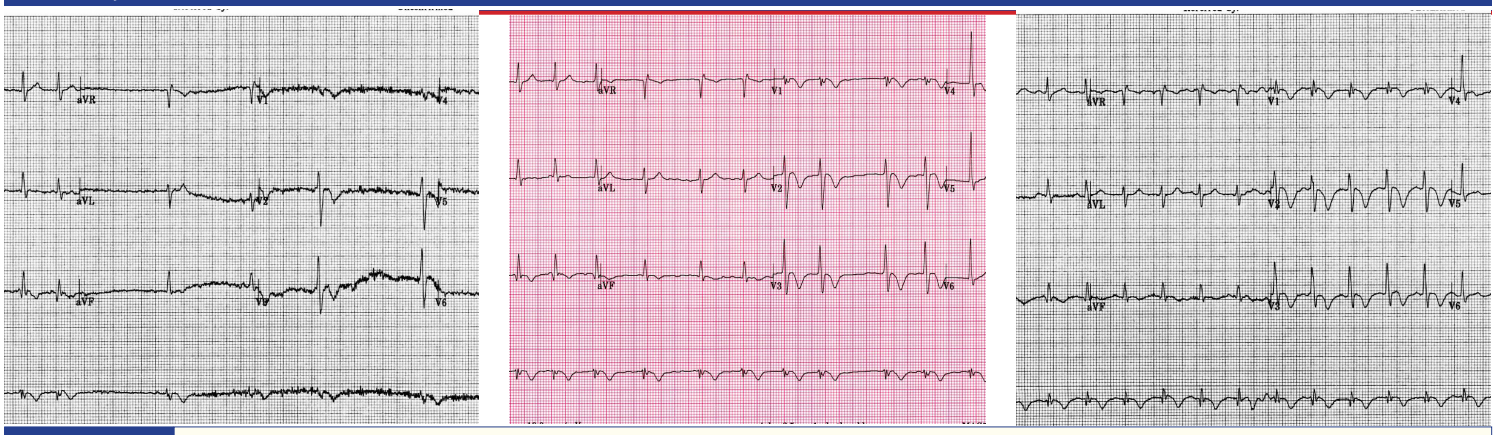

Figure:1 This is ECG is recorded during syncope. Initially, there is atrial fibrillation, average rate 125 bpm. There is sudden ventricular rate slowing. There is an S1-Q3-T3 pattern and inverted T waves in the anterior precordial leads, which are findings consistent with pulmonary embolism

in 2005, 3.03 million individuals in the United States had atrial fibrillation and the projected prevalence may be 7.56 million by 2050.

Both Can Precede The Other

Case study#1: PK, a 35 years old male bartender was brought to the emergency department (ED) for recurrent syncope. He had worked the night before and following an episode of syncope, went home early from the bar. When he awoke the next morning, he had symptoms of dizziness, fatigue, and shortness of breath. Later that day he had another syncopal event and was brought to the hospital. Pertinent medical history included the fact that he had fractured ribs from a motor vehicle accident 3 weeks earlier and more recent 3 days of nausea and vomiting. His medicines on presentation included nuprin for pain and LIPO 6 (for weight loss). In the ED, he was found to be in atrial fibrillation with a ventricular response rate of 100 bpm and a systolic blood pressure less than 100 systolic. His respiratory rate was 18/ minute, temperature 100.4°F (38°C) and weight of 180 lbs. (81 kg). On physical examination, the jugular venous pressure was elevated and the pulse irregularly irregular. His lungs were clear and there were no additional cardiovascular findings. Although he was awake and oriented, he appeared anxious and agitated. Given his hemodynamic compromise, direct current cardioversion was performed of atrial fibrillation with two unsuccessful attempts. Cardiology was consulted and a new ECG (Figure 1) was performed as the patient has another witnessed episode of syncope. An urgent chest CT was performed but unfortunately the patient succumbed from what was eventually found to be massive bilateral pulmonary emboli in the ED.

Syncope

This case illustrates several points: atrial fibrillation rarely causes syncope and does not usually cause hypotension when ventricular rates are normal. One must consider the possibility that another another factor was involved. The patient had recurrent syncope with alternating tachycardia (atrial fibrillation) followed by profound sinus bradycardia suggesting some autonomic nervous system input. This was a young health individual on an NSAID plus a sympathomimetic weight loss supplement and was dehydrated from nausea and vomiting. He presented with shortness of breath, periodic hypotension with bradycardia alternating with tachycardia and an ECG with an S1-Q3-T3 pattern. The syncope in this instance was due to pulmonary emboli, which had lead to the initial presentation of atrial fibrillation.

Table 1: Clinical Presentation and Diagnosis

Metabolic	Hyperventilation, hypoglycemia, intoxication	Slow	Slow
Neurological	CVA, TIA, seizures	Fast	Slow
Cardiac	Structural (stenosis, obstruction), Arrhythmia, Neurocardiogenic	Fast	Fast

A thorough analysis of the history is mandatory and it is still integral to determining the correct diagnosis. The history in case #1 indicates that syncope had a "fast onset" and "rapid offset". Most often this would point to a mechanism that is either cardiac, autonomic reflex, autonomic failure or postural in origin and not cerebrovascular in nature. This is not related to intoxication, hyperventilation or hypoglycemia since the onset of repeated syncopal spells is not one of slow onset and slow recovery.[3]

Atrial Fibrillation

In case #1, the aggressive approach to treating atrial fibrillation with direct current cardioversion in the emergency department reflects the use of rigid algorithmic logic (that can occasionally be seen in the ED). A patient presents with atrial fibrillation and syncope and is found to be hypotensive. The algorithm would dictate using direct current cardioversion to treat the atrial fibrillation when a patient presents with hypotension, pulmonary edema, symptomatic angina pectoris or acute myocardial infarction. However, algorithms do not take into account that the atrial fibrillation is not directly responsible for the hypotension but is just an innocent bystander. In the ECG shown, atrial fibrillation spontaneously alternates with sinus bradycardia during the episode of syncope, the mechanism of which seems related to an autonomic nervous system factor. We must assume that the initiating factor is adrenalin related to hypotension or possibly a neurocardiogenic vagal triggered mechanism. In this case, direct current cardioversion is inappropriate at this time in the ED.

Both Can Be Induced By An Increase In Vagal Tone

Case Study #2

DK, a healthy 74 years old female is standing in her kitchen when she developed the sudden onset of nausea, followed by syncope. She presented to the emergency department (ED) in normal sinus rhythm. The physical examination and baseline laboratory evaluation were normal. In the ED, she had more nausea and a repeat syncopal episode. Telemetry monitoring showed sinus bradycardia followed by PR interval prolongation, complete AV block, asystole, then atrial fibrillation. (Figure 2) Atrial fibrillation persisted initially with a slow

Table 2: Syncope: Risk Stratification Studies

European Society of Cardiology (ESC)	**2004 (ref. 15)**
Evaluation in the ED Study (SEEDS)	2004 (ref. 16)
Osservatorio Epidemiologico sula Sincope	
Nel Lazio (OESIL)	2003 (ref. 17)
Short Term Prognosis of Syncope (STePS)	2008 (ref. 18)
San Francisco Syncope Rule (SFSR)	2004 (ref. 19)
Evaluation of Guidelines in Syncope Study	
(EGSYS)	2008 (ref. 20)

Table 3: High Risk Syncope

Cardiac Diagnosis:
Clinical: Syncope with exercise, Family history of SCD,
Previous MI.
Structural disease: low EF, Hypertrophic CM, Dilated CM
ECG: LBBB; RBBB+ LAFB; IVCD; LQT; Brugada; WPW;
Bradycardia < 50 bpm; Epsilon wave of ARVC/D
Rose Criteria: "BRACES":
Central Nervous System Event:
TIA; CVA (with focal neurological signs); New seizures

junctional escape rhythm then as the ventricular response increased there was spontaneous recovery.[4] Tilt table testing replicated syncope and atrial fibrillation. There is both vagal induced syncope and vagal induced atrial fibrillation.[4]

Syncope

In classic vasovagal syncope, patients may have a prodromal picture consisting of a flushed feeling, diaphoresis, nausea, abdominal pain or discomfort, lightheadedness and pallor.[5] The elderly may not have this classical prodrome or it may be greatly abbreviated.[5] The classic triggers include prolonged standing, hot temperatures, emotional stress (like fear), venipuncture, pain, dehydration and systemic illness. It can also occur while seated and may be precipitated by alcohol.[5] The prevalence of vasovagal syncope ranges from 8-37% and all of reflex-mediated syncope ranges from 9-49% of all reflex-mediated syncope.[1] On average, a neurocardiogenic mechanism will be the cause of syncope about 18% of the time while some form of organic heart disease accounts for 4% and cardiac arrhythmia another 14%.[1] Vasovagal syncope may be the explanation in as many as 31% of those over the age 65 years. With the advent of Tilt Table assessment of syncope, the incidence of unexplained syncope has been reduced by ½ to 17-18%.[1]

Using head up tilt testing, Brignole et al.[6] described three patterns of vasovagal syncope. The classic pattern is a (1) reflex decrease in blood pressure and heart rate, (2) a cardio-inhibitory (bradycardic) variety and (3) a dysautonomic response. Elderly patients tend to display the dysautonomic response with a slow decline in blood pressure with head up tilt. In the elderly, passive tilt table testing is positive in 32%-36% as compared to a younger population, in whom passive tilt table testing is positive in 60%-70%. The addition of nitroglycerin as a provocation agent increases the number of positive outcomes to 60%-70% in the elderly. This agent is safer than isoproterenol infusion is this population. Isoproterenol can be dangerous in those with ischemic heart disease, obstructive hypertrophic cardiomyopathy, aortic stenosis and accelerated hypertension. Head-up tilt table testing is very useful in elderly patients in helping to confirm one's clinical impression of vasovagal or dysautonomic syncope.

Atrial Fibrillation

Coumel first recognized bradycardia-induced atrial fibrillation and ascribed this to vagal stimulation.[7-8] Attuel demonstrated that atrial refractory periods in patients with vagal induced atrial fibrillation shorten with slowing of the heart rate. This paradoxical finding linked with an increase in atrial dispersion of refractoriness is the mechanism for vagal induction of atrial fibrillation.[10] The patient population of vagal induced atrial fibrillation favors men over women (ratio 4:1) usually between the ages of 25 and 60 years. Despite recurrent bouts of atrial fibrillation over several years, there seems little progression to permanent fibrillation. Episodes last from a few minutes to a few hours and tend to occur mostly at night or at rest. There is an association with gastrointestinal symptoms of nausea and indigestion as well as with alcohol ingestion.[11] Episodes can often trigger frequent urination. Digoxin, beta-blockers and calcium antagonist, (verapamil, diltiazem) are ineffective. Exercise and faster heart rates are salutary. It is generally thought that atrial fibrillation requires a critical mass of atrial tissue coupled with shortened atrial action potentials and increased dispersion of atrial refractoriness. Vagal mediated atrial fibrillation is usually in the setting of structurally normal atria. Therefore, the major factor in vagal facilitated atrial fibrillation is related to the degree of refractory period dispersion created by vagal shortening of atrial action potentials.[11] In case #2, this recently published example (4) of vagal induced atrial fibrillation is linked to vasovagal syncope. In this instance, tilt table testing was able to replicate both entities.

Both are Associated with Sinus Node Dysfunction

Case Study #3

HV was a 74 years old female with a history of paroxysmal atrial

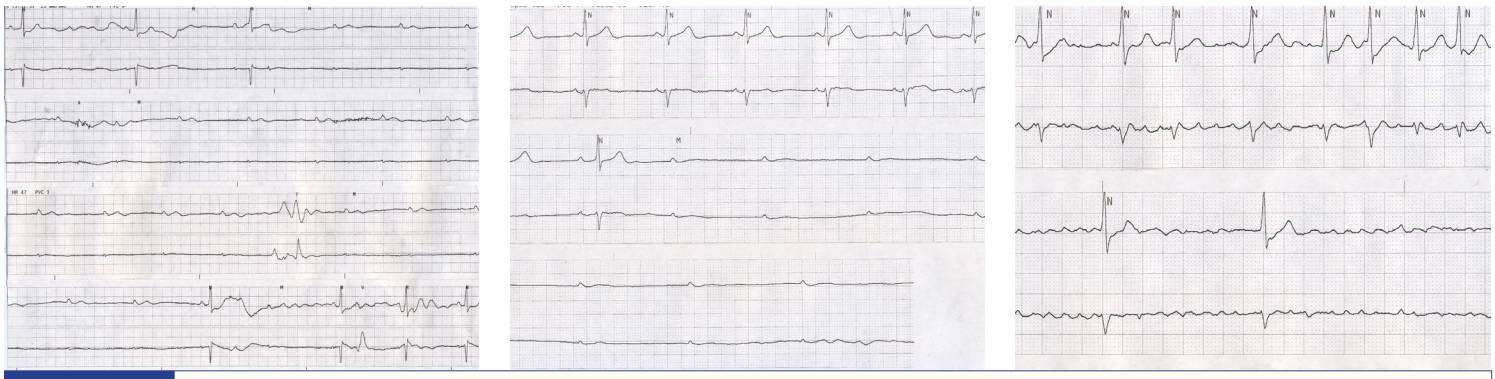

Figure:2 With the onset of vasovagal syncope, this continuous recording shows profound sinus slowing then complete AV block for 31 seconds followed by vagal induced atrial fibrillation with a slow ventricular response

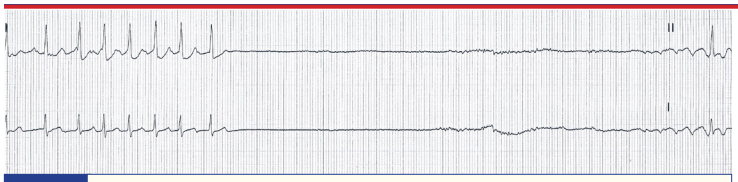

Figure:3 **During transport, the patient is given an intravenous injection of diltiazem. This recording during transport confirms the diagnosis of tachycardia-bradycardia syndrome with atrial fibrillation suddenly terminating and resulting in a 7.2 second pause followed by resumption of atrial fibrillation**

fibrillation and recurrent syncope over a 4 year period. She had previously been on anticoagulation but this had been discontinued when she had a meningioma removed and had never been reinitiated. She continued to have infrequent palpitations. Recurrent atrial fibrillation had been documented on ECG at least once about one year prior. She described three distinct syncopal episodes, occurring 9 months, 3 months and one week prior to the current episode that had brought her to the ED. On the day of admission, she awakened with an upper respiratory infection. Her granddaughter noticed that she had seizure like activity and was unresponsive. She awoke spontaneously and appeared neurologically intact. Shortly there after, she had more seizure like activity that once again spontaneously recovered. Emergency medical personnel were called and she was found to be in atrial fibrillation with a rapid ventricular rate at 160 bpm on arrival. During transport, she was given a single dose of intravenous diltiazem. Syncope recurred in route to the ED. (Figure 3) She also had several further episodes of syncope and near-syncope in the ED. (Figure 4) Tachycardia-bradycardia syndrome was documented and a permanent dual chamber pacemaker was implanted.

Syncope

In older individuals, syncope when associated with paroxysmal atrial fibrillation should suggest the presence of underlying sinus node dysfunction. Tachycardia-bradycardia syndrome is the most common presentation of sick sinus syndrome. Syncope occurs as tachycardia terminates with protracted sinus pauses. Failure of the sinus node to overcome overdrive suppression by atrial fibrillation causes sinus arrest. Reduced sinus node automaticity is the major problem. These patients have suppression of their escape or subsidiary pacemakers by the overdrive suppression of atrial fibrillation. Subsidiary pacemaker failure is enhanced by medications such as digitalis, beta-blockers and the calcium antagonist diltiazem or verapamil. In case #3, the patient unfortunately had suffered recurrent episodes of syncope which were not recognized until she presented with seizure-like activity. The week prior, she had presented with a fall and resultant head trauma. Her superficial wound was cleaned and closed with stitches and she was discharged from the ED. Given that atrial fibrillation had been documented on previous ECG recordings in the electronic medical record in this case, the connection between recurrent syncope and atrial fibrillation should have suggested a clinical diagnosis of tachycardia-bradycardia syndrome prior to the more severe presentation of seizure activity from sinus arrest. Permanent pacing is recommended in patients with recurrent syncope in the setting of tachycardia-bradycardia syndrome to prevent symptoms.[12]

Atrial Fibrillation

Case #3 is a classic version with documented paroxysmal atrial fibrillation alternating with sinus bradycardia. It depicts how the algorithm to treat one particular entity, the tachycardia fails to take into account the second entity, the bradycardia. The intravenous diltiazem provided in the ambulance to treat her rapid ventricular rates accentuated the frequency and duration of sinus pauses and the recurrent seizure like activity that accompanied these pauses in the ED. Sometimes the approach that "the best medicine is less medicine" applies. The treatment of atrial fibrillation in this syndrome requires permanent pacing in conjunction with either antiarrhythmic agents or rate control drugs aimed at the AV junction. Atrial pacing alone generally does not help deter the recurrence of episodes of atrial fibrillation. However, ventricular pacing alone is recognized to cause an increase in the number of episodes of atrial fibrillation. Atrial fibrillation in those with sick sinus syndrome is mostly related to the extent of atrial scaring and fibrosis. Atrial fibrosis may be diffusely distributed with predominance in the areas of the sinus and AV nodes. Other influences, such as the degree of AV valvular regurgitation and the underlying imbalance between the parasympathetic and sympathetic limbs of the autonomic nervous system may also carry impact. Importantly, in the tachycardia-bradycardia syndrome, prognosis and mortality is linked to underlying cardiac pathology and function as well as systemic pathology. The arrhythmia is generally not the direct determinant of mortality given the currently available treatment modalities.[12]

Both Can Be Challenging

Case Study #4

DZ was a 57 years old male with palpitations and a remote history of syncope. He also had a prior history of nephritis with stage 3 renal insufficiency and persistent hyponatremia. He complained of persistent palpitations occurring generally at night and unrelated to exercise or emotion. An ECG on presentation documented atrial fibrillation with a rapid rate. (Figure 5) He was placed on flecainide 100 mg orally twice daily with resolution of atrial fibrillation and the associated palpitations. A follow up ECG showed sinus rhythm but on further review, also demonstrated type I Brugada pattern. (Figure 6) He has converted from atrial fibrillation to sinus rhythm on this agent. He has no symptoms of syncope or palpitations on flecainide even with the Brugada pattern ECG. Flecainide was discontinued and without any antiarrhythmic agent, he developed symptomatic

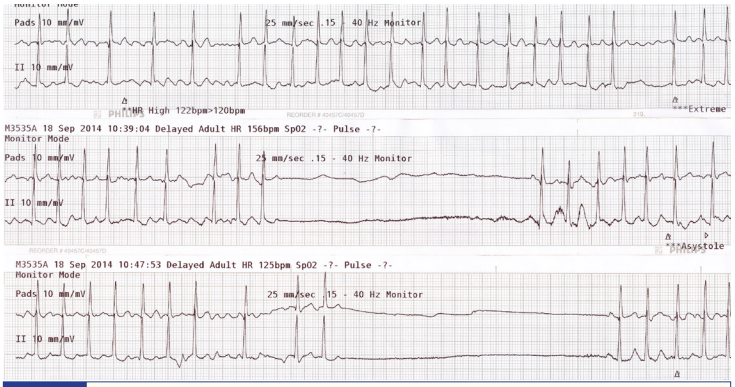

Figure:4 **There are 3 separate recordings in the emergency department. Top: There is atrial fibrillation with an average rate at 140 bpm. The patient is awake an alert. Middle: There is atrial fibrillation that terminates with a resultant 4-second pause and near syncope. There is a single sinus beat then the return of atrial fibrillation with a rapid ventricular response. Bottom: There is another symptomatic episode when atrial fibrillation terminates with a resultant 4.4-second pause followed by a single sinus beat then recurrent atrial fibrillation and a rapid ventricular response**

atrial fibrillation again. He was hospitalized and quinidine gluconate 324 mg was started orally every 8 hours. On quinidine, he converts to sinus rhythm and the ECG was normal.

Syncope

This patient had syncope but this occurred in the setting of atrial fibrillation and was orthostatic related. In this patient, the type I Brugada pattern ECG was provoked by the class IC antiarrhythmic agent flecainide. He remained asymptomatic in sinus rhythm on flecainide. With discontinuation of flecainide, his ECG normalized but atrial fibrillation recurred. The class IA antiarrhythmic agent quinidine gluconate was successful at restoring sinus rhythm. This agent has both sodium channel and potassium Ito channel blocking activity. Inhibition of the potassium Ito channel helped to reverse the Brugada ECG pattern. Syncope in the setting of an ECG documenting Brugada pattern is an indication for placement of an ICD. However, drug or fever induced Brugada pattern ECG has a more benign prognosis and generally does not warrant further testing or ICD placement.

Atrial Fibrillation

Atrial fibrillation is a commonly seen arrhythmia in patients with Brugada syndrome. The traditional antiarrhythmic agents used to treat atrial fibrillation may be contraindicated in this setting. Specifically, the class IA agents (procainamide, disopyramide) and IC agents (flecainide, propafenone) should be avoided as well as amiodarone, the class III antiarrhythmic. Quinidine may be useful at treating both atrial fibrillation and the ventricular arrhythmias seen in patients with Brugada syndrome. Quinidine has a salutary effect on the ventricular arrhythmias and Brugada ECG pattern with the inhibition of the potassium Ito channel. The complexity of trying to treat atrial fibrillation with Brugada syndrome is not just challenging but may in itself be potentially lethal.

Both Can Be Potentially Lethal

Case Study #5

SW was a 35 years old male who suddenly develops palpitations at home followed by syncope. He is brought to the hospital by emergency services with tachycardia and hypotension. The ECG on admission revealed an irregular wide QRS complex tachycardia at a rate 215 bpm. Adenosine was given intravenously without any adverse effects but the rhythm does not change. The patient was seen by our cardiology consult service and following sedation had direct current cardioversion performed with a single 200 joules synchronized biphasic shock. The ECG (Figures 7, 8) was diagnostic of atrial fibrillation with pre-excitation and Wolff-Parkinson-White syndrome. The patient subsequently underwent electrophysiologic testing and successful catheter ablation of a left lateral accessory pathway.

Syncope

As mentioned previously, atrial fibrillation rarely causes syncope. The notable exception is in the patient with Wolff-Parkinson-White (WPW) syndrome and a rapidly conducting accessory pathway. In this setting, syncope is seen when ventricular rates are exceedingly rapid. Syncope or near syncope with WPW are an indication for electrophysiology testing and catheter ablation to eliminate the accessory pathway.

Atrial Fibrillation

Atrial fibrillation may be seen in as high as a third of WPW patients. It is frequently associated with and triggered by the rapid rates of atrioventricular reentrant tachycardia. Wolff-Parkinson-White is a critical diagnosis in a young individual presenting with the ECG showing an irregular, rapid wide QRS complex tachycardia with varying degrees of QRS width. Patients resuscitated from cardiac arrest with atrial fibrillation and WPW rarely present with de novo ventricular fibrillation. Nearly all have mildly symptomatic episodes of tachycardia if not an overt presentation. Those at risk of sudden death have accessory pathways with very short antegrade effective refractory periods and the shortest R-R interval of less than 250 milliseconds. Agents that block conduction over the AV node and facilitate conduction over the accessory pathway are potentially lethal. Avoid the use of digoxin, diltiazem, verapamil and adenosine. Patients with atrial fibrillation and WPW should be referred to an electrophysiologist for evaluation and catheter ablation of the accessory pathway.

Both are the Focus of Algorithmic Therapy

In the five cases presented above, all are examples of syncope coupled with atrial fibrillation that when initially seen in the emergency department presented diagnostic and therapeutic dilemmas. All presented with or developed an arrhythmia, atrial fibrillation in the ED which tended to cause confusion in the approach to management. In 4 cases, the diagnosis responsible for syncope were: acute pulmonary embolism (case 1), vasovagal syncope (case 2), tachycardia bradycardia syndrome (case 3) and WPW and atrial fibrillation (case 5). In case 4, the syncope was remote from the ED presentation in atrial fibrillation. In all, the approach involved focusing on atrial fibrillation and rate control rather than focusing on making a diagnosis for syncope. This is an unfortunate common emergency department approach to the problem of syncope, which tends to focus on treatment of the rhythm instead.

The Concept of a Syncope Unit

There are several well thought out and constructed algorithms for risk stratification of syncope. (Table 2)[13-22] These are designed to aid in identifying individuals with syncope at high risk for cardiovascular events, life threatening arrhythmias and short-term risk of mortality.[21,22] Most emphasize the presence of structural heart disease, coronary disease in particular prior infarction and left ventricular dysfunction with heart failure. The ECG criteria that may point to an arrhythmic mechanism for syncope include the presence of bundle branch block, bifascicular block, intraventricular conduction delay, bradycardia (<50 bpm), pre-excitation, prolonged

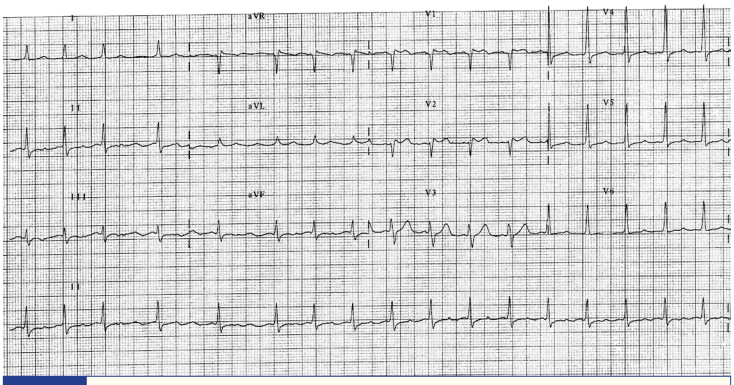

Figure:5 There is atrial fibrillation with an average ventricular rate at 90 bpm. The QRS complexes are narrow with a normal axis at +35 degrees. There is 1 mm J-point elevation with concave ST segments in V1 and V2 suggestive of a type 3 Brugada pattern

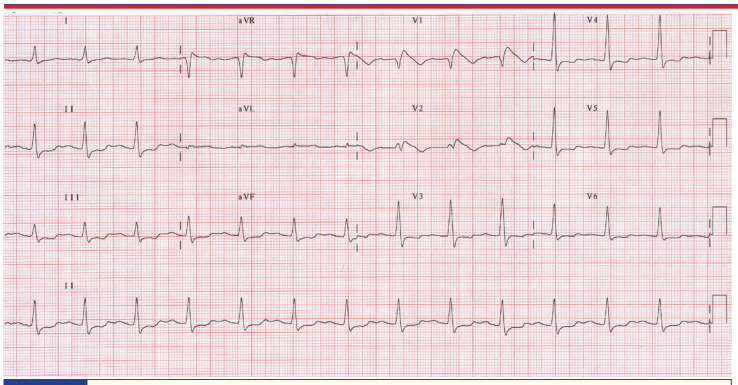

Figure:6 This ECG is recorded on Flecainide 100 mg orally bid. There is sinus rhythm with a type I Brugada pattern showing V1 and V2 ST elevation with inverted T waves

QT interval, Brugada pattern and epsilon wave of arrhythmogenic right ventricular cardiomyopathy. The ROSE (" Risk Stratification of Syncope in the Emergency Department) study included historical parameters, examination findings, biochemical, biomarkers and hematologic variables.[14] This study does not focus strictly on cardiac risk but other serious medical co-morbidities. All of these risk stratification studies are aimed at selecting the ED patient to be admitted for evaluation. (Table 3)[21] The ROSE Study may be the best at defining the individual patient that merits hospitalization. The ROSE rule recommends admission for any one positive factor. Their mnemonic encompasses these risk factors, "BRACES" which includes: 1. BNP ≥ 300 pg/ml; 2. Bradycardia ≤50 in or pre ED; 3.Rectal examination positive for occult blood; 4.Anemia – hemoglobin ≤ 90 g/l; 5. Chest pain with syncope; 6. ECG with Q waves; 7. Saturation ≤ 94% on room air[14]

The diagnosis of an episode of syncope seen in the ED is made from history, physical examination, ECG or routine laboratory test in 50%. A diagnosis is established in another 21% of those sent to a "Syncope Unit" with still an unexplained diagnosis. Most specialized "Syncope Units" use a combination of algorithms that employ both (1) etiology and (2) mechanism.[22] The guidelines suggested by the European Society of Cardiology seem most practical.[23] Tilt table testing is useful for atypical presentations of neurocardiogenic syncope. Electrophysiologic testing is recommended for suspected

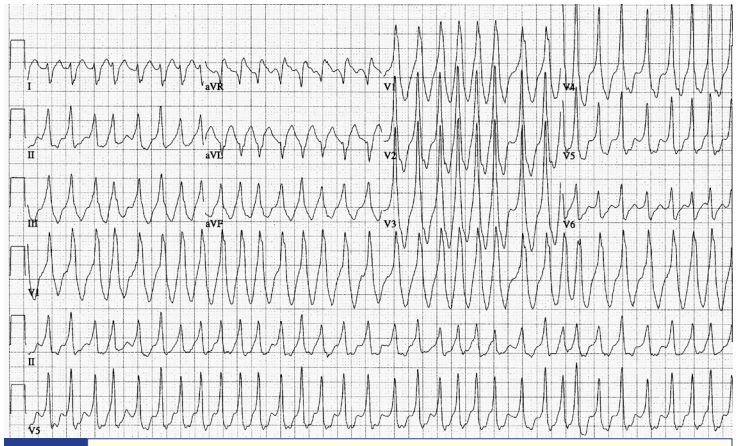

Figure:7 This ECG is diagnostic of Wolff-Parkinson-White syndrome. It shows a rapid irregularly, irregularly wide QRS tachycardia at a ventricular rate of 220 bpm and is atrial fibrillation. There is antegrade conduction over the left lateral accessory pathway (RBBB configuration, right axis) with varying QRS widths

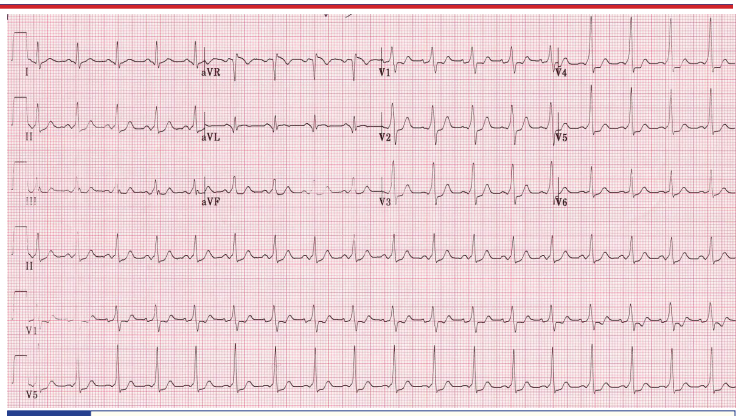

Figure:8 There is sinus rhythm after direct current cardioversion with a short PR interval and delta wave in most leads diagnostic of Wolff-Parkinson-White syndrome

cases of arrhythmogenic syncope. Exercise stress testing may be beneficial in those with a history of exercise related syncope. Short term monitoring with a Holter or loop recorder is employed universally. The real break through in diagnosing difficult cases has been the general adaptation of implantable loop recorders. When used in unexplained syncope, 32% have a diagnosis in 18 months and nearly 50% in 24 months.[22] There is nothing magical about the specialized "Syncope Unit". All employ useful diagnostic algorithms and appropriate useful test but more importantly, they all have individuals that do not rely on a test or the algorithm for diagnosis.

In summary, syncope is very common. The diagnosis is identified from the history and physical in about 45%-50% of cases.[1,22] The number of patients with unexplained syncope still remains high, at around 17 %. Neurocardiogenic syncope accounts for nearly a third of all cases. The high-risk subgroups with a cardiac diagnosis are those with structural disease and arrhythmias that average about 4% and 14% respectively. This particular group has a 33% one-year mortality rate.[1] Most patients have a benign cause and a very low mortality risk.[22] There are adequate risk stratification protocols for recommending who should be hospitalized from the ED.[21-23] Our five cases presented here would indicate that there is a clinical disconnect when it comes to diagnosis of the etiology of syncope. The algorithm-designed approaches to the diagnosis of syncope and atrial fibrillation are intended to bridge this disconnect. Instead, use of a rigid algorithm approach may tend to camouflage the real clinical issues. Occasionally, treatment of symptoms can cloud the diagnosis of the true underlying disease. Unfortunately, it seems apparent that algorithms have replaced critical deductive thinking.

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Electrical Storm: Incidence, Prognosis and Therapy

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Abstract

The term "electrical storm" indicates a life-threatening clinical condition characterized by the recurrence of hemodynamically unstable ventricular tachycardia and/or ventricular fibrillation, in particular in patients with ICD implanted for primary or secondary prevention. Although there isn't a shared definition of electrical storm, nowadays the most accepted definition refers to three or more separate arrhythmia episodes leading to ICD therapies including antitachycardia pacing or shock occurring over a single 24 hours' time period. Clinical presentation can be dramatic and triggering mechanism are not clear at all yet, but electrical storm is associated with high mortality rates and low patients quality of life, both in the acute phase and in the long term. The first line therapy is based on antiarrhythmic drugs to suppress electrical storm, but in refractory patients, interventions such as catheter ablation or in some cases surgical cardiac sympathetic denervation might be helpful. Anyhow, earlier interventional management can lead to better outcomes than persisting with antiarrhythmic pharmacologic therapy and, when available, an early interventional approach should be preferred.

Introduction

Electrical storm is a state of cardiac electrical instability characterized by multiple episodes of ventricular arrhythmias within a relatively short period of time.[1] The clinical definition of electrical storm is varied, somewhat arbitrary, and is a source of ongoing debate.[2] Before cardioverter defibrillators (ICDs)reached a wide usage in clinical setting, the term 'electrical storm' was referred to the occurrence of two or more ventricular tachycardia (VT) or ventricular fibrillation (VF) in a 24 hour period.[3] At present, the most commonly accepted definition is 'three or more separate arrhythmia episodes leading to ICD therapies including antitachycardia pacing (ATP) or shock occurring over a s 24 hour period,[4-6] but there is a variety of other definitions.[7] This definition might be somewhat inadequate as it fails for those VT which are slower than the programmed detection rate of the ICD. Besides, ventricular tachyarrhythmias terminating with appropriate ICD therapy, are excluded from this definition, while those recurring shortly after (< 5 minutes) a successful therapy, are included by only some authors.[8,9]

Electrical storm can occur during the acute phase of a myocardial infarction (MI) or when the patient has a structural heart disease or an inherited arrhythmic syndrome. In addition, more and more patients are expected to undergo ICD implantation, as the prevalence of congestive heart failure rise continuously.[10]

Key Words:
Electrical Storm, Ventricular Tachycardia, Ventricular Fibrillation.

Disclosures:
None.

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Incidence and Basic Epidemiological Aspects

According to the commonly accepted definition of electrical storm, incidence is about 10% to 20% in patients who have an ICD for secondary prevention of sudden cardiac death.[8,11,12] The incidence is lower when ICDs are placed for primary prevention:[13] in the MADIT II study, 4% of patients developed electrical storm on an average of 20.6 months.[14]

Most of the arrhythmic episodes that occur during an electrical storm seems to be episodes of monomorphic VT (with an incidence of 86-97%), VF alone accounts for 1-21% of episodes, mixed VT7VF 3-14% and the incidence of polymorphic VT is lower (2-8%).[4,5,8,9,12,14-18] Patients with a prior history of VT are more likely to experience VT storm and a similar correlation is reported for patients with VF.[14,18] One of the earliest studies reported an average time of electrical storm onset of 4-5 months after ICD implantation.[15] More recent studies have reported a period of 2-3 years.[16,18] No adequate triggers have been identified yet, but some studies suggested that ischemia, infarction, severely compromised left ventricular function, chronic renal failure, hypo- or hyperkalemia and older age can be important risk factors for the onset of electrical storm.[4,9,12,14,15,17] A triggering mechanism is only identified in 10-25% of patients with electrical storm, while the majority of patients have no perceptible change in baseline cardiovascular health.[5,9,12,15] The role, as risk factor, of monomorphic VT without immediate hemodynamic failure, especially when successfully treated with ATP, is not certain at all. It is important to understand if some VT episodes do not represent a

Table 1: Definition, incidence and prognosis of electrical storm

Author	Definition	Incidence	Prognosis
Kowey[1]	≥ 2 hemo-dynamically relevant VT in 24 h	All patients	↓
Credner[15]	≥ 3 VT in 24 h	14/136 (10%)	Ø
Nademanee[11]	≥ 20 VT in 24 h or ≥ 4 in 1 h	All patients	↓ (1-year mortality 95% on AAD and 33% on β blocker)
Exner[8]	≥ 3 VT in 24 h	90/457 (20%)	↓ (RR 2.4)
Greene[4]	≥ 3 VT in 24 h	40/227 (18%)	Ø
Bansch[12]	≥ 3 VT in 24 h	30/106 (28%)	↓
Verma[18]	≥ 2 VT requiring shock in 24 h	208/2028 (10%)	↓
Wood[19]	≥ 3 VT in 24 h	50/521 (24%)	Not analyzed
Stuber[16]	≥ 3 VT in 2 weeks	51/214 (24%)	↓ (5 years mortality 33% vs 13%)
Hohnloser[5]	≥ 3 separate VT in 24 h	148/633 (23%)	Ø
Brigadeau[17]	≥ 2 separate VT in 24 h	123/307 (40%)	Ø
Gatzoulis[9]	≥ 3 VT in 24 h	32/169 (19%)	↓ (mortality 53% vs 14% during 33 ± 26 months)
Sesselberg[14]	≥ 3 VT in 24 h	169/719 (24%)	↓
Guerra[20]	≥ 3 VT in 24 h	857/5912 (14%)	↓ (RR 2.15)

VT = ventricular tachyarrhythmia; AAD = antiarrhythmic drugs; RR = relative risk; ↓ = reduced prognosis; Ø = no influence on prognosis.

higher risk and if there is a threshold of arrhythmia or therapy frequency that may cause adverse outcome.[7]

Prognosis

Most studies suggest that electrical storm is an independent adverse prognostic factor, associated whit higher mortality in both secondary and primary prevention.[6,7,17,18] The mortality rate is also increased after storm episodes in patients with non-ischemic cardiomyopathy.[12,21,22] Electrical storm is also associated with an increased rate of hospitalization and might have a negative impact on patients' quality of life.[8,9,19,23] Despite the certainty of these data, is still not clear whether electrical storm contributes to higher mortality directly or is a consequence of advanced heart disease or systemic illness.[24]

In patients implanted with ICD for primary prevention, electrical storm has been associated with higher mortality. In MADIT II study, patients with electrical storm had a significantly higher risk of death: the hazard ratio for death in the first 3 months, after the electrical storm, was 17.8, compared with patients with no VT/VF. The hazard ratio decreased to 3.5 after these first 3 months.[14]

In the AVID trial for secondary prevention, electrical storm was a significant independent risk factor for subsequent death (RR 2.4, $p = 0.003$). In this trial, 38% of patients with electrical storm died during follow-up, compared to 15% of those without electrical storm. The risk of death was higher within the first 3 months and then decreased8. Gatzoulis et al. studied 32 patients with ICD for secondary prevention whom presented electrical storm: 53% of patients died during 3 years of follow-up, compared with 14% of ICD patients who did not experience electrical storm ($p < 0.001$).[9] This data suggest that electrical storm is a strong independent predictor of poor outcome in ICD patients.

A recent meta-analysis of 5912 patients (857 with electrical storm) compiled from 13 studies, found that electrical storm is a strong mortality risk factor and it is associated with an increased combined risk of death (RR 3.15; 95% IC 2.22-4.48), heart transplantation and hospitalization for acute heart failure (RR 3.39; 95% IC 2.31-4.97). Besides, ICD for secondary prevention, monomorphic VT as triggering arrhythmia, lower ejection fraction and class I anti-arrhythmic drug therapies are all associated with electrical storm and could be used to define specific populations with higher risk to develop electrical storm.[20]

It is not clear yet if the ventricular tachyarrhythmias or repeated ICD shocks themselves contribute to cardiac mortality or are secondary to a degenerating cardiac status. Only few evidence are reported by some studies about this issue and additional studies are needed for more clarity. A potential mechanism is suggested by the experimental observation that recurrent VF results in increases intracellular calcium concentrations which might contribute to deterioration of left ventricular systolic function.[25,26] Repeated shocks, moreover, can cause myocardial injury leading to acute inflammation and fibrosis.[27-29] Lastly, myocardial injury or stunning from recurrent defibrillations may activate the neurohormonal cascade responsible for worsening heart failure and cardiovascular mortality.[11,30,31]

Electrical storm also increases the rate of hospitalization and adversely affects the quality of life of ICD patients, in addition to undermine the perception of security provided by the device. A sub-analysis of the SHIELD trial showed that electrical storm increases by about 3 times arrhythmia-related hospitalization ($p < 0.0001$) compared with patients with isolated VT/VF. A recent review pointed out how ICD therapies, especially frequent and repeated shocks, have significant psychological effects on both patients and their families.[32] Besides, results from AVID trial suggested that both sporadic shocks and adverse symptoms were associated with reduced physical and mental well-being.[8]

Management of The Electrical Storm: Pharmacologic Therapy

Electrical storm is a clinical emergency. The physical and emotional distress that patients experience in case of electrical storm and frequently recurrent shocks may increase the sympathetic tone and facilitate further arrhythmias.[9] In this patients sedation may help prevent psychological distress.[11,33] The psychological effects of shocks, also related to pain, should be consider both early and subsequent to electrical storm, and a psychological approach to the patient should be considered, if necessary.[32]

Antiarrhythmic drugs may stabilize ventricular rhythm in many electrical storm patients.

β-Blockers

Patients with electrical storm undergo an increase of the sympa-

Table 2: Time to first occurrence and arrhythmias causing electrical storm

Author	Time after ICD implantation	Arrhythmias
Credner[15]	133 ± 135 days	64% mVT, 21% VF, 14% mVT+FV (patients)
Exner[8]	9.2 ± 11.5 months	86% mVT, 14% VF or VT+VF (initial episodes)
Greene[4]	599 ± 710 days	97% mVT, 3% pVT+VF (episodes)
Bansch[12]	NA	87% mVT, 8% pVT/VF, 4% different mVT (electrical storms)
Verma[18]	814 ± 620 days	52% mVT, 48% VF (patients)
Stuber[16]	629 ± 646 days	93% mVT, 7% pVT (electrical storms)
Hohnloser[5]	Median 7 months	91% mVT, 8% mVT+VF, 1% VF (electrical storms)
Brigadeau[17]	Median 1417 days	90% mVT, 8% VF, 2% pVT (electrical storms)

mVT = monomorphic ventricular tachycardia; pVT = polymorphic ventricular tachycardia; VF = ventricular fibrillation

thetic tone and this can provoke further recurrent ventricular arrhythmias. The use of β-blockers, in particular those which antagonize both β1 and β2 receptors, has been shown to increase the fibrillation threshold and decrease the incidence of sudden death.[11] In the MADIT II study, patients with ischemic cardiomyopathy who received high doses of β-blockers (metoprolol, atenolol or carvedilol) had a 52% relative risk reduction for recurrent VT/VF requiring ICD therapies compared with those who did not take any β-blocker.[13] Adding β-blockers intravenously in electrical storm patients already on oral β-blocker therapy may help to suppress electrical storm episode.[34]

Amiodarone

Amiodarone has been widely used for the treatment of electrical storm.[35] In acute, rapid intravenous administration amiodarone blocks fast sodium channels, inhibits norepinephrine release and blocks L-type calcium channels, but does not prolong ventricular refractoriness. Conversely, prolonged ventricular refractory periods have been seen in patients in oral amiodarone therapy.[36] Amiodarone is also effective as adjunctive therapy to prevent recurrent ICD shocks.[37] The OPTIC study compared β-blocker, sotalol and β-blocker plus amiodarone in the prevention of ICD shocks. At 1-year follow-up, patients treated with sotalol or amiodarone plus β-blocker had a 56% risk reduction compared with patients treated with β-blocker alone.[38] As for β-blockers, intravenous amiodarone may be an effective drug even in patients already in chronic oral amiodarone therapy.[39]

Azimilide and Dofetilide

They belong to a class III antiarrhythmic. In the SHIELD study, azimilide (which blocks the calcium channels and prolongs the refractory period) reduced significantly the recurrence of shocks and symptomatic arrhythmias treated by ATP.[40] In a prospective study, conversely, azimilide did not significantly reduce the number of patients with electrical storm.[5]

Dofetilide selectively blocks the rapid component of the delayed rectifier potassium current and it is principally used for the treatment of atrial fibrillation. Only one small study reported efficacy and safety of dofetilide in the treatment of VT/VF after amiodarone intolerance or failure.[41]

Both azimilide and dofetilide were associated with a high incidence of Torsade de Pointes.[5,7]

In summary, the decision to prescribe an antiarrhythmic drug to an electrical storm patient should be individualized, taking into account not only the efficacy but also the increased risk of drug-related proarrhythmia and side effects. Antiarrhythmic drugs, in effect, reduce the number of ICD shocks, but they are associated with a relatively high incidence of side effects.[42] This, combined with the sometimes-limited efficacy of antiarrhythmic drugs, has prompted the need for the development of non-pharmacologic treatment strategies.

Management of the Electrical Storm: Catheter Ablation

As the majority of electrical storms consist of monomorphic ventricular tachycardia episodes characterized by a basic re-entry mechanism, catheter ablation is an important solution to stop electrical storm onset. With increasing experience and the rapid growth of ablation technologies, VT catheter ablation can be performed safely and with low complication rate.[43] A meta-analysis of 471 patients with electrical storm, compiled from 39 publications (case report and cohort studies), found a high initial success rates for ablation of all ventricular arrhythmias (72%), a low procedural mortality rate (0.6%) and a recurrence rate of 6%. In this review, the recurrence rate was significantly higher after ablation for electrical storm due to monomorphic VT compared with VF or polymorphic VT with underlying cardiomyopathy (OR 3.8; 95% CI 1.7-8.6).[44]

Table 3: Efficacy of catheter ablation for electrical storm treatment

Author	Population (n)	Results
Nayyar[44]	471	Success rate 72%
Reddy[45]	128	↓ ICD shocks of 22% ↓ VT of 21%
Kuck[46]	110	Survival free from VT/VF 47% with ablation vs 29% in control group
Deneke[34]	32	Success rate 94%
Carbucicchio[48]	95	Success rate 72%

VT = ventricular tachycardia; VF = ventricular fibrillation

There are two randomized trials that compared ICD implant and early prophylactic ablation after ICD implantation for secondary prevention in patients with a history of myocardial infarction (MI). Both showed that catheter ablation significantly decreased ICD therapies. In the first study, Reddy et al. (2007) enrolled 128 patients with VT not treated with antiarrhythmic drugs. Over a mean follow-up of 22.5 months, prophylactic substrate-based catheter ablation reduced ICD shocks from 31% to 9% ($p = 0.003$) and VT from 33% to 12% ($p = 0.007$).[45] In the second study, 110 patients with prior MI have been randomized to either catheter ablation or no additionally treatment. 35% of patients were treated with amiodarone at baseline and 25-30% were treated with amiodarone at 1 year. After catheter ablation, the number of appropriate ICD therapy events per patient and per year was significantly lower than in the control group, with a median of 0.2 versus 3.0 ($p = 0.013$).[46] Recent reports about ablation for electrical storm have shown not only a reduction in recurrent electrical storm, but also a survival benefit. A first study (2001) with 19 electrical storm patients who underwent catheter ablation, showed a procedure success rate of 79% and there were no deaths over a 26-week follow-up.[47] A prospective study (2008) enrolled 95 drug refractory electrical storm patients who had frequent ICD shocks. After one to three ablations, 89% of patients did not have any inducible clinical VT by programmed electrical stimulation. At a median follow-up of 22 months, 92% of patients was free of electrical storm and 66% was free of VT recurrence.[48] Recently, Deneke et al. studied 32 electrical storm patients, 27 undergoing catheter ablation within 24 h after admission and 5 underwent acute ablation within 8 h. The acute success rate was 94% and electrical storm recurrence or death was observed in 6% (acute ablation group) and 9% (control group) during a 15-months follow-up.[49]

Despite the lack of high-quality evidence supporting the benefit of intervention, if pharmacologic management fails and a catheter ablation facility with adequate expertise is available, the patient should be rapidly referred. Currently, the relative merits of early ablative therapy in comparison to early pharmacologic therapy are still unknown. A recent study compared the outcomes of catheter ablation between patients who were referred for ablation early and those who were only referred after drug therapy failure. Results shown that catheter ablation has a potential to reduce patient mortality and improve patients' quality of life.[50] Early intervention is also supported by other studies, which report a high mortality rate while awaiting catheter ablation for electrical storm.[49,51]

Most studies reported in the literature included patients with ischemic heart disease, but it is not clear if the outcomes would be sim-

ilar for patients with non-ischemic disease. Furthermore, there are no randomized controlled trial to date, highlighting the benefits of catheter ablation in comparison to the pharmacologic management of electrical storm. Likewise, it is not known the optimal timing of catheter ablation or whether ablation has a long term mortality benefit.

Management of the Electrical Storm: Surgical Treatment

There are limited data about the surgical management of electrical storm. Thoracic epidural anaesthesia (TEA) and the left cardiac sympathetic denervation (LCSD) can be used for their antiarrhythmic effects.[52,53] Bourke et al. studied 14 patients with frequent VT episodes: 12 patients had electrical storms and 8 had prior catheter ablation. Both TEA (9 patients) and LCSD (8 patients) were associated with a subsequent decrease in arrhythmia burden.[54] If LCSD is ineffective, adjunctive right sympathetic denervation can be carry out. Ajijola et al. reported a study result of bilateral cardiac sympathetic denervation in 6 electrical storm patients: after surgery complete response was observed in 4 patients, partial response at the therapy or no response in 2 patients.[55] Another recent study showed that bilateral cardiac sympathetic denervation is more beneficial than left CSD, with a ICD shocks-free survival of 48% (versus 30% of left cardiac sympathetic denervation) at mean follow-up of 1 year and a significant reduction in ICD shocks in 90% of patients ($p < 0.001$).[56]

Discussion

Electrical storm is an emergent life-threatening clinical condition. Even though there is not just one definition of electrical storm, it is known that this phenomenon is associated with adverse effects on patients' survival and quality of life. Although there is still a lack of clarity about triggering mechanism and role of electrical storm in accelerating mortality, it is mandatory to intervene aggressively when electrical storm occurs. Treatment of this clinical event often includes several simultaneous drug therapies (β blockers and amiodarone) and a subsequent step to nonpharmacologic therapies in drug-refractory patients, such as catheter ablation. Further researches should clarify timing and specific role of both drug therapy and catheter ablation to improve clinical care.

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Ischemic Stroke: Risk Stratification, Warfarin Teatment and Outcome Measure

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Abstract

Stroke is a focal neurological syndrome of vascular basis, which may be due to ischemic thrombo-embolism or intra-cerebral haemorrhage. This condition has to be treated on emergency basis as it may cause an irreversible neurological damage. Warfarin has been a widely used oral anti-coagulant in treating ischemic stroke patients. This review highlights the benefits and challenges of warfarin treatment in stroke patients and discusses about the importance of risk stratification scores & bleeding scores in estimating the bleeding risk associated with warfarin treatment. This review also highlights the use of stroke outcome measures in identifying the patients with post-stroke disabilities to provide patient specific treatment.

Introduction

Stroke is a focal neurological syndrome, which is characterised by acute neurological deficit that may be due to arterial occlusion or intra-cerebral haemorrhage. 85 to 95% of strokes are ischemic and 10-15% is due to intra-cerebral haemorrhage (ICH) (Muir 2013). Based on duration four neurological phenomena have been defined for stroke: TIA (Transient ischemic attack), reversible ischemic neurological deficit (RIND), stroke in evolution, and Completed stroke. TIA is also called as mini stroke as it is a localized transient brain ischemia, which is sudden, and can be reversible within 24 hours. RIND is a neurological impairment, which can take more than 24 hours time to recover. Stroke in evolution can be defined as the symptoms associated to it only worsen over time. A completed stroke can be defined as a condition in which neurological signs and symptoms remain stable for more than 24 hours (Fatahzadeh & Glick 2006).

Epidemiology

Stroke is the third major cause of death in United States, Europe, and most parts of the world. Worldwide stroke accounts for approximately 5.5 million deaths annually and major cause for disabilities. Approximately 150,000 incidences of strokes take place annually in UK alone (Muir 2013). It has been a disease of aging population older than 65 years and every year the population of this age continuing to increase by 9 million per year. By 2025, the worldwide population of people aged more than 65 years is estimated to be approximately 800 million that shows us the risk and economic impact of this problem on the world (Mukherjee & Patil 2011).

Key Words:
Stroke, Ischemic Stroke, Risk Stratification Schemes, Stroke Outcomes, Stroke Outcome Measures, Warfarin Treatment.

Disclosures:
None.

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Classification

Stroke can be classified based on the Oxfordshire Community Stroke Project (OCSP). It has been the standard classification in categorising the acute ischemic stroke patients based on the occlusion and the part of the brain which would be affected. Different types of clinical features would depend on the major intra-cranial arteries that are affected by the occlusion and the portion of brain that has been affected. OCSP classifies infracts based on their location in the intra- cranial arteries.

OCSP classification:

1. Total anterior circulation infracts (TACI)
2. Partial anterior circulation infracts (PACI)
3. Posterior circulation infracts (POCI) and
4. Lacunar infracts (LACI) (Sean J. Pittock).

Patients can be classified to be with TACI if they are with a combination of higher cerebral dysfunction, homonymous visual field defect, and sensory deficit at two areas of face, arm and leg. Patients with PACI can be classified if the patients have any two components of TACI or higher cerebral dysfunction. Patients are considered to have LACI if there is a pure motor or sensory stroke, sensori-motor stroke, and ataxic hemiparesis. Patients with a posterior circulatory dysfunction and ipsilateral cranial nerve palsy with motor and sensory deficit are considered to have POCI (Li et al. 2003).

Risk Factors

There has been a great deal of investigating different risk factors

Table 1: Risk factors for stroke

Risk Factors	Reference
Age	Marinigh et al. 2010, Bentsen et al. 2014
Gender	Koton et al. 2013, Nolte et al. 2005
Diabetes	Béjot & Giroud 2010, Kaarisalo et al. 2005
Smoking	Edjoc et al. 2013, Tse et al. 2012
Hypertension	Mancia 2004, Dahlöf 2007, Gorgui et al. 2014
Coronary Heart disease	Iwasaki et al. 2014
Atrial Fibrillation	Bansil & Karim 2004, Mizrahi et al. 2014

that increase the incidence of the stroke and these have been summarized in Table 1. A major factor that increases the occurrence of stroke is atrial fibrillation. Atrial fibrillation (AF) increases the risk of stroke and thromboembolism by 5 folds and considered as a major risk factor (Jover et al. 2012).

Atrial Fibrillation (AF)

Atrial fibrillation is a clinically encountered arrhythmia and encompasses lone atrial fibrillation to paroxysmal AF to chronic atrial fibrillation. Atrial fibrillation is mostly associated with heart failure, aging and diseases related to aging (Mathew et al. 2009). Atrial fibrillation has been associated with cardio embolic stroke, which can be neurologically devastating (del Conde & Halperin 2013). The major clinical feature of AF is a decrease in atrial contractility and increased atrial compliance, which leads to mechanical remodelling of the heart. This leads to stretching in the atrial myocardium and this atrial remodelling increase the atrial fibrosis and decreases the conduction velocity, which also shortens the refractory period in atria (Mathew et al. 2009). AF is also caused due to an irregular and increased conduction of impulses in atrial part of the heart. AF reduces the flow velocity of the left atria and causes delayed emptying from the atria which leads to thrombus formation. Strokes caused by AF have higher fatality when compared to other risk factors due to the formation of large thrombi in the atria which may occludes in the cerebral arteries causing infarction and stroke (Alberts et al. 2012).

Risk Stratification Schemes

There are two risk stratification scores for stroke and thromboembolism, which are mostly used to assess the risk of stroke in patients with non-valvular atrial fibrillation. The two schemes, which are in use, are CHADS2 scheme and CHA2DS2-VAScscheme. Both the schemes have been summarized in table 2 & 3.

CHADS2 Score

The US practise guidelines recommended the use of CHADS2 score (assigns score for congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, transient ischemic attack or prior occurrence of stroke). This scheme assesses different risk factors and most important of those are the age and prior stroke. It assigns a score for each risk factor with '1' except prior stroke which is assigned '2' which makes up score '6' in total (Poli et al. 2007). The patients with a score of 6 showed an increase of 2.5 to 2.7 folds in the hospitalization risk due to stroke (Naccarelli et al. 2012). Pre-admission CHADS2 score relates to the severity and stroke outcomes in patients with atrial fibrillation (Sato et al. 2011).

CHA2DS2-VASc Score

The European guidelines recommended the use of a new risk stratification scheme called CHA2DS2-VASc scheme, which was superior to the CHADS2 scheme as it also assesses additional risk factors that were previously underestimated. CHA2DS2-VASc score (assigns score for congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, transient ischemic attack or prior stroke – vascular disease, age 65-74 years, sex (female)) is used to assess all the possible risk factors, and scores them '1' for all the factors except age≥75 years and prior stroke which are given '2' where, the maximum score is '9' (Chao et al. 2011).

This scheme assesses additional risk factors such as vascular diseases such as myocardial infarction, peripheral artery disease, and complex aortic plaque. The patients with a score of '9' show an increase of 3.0 folds in the hospitalisation risk due to severity of the condition (Naccarelli et al. 2012). The CHA2DS2-VASc scheme is more advantageous when compared to CHADS2 scheme as it also assesses additional risk factors and is also useful in identifying patients who despite having a CHADS2 score of '0', still have a high risk of stroke and can be prescribed anticoagulants. It is also used to identify the patients who will truly benefit from the antithrombotic agents and also who are at low risk of stroke with a CHA2DS2-VASc score equal to '0' (del Conde & Halperin 2013). The score '2' in both the schemes recommends the use of anti-platelet or anticoagulant therapy. The score '1' which is risk factor specific can also be considered for anti-coagulant therapy according to the recent guidelines. In both scoring systems Age and prior stroke are considered as major risk factors (Wadke 2013).

Warfarin

Mechanism of Action

Warfarin is a vitamin K antagonist, which has an inhibitory effect on the vitamin K cycle which in-turn inhibits the vitamin K dependent coagulation factors II, VII, IX and X. Warfarin inhibits the synthesis of vitamin K dependent coagulation factors (II, VII, IX, X, protein C and protein S) by inhibiting the γ-carboxylation of glutamate residues of these clotting factors, which ultimately inhibits them to bind with Calcium. The principle mechanism behind the anti-coagulant effect of warfarin is that it inhibits the reduction of oxidized vitamin K which is essential for the activation of clotting factors by carboxylation. This inhibits the formation of functionally active prothrombinase complex, thrombin and fibrin which, ultimately gives an anti-coagulant effect. The figure 1 shows us the coagulation pathway and inhibitory effect of warfarin (Riley et al. 2000). Warfarin is mainly used to prevent venous thromboembolism and systemic embolism in patients with atrial fibrillation or prosthetic heart valves (Eriksson & Wadelius 2012).

Pharmacokinetics

Warfarin is a highly plasma bound drug which is completely absorbed from the upper intestinal tract and reaches peak plasma level in one hour. It is 98-99% plasma bound and has a half-life of 40 hours. Warfarin is metabolised by microsomal hepatic enzymes and

Table 2: CHADS2 Scheme

CHADS2 Acronym	Score
Congestive heart failure	1
Hypertension	1
Age≥75 years	1
Diabetes mellitus	1
Stroke/TIA/TE	2
Maximum score	6

converted into hydroxylated inactive metabolites which, undergo conjugation with glucuronic acid and the conjugates are excreted in urine and faeces (Riley et al. 2000).

International Normalization Ratio (INR) & Anti-Coagulation

According to WHO guidelines, INR has been defined as, 'For a given plasma or whole blood specimen from a patient on long-term oral anticoagulant therapy, a value calculated from the prothrombin-time ratio using a prothrombin-time system with a known ISI (international sensitivity index) according to the formula INR = (PT/MNPT)ISI.' Determination of INR is mandatory for the controlled use of oral anti-coagulants (van den Besselaar et al. 2004). INR has been a great form of TDM (Therapeutic drug monitoring) in the patients who are on warfarin. The British Society of Haematology and the American college of Chest Physicians recommend a therapeutic range of INR as 2-3. It has been observed that an increase in INR more than 4.5 has shown an exponential increase in the risk of bleeding. The monitoring should start from second and third dose which should be continued until the INR reaches an optimal level and this frequency can be reduced when the stable dose administration is achieved (Hu et al. 2012).

Warfarin Treatment- Risks and Benefits

Benefits

Warfarin is a potent anti-coagulant and it has been shown that it can cause a great decrease in the risk of stroke when compared to other anti-coagulant drugs. In a meta-analysis warfarin decreased the risk of stroke by 64% when compared to placebo and 40% when compared to anti-platelet drugs (Deedwania 2013).

Practical Issues

There are many practical issues in usage of warfarin as anti-coagulant. The guidelines recommend the regular monitoring of INR values and the optimal INR which should be maintained would be 2.0-3.0 to obtain an optimal anti-coagulant effect and minimize the risk of bleeding. However, it is a very hard task to maintain the INR range as it is affected by drug-drug interactions, drug-food interaction and genotype variation. Age has been the most important factor that has great effect on INR value. So, estimation of INR on regular basis and dose adjustment has been a major drawback in the usage of warfarin (Deedwania 2013).

Drug Interactions

Drug interactions can alter the anti-coagulation effect of warfarin and that can lead to over or under-coagulation effect. Warfarin has two isomers and the enzymes responsible for their metabolic elimination are different. (S)-warfarin is eliminated by enzyme CYP2C9 and (R)- warfarin eliminated by CYP1A1/CYP1A2/CYP3A4. The drugs which, induce these enzymes can cause an increased elimination of warfarin (e.g.Carbamazepine, phenytoin, and rifampicin) and the drugs which inhibit these enzymes will in turn inhibit the elimination of warfarin and increases the anti-coagulant effect (e.g. amiodarone) (Eriksson & Wadelius 2012). Most of the corticosteroids, cimetidine, omeprazole, thyroxine, and allopurinol enhance the anti-coagulant action of warfarin (Shannon 2007).

Effect of Dietary Intake

Vitamin K containing food causes variability in the efficacy of warfarin as it is responsible for the production of coagulation factors. Vitamin K is present in different green vegetables such as broccoli, sprouts and spinach. There have been studies showing that an intake of 100μg of vitamin K for 4 consecutive days can lower the INR by 0.2. So, it is recommended for the patient to have a regular intake so the accurate INR can be calculated and the adjustment of dose can be carried out (Eriksson & Wadelius 2012).

Table 3: CHA2DS2-VASc Scheme

CHA2 DS2-VASc Acronym	Score
Congestive heart failure/ Left ventricular dysfunction	1
Hypertension	1
Age≥75 years	2
Diabetes mellitus	1
Stroke/TIE/TE	2
Vascular disease	1
Age (65-74 years)	1
Sex (female gender)	1
Maximum	9

Genetic Factor

Individuals have a different level of sensitivity according to the genetic variation. A mutation in the gene VKORC1 that encodes the vitamin K epoxide reductase, an enzyme which is the major target for warfarin can cause increased resistance to warfarin. It has been also found that genetic variation in CYP2C9 showed impaired metabolism of warfarin. Therefore, these two genes have been the genetic determinants of warfarin dose (Yang et al. 2013) (Supe et al. 2014).

Bleeding Risk

The bleeding risks can be of three types:

Intracranial Haemorrhage: The risk of intracranial haemorrhage is very less when compared with the benefits of using warfarin. Intracranial haemorrhage mostly occurs in patients who are older than 75 years and with uncontrolled hypertension which is usually more than 160mm Hg systolic blood pressure and prior stroke.

Extra-cranial Haemorrhage: The risk of extra-cranial haemorrhage is very low significant and less life threatening when compared to intracranial haemorrhage. Falls: The risk of bleeding after falls is very low and is considered of less importance when it is weighed against the benefits of warfarin (del Conde & Halperin 2013).

Bleeding Risk Schemes

The major adverse effect in the usage of anti-coagulants is bleeding and for the patients who are on anticoagulants and with an INR scores of more than 5.0 the risk of bleeding increases exponentially (Shannon 2007). There are different types of bleeding scores which have been developed to estimate the bleeding risk for individual patient and they are:

HAS-BLED Score

European guidelines recommended a bleeding risk score which is called the HAS-BLED score (assigns score to hypertension, abnormal renal/liver function, stroke – bleeding history, labile international normalization ratio, elderly (Age>65 years), and drugs/alcohol concomitantly) which is calculated as 1 point for each factor with a maximum score of 7 (Kiviniemi et al. 2014). This score is used to assess the bleeding risk in atrial fibrillation patients. The patients with HAS-BLED score 0-2 have low risk of bleeding and with more than 3 have high risk of bleeding which should be treated by reversing the anticoagulant effect and by maintaining the INR by dose adjustments (Lip 2011).

HEMORR2HAGES Scheme

It is a bleeding score, which is the only score that includes the

Table 4: Modified Rankin Scale

Scale	Modified Rankin Scale (mRs)
0	no symptoms
1	No significant disability able to perform all usual duties and activities
2	slight disability able to look after own affairs without assistance
3	moderate disability Requires some help, but able to walk without assistance
4	moderately severe disability Unable to walk without assistance and unable to attend to own bodily needs without assistance
5	Severe disability Bedridden, incontinent, and requires constant nursing care and attention.
6	Dead

genetic factors. HEMORR2HAGES scheme (assigns points for hepatic or renal disease, ethanol abuse, malignancy, older age (greater than 75), reduced platelet count or function, re-bleeding risk, uncontrolled hypertension, anaemia, genetic factor, excessive fall risk, and stroke) is used to assess different risk factors and scores one for all the risk factors except re-bleeding risk which is scored two points (del Conde & Halperin 2013). This is the only scoring system, which considers genetic factors (CYP2C9), excessive fall and stroke (Alberts et al. 2012).

Measuring Stroke Severity

NIHSS (National Institutes of Health Stroke Scale)

Stroke severity can be measured using a severity scale, the National Institutes of Health Stroke Scale (NIHSS) that includes 15 item scales that include assessment of motor function and sensory function, level of consciousness and orientation. It ranges from 0 to 34 where if the patient score is below 10 they are likely to have a favourable outcome after 1 year when compared to patients with a score of more than 20. Patients with severe stroke and with a score of more than 22 have poor prognosis (Institutes et al. 2009). NIHSS shows a high accuracy of prediction of ADL (activities of daily living) dependency by the patients post-stroke (Kwakkel et al. 2010).

Measuring Outcomes After Stroke

The outcomes after stroke can be measured using different neurological and disability rating scales.

Table 5: Glasgow Coma Scale

Glasgow Coma Scale		
Eye opening	Spontaneous	4
	To speech	3
	To pain	2
	None	1
Verbal response	Orientated	5
	Confused conversation	4
	Words (inappropriate)	3
	Sounds (incomprehensible)	2
	None	1
Best motor response	Obey commands	6
	Localize pain	5
	Flexion Normal	4
	Abnormal	3
	Extend	2
	None	1
Total Coma score		3/15 15/15

The Modified Rankin Scale

The modified Rankin scale has been devised to assess the disability after stroke. It is a measure of functional independence, which incorporates the WHO components such as body function, activities and participations. A patient using adaptive but still does not need any assistance is considered independent and a patient who takes aid of another person is considered dependent (Kasner 2006). This scale ranges from 0 to 6 where 0 indicates no symptoms; and 1-2 indicates mild disability; 3 shows moderate disability; and 4 to 5 show severe disability and 6 is death. This shows favourable out-come with a score of 0-1 and unfavourable score of 2-6. Table 4 shows Modified Rankin Scale in detail (Institutes et al. 2009). It has been shown that modified rankin scale can be used to study the quality of life in stroke survivors (Singhpoo et al. 2012).

Glasgow Coma Scale

Glasgow coma scale has been a simple measure of conscious level and this scale has been widely accepted by Neurological units in most of the English speaking countries. It has been a cumulative measure of arousal, awareness, and activity, which have been termed as eye opening response, best verbal response and best motor response. The maximum score calculated is 15 and this is further categorised in as minor (GCS ≥ 13), moderate (GCS 9–12), and severe injury (GCS<9). The components of GCS are better described in Table 5 (Barlow 2012) (Matis & Birbilis 2008).

Barthel Index (BI)

BI is a scale, which consists of 10 items that measure the function in terms of activities such as, daily living and mobility. The scale ranges from 0 to 100 the higher the score, more the patient is independent. The score 100 indicates that he is independent in feeding, dressing, getting in & out of bed, bathing, can walk at least one block; and can ascend and descend stairs without help (Katz for the Association of Rheumat 2003). A study investigating the accuracy of Barthel Index revealed good discriminative properties at 6 months post-stroke (Kwakkel et al. 2011).

Six Simple-Variable (SSV) Model

Six simple variable model has been developed in Oxfordshire Community Stroke Project (OSCP) to predict the survival free of dependency (modified Rankin scale <3) (Dennis 2008). SSV model is useful in measuring the dependency and death in stroke patients. This model includes six different variables such as age, verbal component of Glasgow coma scale (GCS), and arm power, ability to walk, pre-stroke living condition and pre-stroke dependency (Institutes et al. 2009). SSV model predicts the outcome of stroke patients with cerebral infracts with a great precision (Li et al. 2012).

Conclusion

Both the risk stratification and bleeding scores carry valuable information of the stroke patients. Treatment with warfarin can be decided on the basis of pre-admission CHADS2 and CHA2DS2-VASc scores of the patients. The bleeding scores and regular monitoring of INR values are helpful in preventing bleeding risk associated with warfarin. Better understanding of stroke outcome measures would be helpful in treating the patient according to their post-stroke disabilities.

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What Does The Blanking Period Blank?

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Abstract

In the management of paroxysmal, drug-refractory atrial fibrillation, pulmonary vein isolation has become a widely accepted treatment option. Currently, the arrhythmias following any form of myocardial ablation are not considered within a period of three months, known as "the blanking period. Although this period is authority- rather than evidence-based, it has become universally recognized. Indeed, several mechanisms play a role to determine the transient increased risk of post-procedural atrial tachyarrhythmias, occurring early after the procedure. Acute inflammatory changes may be responsible for immediate recurrence, since application of ablative energy on atrial tissue has a pro-inflammatory- and potentially arrhythmogenic effect. Atrial arrhythmias within the first 3 months after ablation are very common (35% to 65% of cases) and their significance as predictor of late recurrences is more significant during the first month. Furthermore, the current biological evidences indicate that the edema of the surrounding and ablated tissue is no longer present after 1 month. In our letter we advocate the reasons why a blanking period of four weeks should appear more reasonable, fostering its clinical importance and utility.

Introduction

In recent years, pulmonary vein isolation (PVI) has become an accepted treatment for paroxysmal, drug-refractory atrial fibrillation (AF). According to the Expert Consensus Statement on Catheter and Surgical Ablation of Atrial Fibrillation, the first three months after any form of myocardial ablation should not be taken into account when reporting procedural outcomes. This "blanking period" has become universally recognized, but it is not well grounded. The early recurrences of arrhythmia such as AF, left atrial tachycardia, atrial flutter are defined as ERAT, reported to occur in up to 40% of patients and they are considered temporary and benign. However, half of these patients, with symptomatic ERAT after ablation will have later relapses.[1-4] Also, a part of arrhythmic episodes occur asymptomatically, making continuous monitoring an absolute condition to report the incidence and predictive value of ERAT during the blanking period.[1]

Key Words:
Ablative Therapy, Atrial Fibrillation, Pulmonary Veins Isolation, Blanking Period.

Disclosures:
None.

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Discussion

Several mechanisms (atrial local inflammation, increased adrenergic tone and changes in fluid and electrolytes balances) play a role in determining the transient increase in the risk of post-procedural atrial tachyarrhythmias occurring early after ablations. Therefore, a blanking period of 3 months after any form of PVI has been accepted, because of the difficulty to distinguish true early recurrences from transient ERAT related to peri-procedural reversible causes.[1-4] The question is on which scientific proof experts have set this time-window. Currently, there is consistent evidence that ERAT mainly occurs during the first two weeks.[5-7] In a very thorough analysis, Joshi et al. have investigated the blanking period during the first three months, continuously monitoring the rhythm with loop-recorders in patients suffering from highly symptomatic lone AF. They reported that ERAT after transcatheter PVI occurred mainly within the first two weeks,[2] as Oral already stated in 2002.[6]

Koyama et al. reported that the freedom from arrhythmia at 6 months after percutaneous ablation for paroxysmal AF was 76% in patients who had ERAT during the first 3 days, while was only 30% in patients with ERAT within 4-30 days.[7] Evidently, immediate AF recurrence has a different mechanism and impact on midterm outcomes. Acute inflammatory changes after ablation may be responsible for immediate recurrence, since application of ablative energy in atrial tissue has a pro-inflammatory effect and thus potentially pro-arrhythmogenic (e.g. modification of action potential duration of atrial and pulmonary veins myocardium).[9] Markers of inflammation (IL-6 and CRP) have shown to be significantly increased only in the first week (at day 2 and 7) after the procedure.[9] Accordingly,

low post-operative dose of corticosteroids proved effective and safe in preventing mid-term AF recurrences.[10]

The ERAT within 3 months following catheter ablation are observed with a prevalence varying from 35% to 65%. The incidence of ERAT is highest in the immediate postablation period and progressively decreases thereafter.[5-7] Again, patients with ERAT after percutaneous ablation were significantly less likely to have long-term freedom from recurrent AF than patients without ERAT. Two interesting findings should be noted: first, the significance of ERAT as predictor of late recurrences becomes more significant after the first month. Such time-dependence of the predicting value of the ERAT relates with the pro-arrhythmic effect of the ablations, again mainly mediated by the inflammatory cascade, which progressively wanes off. Consequently, the time of occurrence of the first relapse impacts mid-term outcomes, since patients who had ERAT within 4 weeks had better outcomes than those with later recurrence. Predicting which early arrhythmias will eventually lead to late recurrences deserves focused research; patient selection plays a key role as well as independent predictors of failure (increased age, hypertension, persistent/permanent AF, left atrial enlargement and incomplete transmurality).[11]

Finally, there is the issue of edema in the anatomical region where ablation energy is delivered. In a pig model it has been demonstrated that tissue edema, following linear ablations in the right atrium, resolved within 4 weeks.[12] Also, the important study of Okada et al., investigating edema in the left atrium after transcatheter radiofrequency PVI, has showed that, although edema is formed in the ablated and surrounding tissue within seconds following ablation, this is no longer present at 1 month follow-up.[13]

In conclusion, a number of issues suggest that the 3-month blanking period is too long. Among them, the most valid one is that the inflammation process after PVI tends to resolve in about 1 week, tissue edema following ablation disappears within one month and that recurrences occurring during the first month do not correlate with long-term failures. A blanking period of 4 weeks after ablations (either surgical or transcatheter) appears therefore reasonable and should not be intended as a clinically useless period. Instead of masking, future trials may consider to monitor ERAT and report their timing as independent endpoints.

The first month thoroughly monitored should be a reliable prediction tool and ERAT can identify patients at high risk of true recurrence in whom a firm management of the rhythm (early cardioversions, repeated ablations) may be appropriated. The current blanking period seems to be more expert than evidence based. Even if the currently accepted blanking period of 3 months could preserve patients from undue early re-ablations, what does it actually blank?

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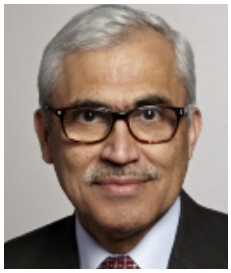

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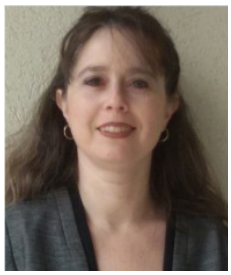

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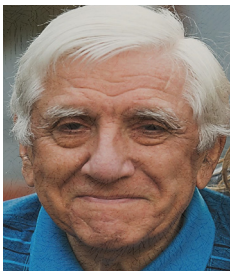

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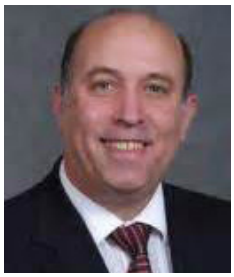

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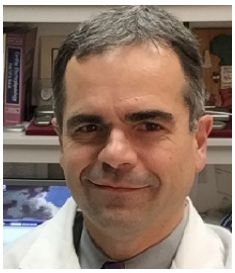

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