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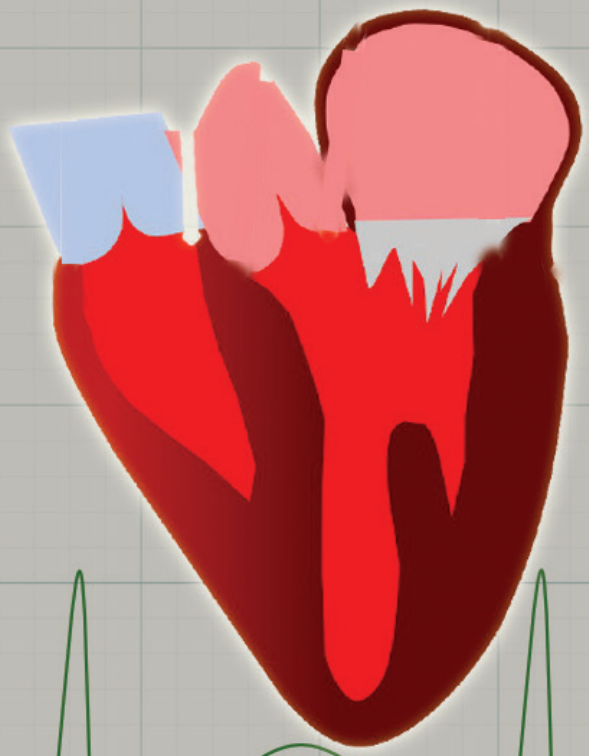

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Dr. Pete Weiss, MD

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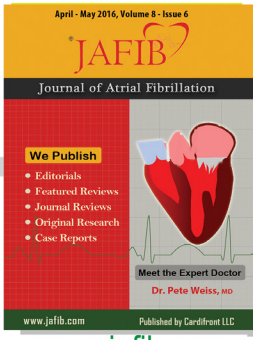

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Dear Colleagues

Welcome to the May issue of JAFIB. We are very proud and excited about the Journal's recent addition to PUBMED index. This has been an important milestone towards which the JAFIB team has worked. Congratulations to one and all.

Heart Rhythm Society's annual sessions concluded in San Francisco few weeks ago. Great to see a lot of you there. Sal Khan, the Founder of Khan Academy was amazing in his Key Note speech. There were several important take home points for higher education academia to take home. Clarity of content and ease of communication to facilitate proper understanding seem to be the fundamental them to his approach in educating the world through open access learning portal. It is with the same spirit that we started JAFIB in 2008. Anyone from anywhere in the world should be able to access important scientific information that changes the world should be available for free. This has been a key element for the success of the journal with more than 30,000 patrons. This year the Journal will go over through some important face lifting with several new features added. We will also create a patient portal that is more robust. Each quarter we will have a print edition featuring special topics that you can subscribe to. Please reach out to us with your bios if you are interested in being reviewers and content developers for patient and physician use.

On behalf of the Journal we want to congratulate the Heart Rhythm Society for yet another successful show. Kudos to John Day for leading by example and the fresh outlook he provided on various issues. Congratulations in order to Michael Gold on his HRS Presidency and we wish him best of luck for a successful term. In a week from now the Annual Cardiostim program will be unveiled in Nice. We hope to see some of you there. This will be a great curtain raiser for summer.

We encourage you to submit your original research, literature reviews, state-of-the-art papers, case reports, meta analyses to the journal for consideration of publication. We will assure faster turn around and reasonable time line for publication.

Have a great summer.
Best wishes

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Editor-in-Chief, JAFIB

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Long-Term Evolution of Patients Treated for Paroxysmal Atrial Fibrillation with First and Second Generation Cryoballoon Catheter Ablation with a Prospective Protocol Guided by Complete Bidirectional Left Atrium-Pulmonary Veins Disconnection after Adenosine as Main Target end Point to achieved. Seven Years Follow-up of Patients with a rough estimation profile of Low ALARMEc Score. A Single Center Report

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Abstract

Introduction: Cryoballoon ablation (CB) has proven effective for treating patients with paroxysmal atrial fibrillation (PAF). We analyzed our seven year follow-up of patients, treated for PAF with first (CB1) and second generation (CB2), with demonstration of LA-PV disconnection with bidirectional block (BB) after adenosine (AD).

Methods: Since November 2008 to May 2015, 128 patients, 97 male (58±7 years), without heart disease, highly symptomatic, refractory to antiarrhythmic drugs (AAD) were treated, and follow-up (1411 ±727 days). Left atrial size: 37±6 mm.

Results: A total of 439 PV were successfully isolated (91.9%). Acute reconduction: 44 PV (9%): 16 after CB; 16 unmasked by AD; 12 extrapulmonary muscular connections (EMC). Main complication was phrenic nerve palsy (PNP): 9 (7 %). On follow-up, 114 patients (89%) remain asymptomatic in sinus rhythm (SR), free of medication. Fourteen patients (11%) had arrhythmia recurrence: 12 male (52±8 years). Early recurrences occurred in 9 male. Late recurrences presented 3 male at 24, 27 and 60 months, and 2 female at 7 and 40 months respectively. All recurrence patients were Redo, and remain in SR without medication during follow-up.

Conclusions: CB alone is very effective and safe for the definitive treatment of patients suffering PAF with 72.6% success rate, increasing up to 89.1% when this protocol is applied in a single procedure. After Redo, all population group (100%), remain in sinus rhythm, freedom of arrhythmia, without AAD, in this very long term follow-up. Checking for BB, AD protocol, and ruling out EMC allowed-us to identified 14.8% of patients with underlying substrate for potential arrhythmia recurrence. CB2 applications entail a highest risk of PNP. Patients with a rough estimated profile of low ALARMEc score (≤ 1) have an excellent long term outcome, being this series the largest follow-up described so far, for patients treated for PAF with CB.

Introduction

Complete electrical isolation of pulmonary veins (PVI) from the left atrium (LA) is crucial to cure patients (pts) with Atrial Fibrillation (AF).[1-4]

The Cryoballoon catheter ablation technique (CB) has proven effective to achieve this electrical disconnection of pulmonary veins (PV) from LA, resulting in a demonstrated effectiveness to treat pts suffering from PAF.[5-11]

However, some observations[12] have shown, at least when first generation CB was used that cryoenergy CB application doesn't produce a homogeneous circumferential lesion in all PV, which is related to their anatomical shape, thickness and size with a non-uniform distribution of the atrial muscle around them.

Key Words:
Cryoballoon, Paroxysmal Atrial Fibrillation, Ablation.

Disclosures:
None.

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Table 1: Demographic and clinical pts/features

128 pts (mean age 53±13)	
Male/female	97 (75.8%) / 31 (24.2%)
Mean age (male/female)	58±7 / 61±10 years
Mean years/ suffering PAF	5±5 years (1-5)
Mean number/ episodes PAF/ year	54±67 (2-200)
Hypertension	36 (28%)
Diabetes	6 (4.7%)
Structural heart disease	NONE

The more elliptic rather than circular variable form at the PV-LA junction level where cryoenergy is delivered can result in a non-uniform and persistent cellular lesion which, as is generally accepted, is the principal cause of PV reconnection after CB ablation.[13] A better quantification of the Cryoablation and the anatomical extent of PV have been better clarify recently.[14] Incomplete lesions with dormant tissue despite a "perfect" occlusion can occur leading to a residual conduction (RC) gaps causing, or responsible for PV reconduction which is the main underlying anatomical substrate for clinical arrhythmia recurrence.[15, 16]

Adenosine has been used to "unmask" RC in apparently isolated PV with RF[17] and the routine use of AD after acute CB-PVI allows to identify incomplete lesions with dormant tissue not evident in basal conditions [18-20] and focal RF applications [21] or freeze "touch-up" [18-20] eliminate such RC.

The only no evidence of PV/ electrical activity on the circular-mapping-catheter at the LA-PV junction level after CB-PVI is not enough to assure complete PV-LA electrical disconnection and checking for entry and exit block is mandatory to confirm it.[22-24]

We analyzed the seven year follow-up experience of our pts, initially treated with CB for PAF, with a prospective protocol with demonstration of complete BB electrical PV-LA-PV block post-cryo and after AD as the main target end point to achieve in all cases.

Methods

Since November 2008 to November 2015, a total cohort of 128 pts (mean age 56±13 years), highly symptomatic, suffering from recurrent PAF, refractory to medical treatment (Table 1), were treated with the "CB" and followed-up.

Prior to CB, all pts were previously treated with membrane active antiarrhythmic drugs: Class IC (88.2%); Class III (2.3%); Beta Blockers (BtB) (84.3%) and BtB +1C: 76.5%.

None with structural heart disease. Morphological and structural data can be showed on Table 2:

Exclusion Criteria:

- Prior Stroke, TIA or thromboembolism.
- Cryoglobulinemia and hematological or coagulation disorders.

Table 2: Morphological and structural LA/PV/LV data

DIAMETERS (mm)	LA	PV (483)	LCT (26)	RCT (3)	Mean LVEF 67±5% (59-79)
AP	37±6 (21-50)	18±5 (8-32)	26±6 (18-35)	28±1 (27-29)	
SI	53±8 (40-75)	20±4 (10-28)	26±5 (17-31)	28±5 (23-33)	Mean LA/ AREA (cm^2) 22±4 (11-32)
TR	46±7 (35-61)				

LA: Left Atrium. PV: Pulmonary Vein. LCT: Left Common Trunk. RCT: Right Common Trunk. LVEF: Left Ventricular Ejection Fraction. AP: Antero-Posterior (parasternal long axis). TR: Transversal. SI: Supero-Inferior.

- Presence of intracavitary thrombi as well as clinically- significant associated comorbidity

Previous Studies And Anatomical Approach: 2D-Transtoracic echocardiogram (TTE) as well as, same day, transesophageal echocardiogram was performed in all cases, to assess cardiac anatomy and to rule out intramural thrombi.

3D/ high resolution/64- slice Multidetector CT scan (Toshiba Aquilion 64, TSX-101A, Tokyo, Japan), and in some alternative cases, RMN (1.5T/ Magnetom Symphony, Siemens, Germany) were used for typification and better definition of cardiac anatomy, morphology, number, caliber and size of PV in addition to internal endoluminal navigation analysis to assess the thickness of the interpulmonary ridge and the morphological shape and size of PV ostium to choose the optimal CB size and the best orientation to address the balloon wedging at the LA-PV junction in an attempt to induce the biggest cryo lesion at the most proximal antral location including the interpulmonary ridge at the carina level in a sort of different morphological anatomical variants, as showed in Figure 1.

Procedure: All pts provided informed consent prior to the procedure. The procedure was approved by hospital's clinical ethics committee. Prior to the procedure, all antiarrhythmic drugs (AAD) were discontinued at least 5 times their half-life; 48 hours for beta blockers and at least 10 days for Amiodarone.

All procedures were performed under general anesthesia with orotracheal intubation under propofol for anesthesia induction, cisatracurium for neuromuscular relaxation (only at the time of intubation), continuous perfusion of remifentanil for analgesia and mechanical ventilation maintained with Sevoflurane gas.

Transeptal Approach: Seldinger technique was used for all vascular access. A decapolar 6 French electrocatheter through an antecubital vein was positioned into the coronary sinus (CS) for pacing and anatomical reference purposes. Cuatripolar/6French catheter was positioned at the A-V-nodal-his bundle junction through left femoral vein, for the same anatomical reference purpose, being moved later to superior vena cava (SVC) for pacing during CB applications at the right sided PV.

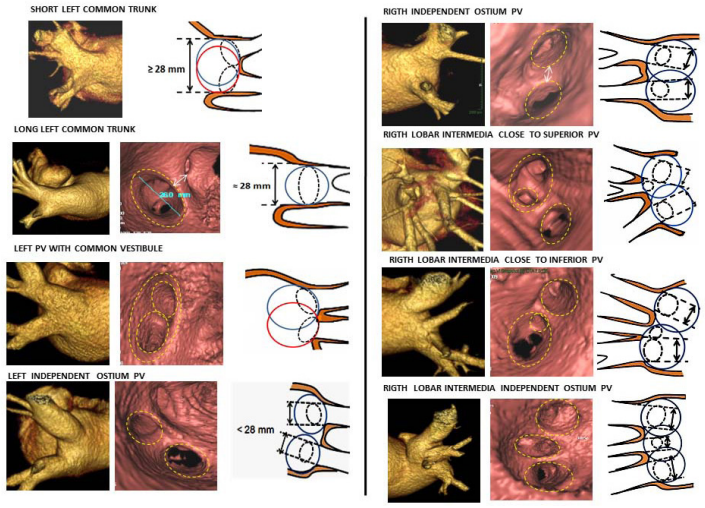


Figure 1: Endoluminal and CT Scan reconstruction anatomical approach, to assess diameter/ shape and sizes of PV/LA-PV junction level and interpulmonary ridge, in relation to the size of CB to be used and the orientation for better PV-LA wedging

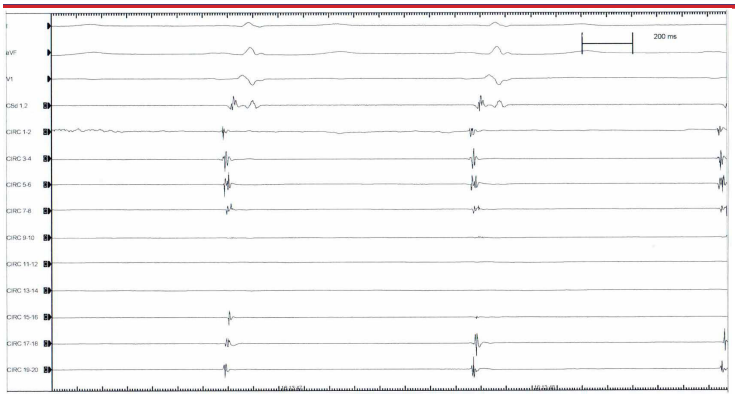


Figure 2A: Atrial far-field and synchronous PV electrical activity as recorded with the circular catheter mapping at the PV-LA junction antral level

Through right femoral vein, an introducer and fast-cath 8.5 French sheet SLO, (Saint Jude medical, Minnesota, USA), was advanced over a 0.32 mm J typed shape guide wire to the SVC. Then, the guide wire is withdrawal, and a modified Brockenbrough needle (BRKO 71 cm beveled cut 30º/ Saint Jude Medical, MN, USA) is advance through the SLO sheet, and descending the whole transeptal assembly to embed fossa ovalis.

After gaining left atrial access, a bolus of 10.000 IU of sodium heparin was administered, followed by continuous perfusion as needed to maintain the activation clotting time ≥300 sec, as previously described.[25] At the end of the procedure, anticoagulation is reversed with protamine and 1grm. of lysine acetylsalicylate given i.v, along with low molecular weight heparine depending on patient's body surface (1 mgr/Kg body weight) given subcutaneously, in addition to 100 mg of flecainide given intravenously in 10 minutes. Continuous intravenous perfusion of sodium heparine adjusted to patient's body weight is started 4 hours later after removing all catheters from the vascular bed. Twenty-four hours later, oral anticoagulation with Vitamin K antagonist dicumarol is started targeting an international normalized ratio (INR) in the range of 2.0 to 3.0, plus additional platelet inhibition with 100 mg of ASA.

PV/Cartography/ Mapping: Once in the LA chamber, the long 0.32mm guide-wire is advanced into the left superior PV (LSPV) and selective PV angiogram is performed, and in the same manner for the remaining veins, Left Inferior (LIPV), Right Superior (RSPV) and Right Inferior (RIPV).

After removing the entire transeptal assembly, keeping the guide-wire in the LSPV, a steerable 15F over-the wire sheath (Flex Cath, Cryocath, Medtronic,USA) is advanced and positioned in the LA. Then basal electrical cartography of the veins is obtained (Figure 2A) with a circular duodecapolar mapping catheter with adjustable diameter (Reflexion spiral, Saint Jude Medical, MN, USA) positioned at the PV-LA junction antrum level, starting on LSPV and followed by LIPV, RSPV and RIPV respectively. We used a 20 pole circular mapping catheter to achieve sharper signals and better recognition between PV potentials and far-field atrial activity. This variable catheter adjustable in diameter is more useful when varying PV size or common ostium encountered, and also, allows for better contact and stability at the ostium of the PV when the circular catheter is fully expanded, leading to relative oversizing. Although, when fully expanded electrobipoles overlap and could cause contact signal artifact and repetition of recorded signals.

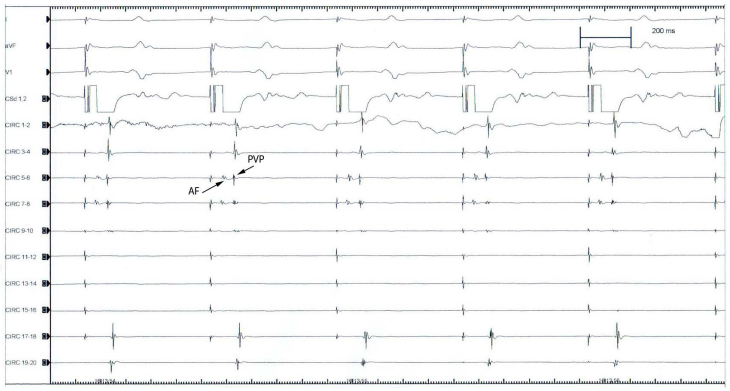


Figure 2B: Asynchronous atrial far-field (Af) and PV electrical potential (PVP) as recorded on circular catheter mapping by pacing CS

After recording the LA- PV junction electrical activity we pace CS to separate atrial far-field electrograms from PV electrical activity (Figure 2.B), as in sinus rhythm it is difficult to distinguish because they are activated synchronously. After 30 minutes of CB applications all PVs were mapping again to assess electrical PV-LA isolation.

Cryoballoon: After withdrawing the circular catheter mapping, a 28 or 23 mm double walled CB catheter (Artic Front, Medtronic, USA) is advanced over the wire up to the LA, inflated and positioned in the PV ostium of each vein and gently pushed against the PV-LA antrum to get a perfect occlusion achieved when selective contrast medium injected (50% ratio with 0.9% saline solution) is full retained into the vein with no evidence of contrast leakage back to the atrium (grade IV) according to the degree of occlusion classification proposed and used by Neumann et al [8] to grade I with poor occlusion leading to an immediate rapid outflow contrast medium back to the LA. Until the second generation CB (CB2) was commercially available (April, 2013) patients were treated with the first generation CB (CB1).

Bidirectional LA-PV-LA Block Protocol

Exit Block: By pacing PV from all 20 poles of the circular catheter mapping at high amplitude voltage (20 mA) with consistent 1:1 PV capture and no evidence whatsoever of any atrial response.

Entry Block: By pacing LA from the CS-Catheter at three different cycle lengths (600, 500, 400 ms) with consistent 1:1 LA capture and no evidence whatsoever of any PV electrical activity in any of the 20 poles of circular-catheter mapping positioned at the LA-PV junction antral level.

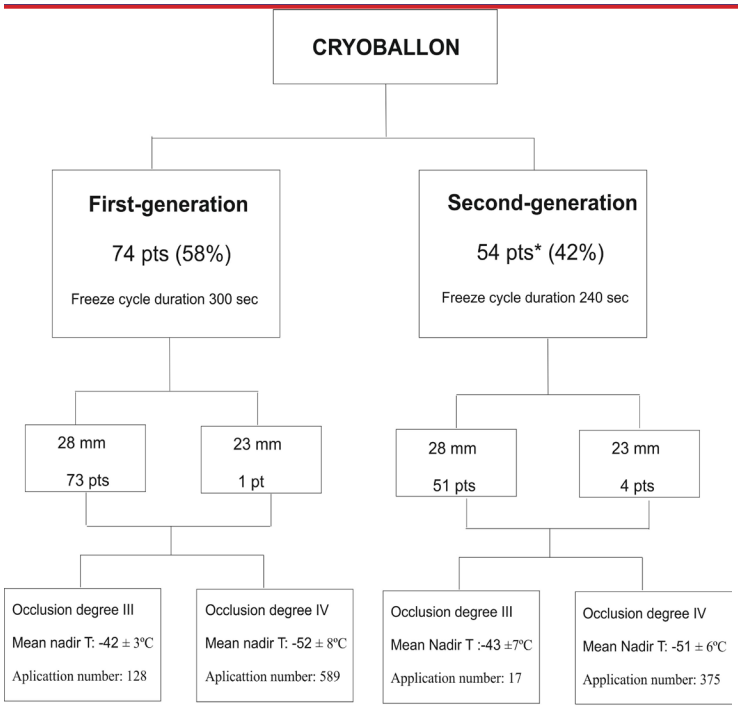
AD Protocol: Included bolus i.v administration of increasing doses (12-18-24… mgrs.), and pacing PV/LA when A-V nodal conduction block occurred.

Extrapulmonary Muscular Connections (Emc)/ Rule-Out Protocol: Included pacing distal vein from the circular catheter mapping after complete BB demonstrated at the LA-PV junction antral level (Figure 4.A) and the demonstration of 1:1 PV-LA conduction resumed. (Figure 4.B)

RF Protocol: Focal RF applications were used for eliminating RC gaps when evident after single CB application or after checking for BB Block, post -AD, or when EMC was demonstrated. (Figure 5).

Sixty second "touch-up" of focal RF was used to eliminate all residual gaps only when evident in no more than 2 pairs of the circular catheter mapping. Otherwise, when more a repeated new CB application was performed.

Phrenic Nerve Physiology Control: Phrenic nerve physiology was



*In 1 pt 28mm was used (proximal application) & 23mm CB (distal application)

Figure 3: Diagram flow showing the type of balloon used for different group of pts, occlusion degree, and temperature reached

monitored in all cases during right-sided PV/CB applications, by placing the cuatripolar electrocatheter in SVC and pacing at 2.000 ms cycle length, checking the intensity of diaphragm contractions by intermittent fluoroscopy and tactile feedback placing the operator's hand on the patient´s abdomen, and immediately stop freezing when intensity of the diaphragm contraction weakens or is suddenly stopped.

Follow-Up Protocol: Before discharge the hospital, TTE was performed in all cases to rule out pericardial effusion and chest-X-ray taked in a deep breath, upright position, to confirm normal phrenic nerve physiology.

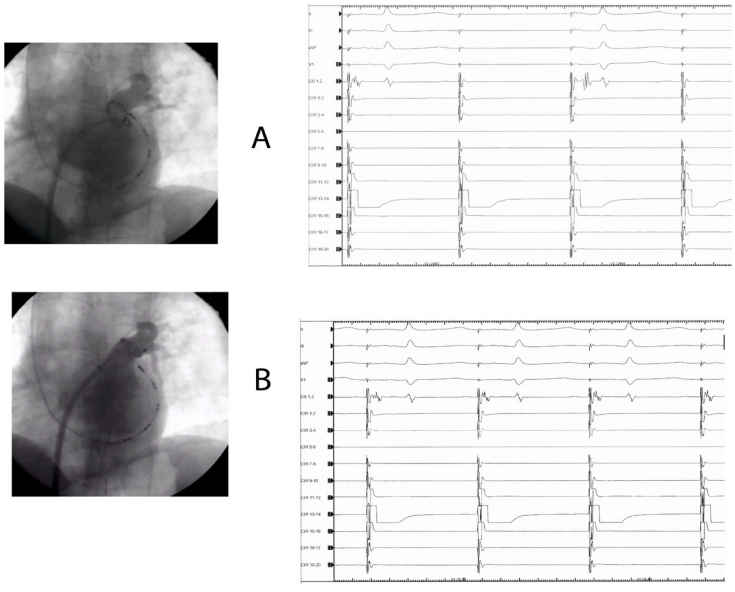


Figure 4: A.Upper panel: Left side: pacing proximal antrum (circular 13-14) showing exit block (right side). B. Lower panel: Left side (same patient): pacing distal vein (circular 13-14), 1:1 PV/LA conduction resumed (right side)

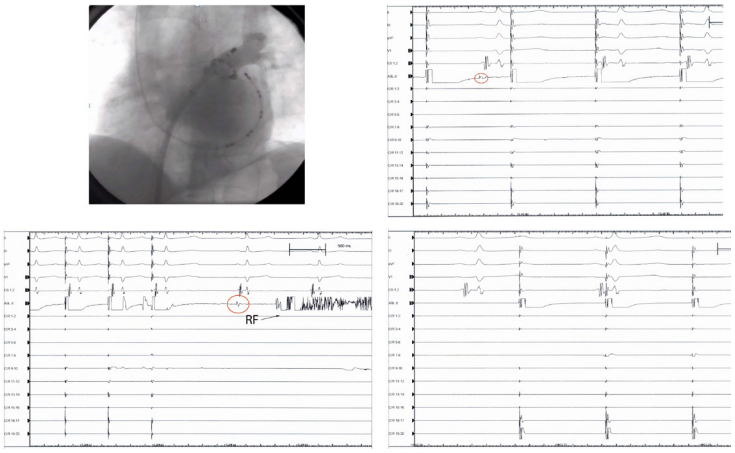


Figure 5: Same patient as figure 4 A, B. Upper panel right side: pacing gap (red circle) distal vein with RF catheter (left side) with: 1:1 PV/LA conduction (third and fourth paced beat) demonstration at the right side recording. Lower panel (left side): pacing gap RF catheter, 1:1 PV/LA conduction is evident (three paced beat). After stop pacing, RC gap is evident (red circle), followed by RF application. After focal RF, exit block is demonstrated (right side)

The immediate follow-up included holter monitoring at 7, 15,30,45,60 and 90 days respectively, and thorax CT-Scan at 30 and 90 days. All pts received AAD, mostly Class IC+ BtB, and oral anticoagulation with vitamin K antagonist dicumarol is started 1 day after PVI, targeting an INR within 2.0 to 3.0 range for at least three months, along with additional platelet inhibition agent (ASA, 100 mgrs/daily).

After a three-month blanking period on medication, all AAD were discontinued, and follow-up started to count. All pts were monitored by continuous daily trans telephonic information in case of symptoms, and monthly ECG holter monitoring was routinely done over 1411±727 days (46.6±24.2 months) of follow-up.

Results

Acute PVI And LA-PV Reconduction

A total of 483 PV including 29 CT (26 Left/3Right), were treated with CB and complete PVI demonstrated in 439 (91.9%). Acute reconduction post CB showed 44 PV (9%) 16 PV out of 483 (3.3%) after single CB. In 16 PV out of 483 (3.3%), RC was unmasked after AD, in 10 patients. In 12 PV out of 483 (2.7%), EMC could be demonstrated in 9 pts.

In six out of 16 of the acute reconnected PVs, RC appear after incomplete CB occlusion (degree III), (Figure 7) and in the same proportional rate after AD, (Figure 8.A,B), all eliminated by focal RF applications (Figure 8C).

Interestingly, all acute PV-LA RC (44 PV) occurred only with CB1.

Follow-Up: Follow-up of 1411±727 days started to count after three month blanking-period when AAD was discontinued.

Arrhythmia Recurrences: On follow-up, 14 pts (10.9%) out of 128 experienced clinical recurrence of the arrhythmia: 12 male (52±8) and 2 female (63±13) years respectively. Early recurrence occurred immediately at the early stage of follow-up in 9 males (mean age

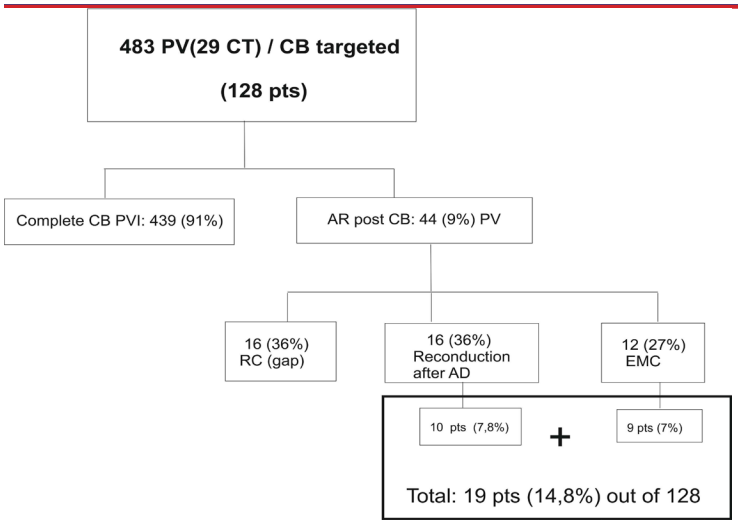


Figure 6: Diagram flow showing total acute reconnected PV and number of patients. AR: acute reconnection

50±7 years), when medication was stopped after the three-month blanking-period. Late recurrences occurred in 3 males (mean age 55±9 years) at 24, 27 and 60 months, and 2 female (mean age 63±13 years) at 7 and 40 months respectively.

All 14 recurrence pts allow for a second procedure (Redo).

In a Redo follow-up of 41±16 months, all 14 pts remain in sinus rhythm without medication.

The remaining 114 pts (89.1%) followed-up 1411±727 days, are asymptomatic, free of drugs, in sinus rhythm.

Seven pts (5.4%) had aphonia. Transient PNP: 7 (5.4%). Permanent PNP: 2 (1.5%), Pulmonary infiltrates (Figure 9): 5 (3.9%).Mild dyspepsia: 2 (1.5%), Severe intraprocedural bronchospasm: 2 (1.5%), Discrete hemoptoic sputum: 2 (1.5%).

No major side effects or complications occurred in our pts treated with CB, with no mortality, none atrioesophageal fistula, and none

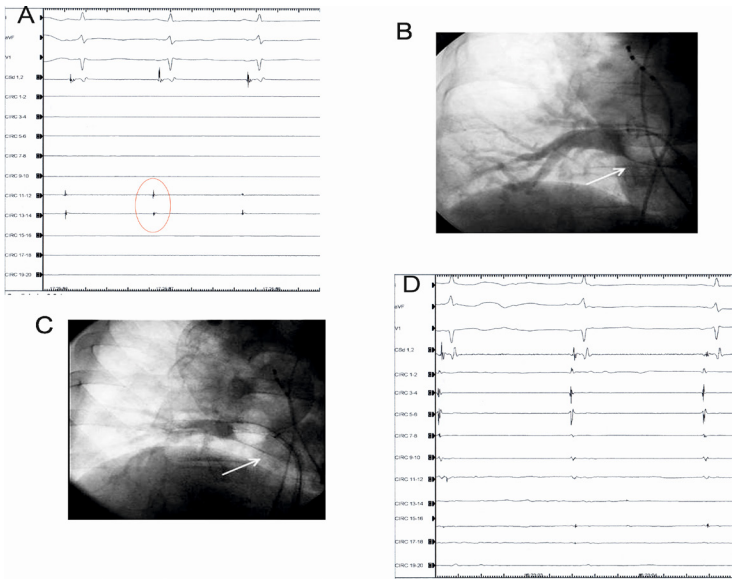


Figure 7: A, Residual conduction gap (red circle) evident after incomplete CB occlusion (B, C) (degree III) with contrast leakage evident (arrow) as compare with PV/LA electrical activity recording in the same patient before the incomplete CB application (D)

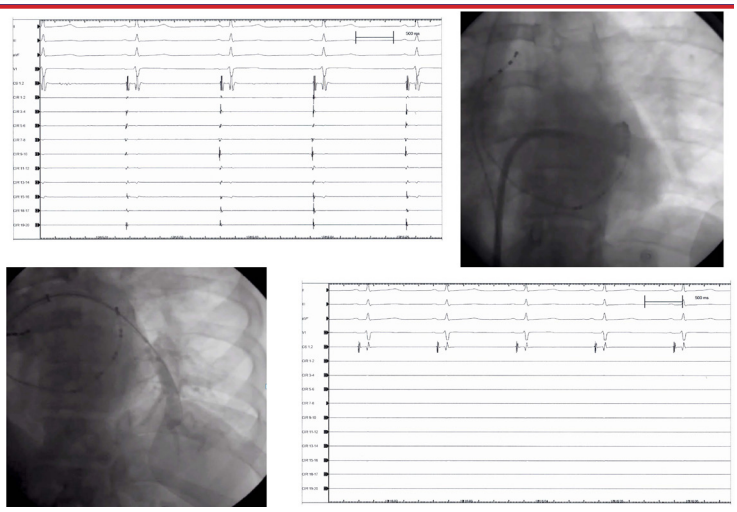


Figure 8A: Upper panel: showing PV electrical activity recorded at the 10 bipoles of the circular catheter mapping (left side) placed at the PV-LA junction antral level (right side). Lower panel: after CB application occlusion degree IV (left side), PV electrical activity is no more recording at circular catheter mapping (right side)

pulmonary vein stenosis.

Side Effects And Complications Follow-Up: Aphonia: lasting ≤ 72 hours. Transient PNP: full complete recovery during the procedure. Permanent PNP: still evident on follow-up (1-3 years). Pulmonary infiltrates: In asymptomatic pts were shown at first month's CT-Scan control performed, there having been no evidence 2 months later on another CT-Scan routinely performed. Mild dyspepsia: quick complete resolution ≤ 72 hours on omeprazole and protective gastric diet. Discrete hemoptoic sputum: lasting ≤ 72 hours. Severe intraprocedural Bronchospasm: requiring 48 hours of treatment in the ICU.

Discussion

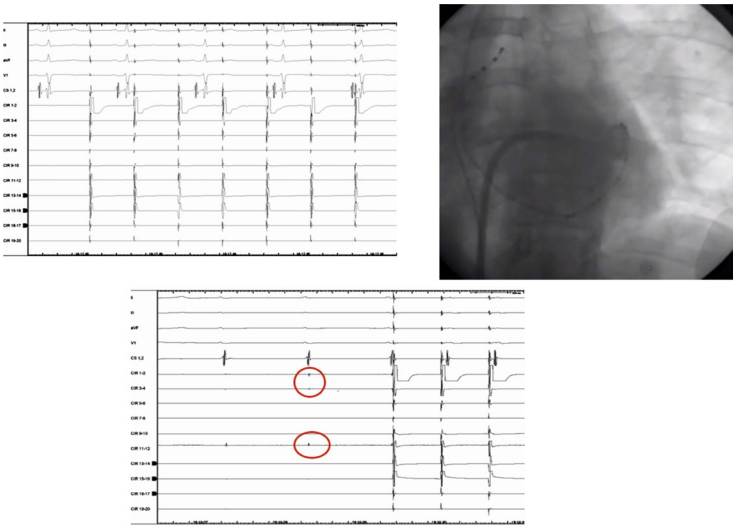


Figure 8B: Same patient as in Figure A. Upper panel: (left side): pacing (circular 1-2) at PV-LA junction antral level (right side), demonstrated exit block. Lower panel: dormant tissue unmasked by AD (red circle), at the time of complete A-V conduction block, and 1:1 PV-LA conduction demonstrated (second and third paced beats), by pacing gap

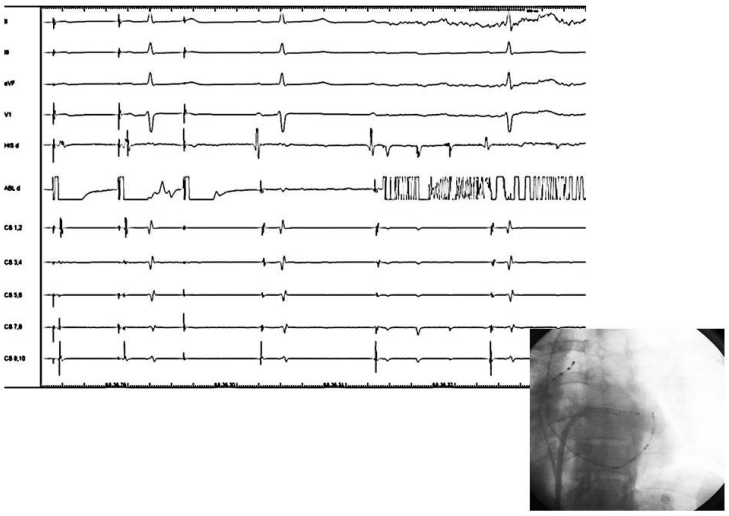


Figure 8(C): Same patient as in Figure 8A and B. By placing RF catheter (lower right side figure) on PV dormant tissue location unmasked by AD, and pacing gap from RF catheter (upper side recording) 1:1 PV-LA conduction showed on first and second (left side) paced beats during AD effect, as evident with completed A-V conduction block, followed by RF application

Over the last few years, CB ablation technology has emerged into the arrhythmia arena as an useful and safe tool to treat pts suffering from atrial fibrillation by achieving through its applications an acute electrical disconnection of the PV from the LA in a range of (90-100 %) in the majority of the series already published,[26] which is the main key to cure this arrhythmia.

Although in the majority of the clinical and randomized studies published, the results of the CB technique do not significantly differ in the short, medium and long-term outcome from those using RF as an energy source,[27-30] this "point to point" technique, can be more tedious, and time-consuming , most likely requiring better operator skill and involving an inherent clinically-significant risk of major complications, sometimes difficult to manage and treat, such as reentry left atrial tachyarrhythmia, thromboembolic events, pericardial effusion, PV stenosis or atrioesophageal fistula [31-34] which can be avoided or minimizing their incident by a "single shot" CB technique.

Since the first human experience published by Van Belle et al [5] treating pts suffering PAF with CB ablation, the technique has become widely-used as useful and safe tool to face the definitive treatment of this disturbing arrhythmia, by achieving ≥ 95% of acute electrical PVI in the majority of the series already published.[26]

Side Effects And Complications:

Aphonia: We cannot say for certain that this complication was

Table 3: Side effects and complications

TYPE	Pts
Aphonia	7 (5.4)%
Transient Phrenic nerve palsy	7 (5.4)%
Phrenic nerve paralysis	2 (1.5)%
Pulmonary infiltrates	5 (3.9)%
Dyspepsia	2 (1.5)%
Bronchospam	2 (1.5)%
Hemoptoic sputum	2 (1.5)%

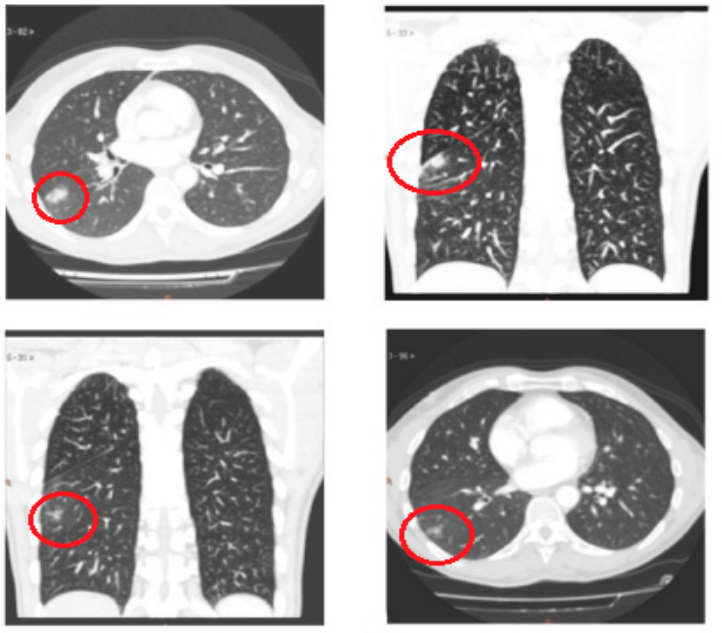


Figure 9: CT Scan slides showing pulmonary infiltrate (red circles)

strictly CB-related, first of all, because as far as we know, it has not been previously described, which is hardly surprising, especially after the findings described in the largest survey published so far,[35] focusing this complications topic in 500 consecutive pts. Although we can argue the possibility that this complication has been associated with endotracheal intubation maneuvers during general anesthesia, as orotracheal intubation, when difficult, can cause some laryngeal or vocal chord trauma, this however was not the case regarding our 7 patients affected in whom the orotracheal intubation, was smoothly performed and non-traumatic. Hence the most logical explanation for this symptom does not seem to have likely had anything to do with this orotracheal maneuvers. We raised the question, of a possible transient injury of the left recurrent laryngeal nerve, as has been warned by Cabrera and colleagues [36] in an unpublished abstract presentation at Hearth Rhythm 2011meeting, especially when CB applications take place deeper into the LSPV, along with the structural displacement towards the anatomical left recurrent laryngeal nerve bed, by strongly wedging the balloon in the venous ostium for a better occlusion.

Moreover, all 7 pts who experienced aphonia were treated with the CB2 which had been designed with a new technological implementation resulting in a more homogeneous intake and distribution of the refrigerant flow around the balloon sphere, increasing the surface contact cooling that might induce deeper lesions with greater likelihood of affecting more extracardiac structures.[35, 39]

PNP occurred in 9 pts (7 %). Only 2 are still permanent after 1 and 3 years follow-up respectively, with not clinical compromise, doing a normal life and completely asymptomatic. This incidental complication rate is consistent with the majority of the largest CB series already published: 4.7%,[10-37] 7%,[5] 7.2%,[35] 7.5%,[8] with some discrete higher incidence 11.1% [9] and 11.2%.[11]

In our series, the common characteristic of this complication was the lower nadir temperature level reached, of ≤ 60° C in the majority of cases (78%) (Table 4). As the majority of pts were treated with the CB1 (74 out of 128), the PNP balloon-related rate was: 5.4% CB1

vs 9.2% CB2 (5 pts out of 54). This higher PNP rate occurring with CB2 as compared to CB1 has been showed by others.[38, 39] In 340 consecutive pts treated by Aryana et al [38] with CB1 (140) and 200 with CB2, PNP occurred with CB1 in 12.1% pts vs 16.2% when CB2 was used. In a similar difference percentage rates Fürnkranz et al [39] reported 8.7 % of PNP with CB2 vs 5.7% when CB1 was employed.

Important to remark in our study that the 2 pts with persistent PNP after 1 and 3 years of follow-up, PNP occurred suddenly at 100 and 156 seconds of CB1 applications, when the lowest temperatures of -70 and -68ºC were respectively reached. In the other 7 pts with transient PNP, the CB applications were immediately stopped as soon as weakness of the diaphragm intensity contraction was adverted.

Table 4: Ocurrence of PNP related to the CB used, time of application and nadir temperature reached

	TºC	Seconds	CB mm	CB Generation	
TRANSIENT PHRENIC NERVE PALSY					78% Mean TºC≥ -60ºC
1	-68	122	28	FIRST	
2	-73	222	28	FIRST	
3	-55	89	28	SECOND	
4	-56	165	23	SECOND	First Gen CB: 55.5%
5	-60	115	28	SECOND	
6	-68	100	28	SECOND	
7	-65	190	28	SECOND	
PERMANENT PHRENIC NERVE PARALYSIS					Second Gen CB: 45.5%
1	-70	100	28	FIRST	
2	-68	156	28	FIRST	

The highest level of PNP (19%) reached with the CB2 observed by Cherchia et al [40] related with the lower CB temperature reached, has move to this group to stop CB applications when -60 º C nadir temperature level is reached, in addition to limiting the freeze application time to 180 seconds, in an attempt to avoid major complications.[41,42,35] At the same time, these authors have proposed a modification technique to prevent PNP, consisting after tight wedging of the inflated CB inside the RSPV ostium, to withdraw it until a small leak of contrast is observed, since the CB volume increases slightly at the onset of CB application. This technical maneuvers described by Casado-Arroyo et al [43] from the same Brussel's group, offers the advantage of a more proximal CB application and it has been suggested to use by others.[44] Martins et al suggest the use of Casado-Arroyo technique, particularly when the vertical projection of the PN reaches the distal part of the CB (Zone B1 in their study) with a 98% of negative predictive value, and Ströker et al [45] had recently emphasized the need to perform a preprocedural anatomic assessment, in order to evaluate the risk of PN injury, such PV orientation, larger PV dimensions, shorter distance to SVC, the presence of early branches originating from the main ostium, and right –sided long CT; anatomical variations which were associated with PN injury.

Pulmonary Infiltrates: Of unknown origin, mostly showed on the right side in distal pleural location, found in 5 asymptomatic pts (3.9%) on CT-Scan control routinely performed 1 month after the procedure, which were no longer evident at the 3-month control CT-Scan performed, at follow-up. Those pulmonary infiltrates, radiologicaly in appearance of inflammatory aspect, producing no clinical impact on pts, strongly suggest a probably origin related with the transmission of cold into the lung parenchyma during CB application, as it has been experimentally demonstrated in dogs [46] as small subtle foci of ablated –related superficial pleural fibrosis.[47]

Bronchospasm: Severe intraprocedural bronchospasm occurred in two pts who had a past medical history of mild chronic bronchitis whom required medical treatment for ≤ 48 hours in the ICU. This complication might have a difficult explanation and could have been due to a combination of several factors working together, such as prior bronchial damage in pts with chronic bronchitis, the possibility of major injury due to ice formation inside the bronchial lumen [48] as well as the possible trigger effect of AD which, although anecdotic, has been described.[49]

Hemoptoic Sputum: Two pts presented discrete hemoptoic sputum on the immediate post- procedure, being otherwise on oral anticoagulation treatment regime and completely asymptomatic. This type of complication might also be due to several factors working together or may even have a different origin. Firstly, as it has been experimentally demonstrated,[50, 51] the expansion of ice within the fragile microvasculature leads to the interruption of vascular integrity, which is the reason for the intramyocardial hemorrhage, as well as the hemoptysis associate with cryo injury to the lung tissues, and secondly, the possibility of bronchial erosion as has been demonstrated [52] as a cause of hemoptysis.

Dyspepsia: Two pts complain of mild dyspepsia. As no esophagogastroduodenal endoscopy study was performed, we cannot assure it was related or not, with some reversible esophageal ulceration.[53]

Epicardial PV-LA muscular connections: Electrically functioning EMC with PV-LA 1:1 conduction (Figure 4 A,B) demonstrated, was found in our pts using this protocol in 12 PV (2.5% of total 483 PV), totaling 27.2% of the all post CB- PV reconducted (44 PV), in 9 pts (7%).

Since the first human demonstration of the presence of electrical conduction between PV was made,[54] other investigators had demonstrated the incidence of the interpulmonary vein electrical connections as being responsible of the maintenance of the arrhythmia in a single pt with PAF,[55, 56] and Takahashi et al demonstrated in 49 consecutive pts, the presence of electrical connections between contiguous PV in 14% of the pts underwent atrial RF catheter ablation to treat their drug-resistant AF.[57]

Perez- Castellano et al [58] using RF catheter ablation for ostial PVI in 100 consecutive pts with drug-refractory atrial fibrillation, found in 3% of the veins, venoatrial epicardial connections inserted at distance from the venous ostium, and 10% with epicardial connections between the ipsilateral PV in 20% of pts resistant to atrial ablation, suggesting a different disconnection approach for PV showing those extrapulmonary epicardial connections associated with an increased rate of early recurrence of conduction.

The morphological evidence of these muscular connections between contiguous veins has been demonstrated by Cabrera et al,[59] confirming the anatomical underlying substrate of such electrically-functioning connections. More recently, Squara et al [60] have demonstrated the prevalence of those electrical connections between ipsilateral pulmonary veins and their implications for ablation and AD testing in 30 pts submitted to RF catheter ablation. They found a high presence of ipsilateral PV connections after antral PVI in up to 65.6% of total PV sets without carina ablation, lowered to 17.7% when the carina ablation was performed, emphasizing the need for carina ablation. Squara et al [60] also described acute reconnection of at

least 1 of the PV to the LA, in 18% of the PV sets.

In our work 44 PV (9.1%) of the total PV faced (483) showed acute reconduction after single CB (Figure 6).As we have not conducted any previous study to assess the prevalence of these possible direct connections between ipsilateral pulmonary veins, and quantifying the incidence rate that the electrical impulse originating from 1 PV would propagate to the adjacent ipsilateral vein, as well as the indirect connections LA muscular sleeves, the only way to demonstrated some EMC in a practical clinical setting is the demonstration of complete BB at the PV-LA junction antral level by pacing from all 10 pairs of poles of the duodecapolar circular catheter mapping, following by demonstration that 1:1 PV-LA conduction resumed by pacing distal vein (Figure 4.A,B) no further than 5-10mm from the endocardium of the interpulmonary isthmus, as Cabrera et al [59] have demonstrated as the limit of distance where the insertion of the muscular connections, can be founded.

By doing so, we found electrically -functioning EMC in 12 (2.5%) of the total PV-LA reconnected after CB-PVI, totaling 27% of the all early- reconducted veins, which is consistent with the figures published by others,[58] having carried out the same protocol, to rule-out EMC, by pacing distal vein after PVI-atrial isolation. Another interesting aspect to be taken in account is that, in the majority of CB-applications the interpulmonary ridge of the PV isthmus at the carina level is, affected, regardless of PV anatomy, (except for long CT) affected by cryo lesion at the endocardial superior and inferior aspects during CB applications at the superior and inferior PV.

Interestingly, those 12 EMC were demonstrated after acute BB was achieved in 9 pts, totaling a 7% of the total population of pts treated.

AD Protocol And Acute Early PV-LA Reconnection: A total of 483 PV including 29 CT were treated with CB and complete CB-PVI demonstrated in 439 (90.9%). Acute reconduction post CB was shown 44 PV (9.1%) (Figure 6): Sixteen PV (3.3% of the total PV; 36% of the reconducted ones), show acute reconnection due to incomplete lesion with "dormant tissue" unmasked by AD,[17,18] by inducing hyperpolarization to restore excitability by activating AD-sensitive potassium channels restoring conduction of dormant PV as it has been better clarified and demonstrated by Datino et al[61]

Arrhythmia Recurrence And Reconduction: For analysis of the location of conduction gaps, the ipsilateral LA-PV junction was divided into four segments in a clockwise sense, starting at 10 o'clock (Superior, inferior, anterior, and posterior, for left PVs, and superior, inferior, septal, and lateral, for right PVs) (Figure 10).

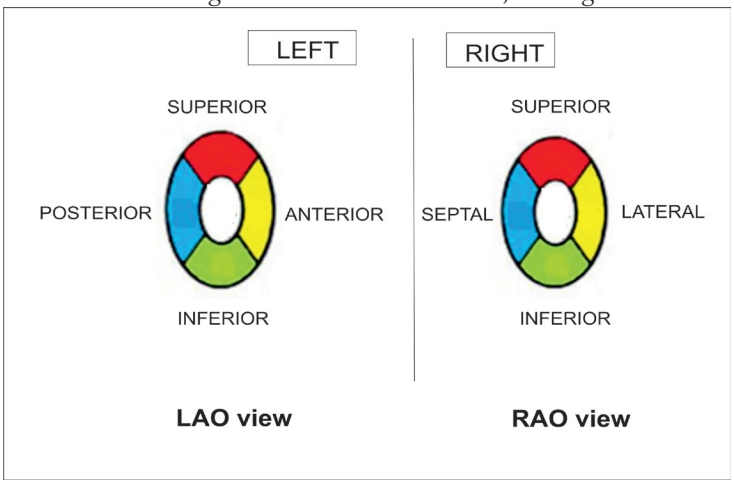


Figure 10: Diagram representation for the different number of RC found in the different segment location

Forteen pts (10.9%) had clinical recurrence of the arrhythmia and allow for a Redo. Fifty-four PV including 2 CT were newly CB treated in a Redo with CB2. Reconduction was encountered in 29 PV (53.7%) in different segment locations (Figure 10.A) revealing the almost even distribution of RC in the superior segments, with greater number of reconductions shown at the inferior aspect of the LSPV. Also the PV showing the largest number of reconduction was the LSPV (37.9%) (Table 5).

Finally, the RC segment distribution on Redo cases was random, being unrelated to those shown at first procedure (Figure 10.B).

Fürnkranz et al [15] find the inferior segments of the LA-PV junction most often affected by reconduction in addition to the LSPV having shown the high rate of reconduction (63%), suggesting that the superior ridge may have contributed to this relatively high rate of reconduction in this LSPV.

In addition to the above, Fürnkranz et al hypothesized in their aforementioned study that the high incidence of inferior conduction gaps might be due to different causes, related to the difficulty sometimes involves in deflecting the sheath/balloon system in order to reach the inferior aspect of PV, resulting in incomplete balloon-time contact. Conversely when approaching superior PV, both sheaths and balloon can be used to create a strong push onto the PV ostium to occlude the blood flow, achieving better occlusion and more permanent tissue cryolesion.

In the original study conducted by Chierchia et al,[19] enrolling 39 pts treated for PAF with CB1, AD testing after CB induced a LA-PV reconnection only in 7 (4.6%) PV which often occurred in the inferior aspect of the lower veins, especially of the right inferior. All these RC gaps being eliminated by further CB applications or focal cryo "Touch-up". Chierchia et al,[16] have also shown a 2.8% early spontaneous reconnection after 30 minutes of CB applications in a cohort of 26 pts treated for PAF with CB1.More recentlyin a study conducted by Ciconte et al [20] in 50 consecutive pts treated for PAF or early persistent AF ≤ 6 months, with CB2, spontaneous (4 veins) and AD-induced (4 veins) PV reconnections occurred in the 4% of initially isolated veins (8 veins) in 6 pts (12%).

Our results are consistent with the aforementioned studies, entailing 36% totally reconnected PV showing spontaneous reconduction, totaling 3.3% of the total 483PV-CB treated. Beside the highest reconduction gaps on the inferior aspect of the LSPV, conversely to the segment location reconduction showed by Fürnkranz et al [15] in 26 pts refered for RF PV ablation after CB first procedure failed, inferior segments showed gaps in 85% and 77% at the lateral and septal location respectively and 42% and 31% respectively at the

Table 5: Number of PV showing reconduction and their percentages of the total PV reconnected

14 pts: 54 PV (2CT)

29 PV reconnected (53.7%)

PV	nº	%
CT	2	6,8%
LSPV	11	37,9%
LIPV	7	24,1%
RSPV	4	13,7%
RIPV	5	17,2%

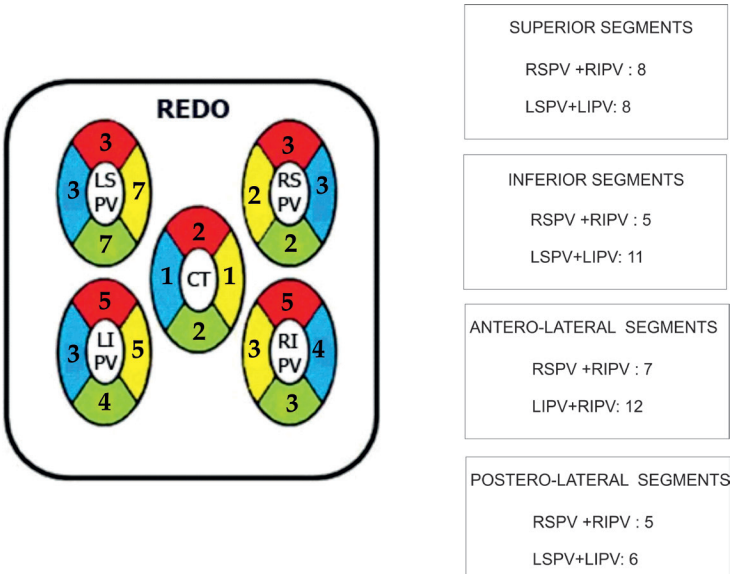


Figure 10A: Segment distribution appearance of RC gaps

lateral and septal aspect of the superior segments, our segment reconduction locations showed a most uniform distribution.

One possible underlying explanation for this, perhaps being the fact that in our pts all procedures were performed by the same operator (JMP) and were evaluated individually case by case, based not only the size of balloon to be used, but also on the orientation to be applied [15] according to PV anatomy, morphology, and angle direction, previously assessed with CT-PV slide reconstructions, in conjunction with the aforementioned endoluminal anatomical approach (Figure 1). All of these factors combined might play an important role toward achieving better occlusions and more uniform lesions adding to minimize possibilities of PV-LA reconduction, which is the principal cause of clinical arrhythmia recurrences.

We have not done any protocol to rule out non PV-Foci, as a potential cause of arrhythmia recurrence,[62] given that all recurrences were Redo, and PV-LA reconduction was evidenced in all cases.

Patient's Risk Profile Of Recurrent Arrhythmia

We have not calculated the individual risk of recurrence of the arrhythmia based on the clinical patient data profile to assess the ALARMEc score, proposed by Neumann's group,[63, 64] but rather a rough estimate for our entire pt population treated, without atrial enlargement, suffering PAF, having normal renal function, with glomerular filtration rate ≥ 68 mL/min, none with structural heart disease, and only 33% of them with some metabolic disorder. We can approximate and estimate an ALARMEc score ≤ 1, according to the most favorable outcome of these patients, in whom the arrhythmia substrate mostly underlying on PV triggers.

Duration Of The Procedure

We experience a rapidly important decrease on the total duration time of the procedure in relation with the learning curve.[65] For the first 10 cases performed the mean time duration of procedure (since the transeptal approach to withrawal LA catheters) was 361 minutes and the mean fluoroscopy time: 86 minutes. For the last 20 pts treated, the mean duration time was 150 ±39 minutes, and fluoroscopy time 35±10 minutes.

Statistical Analysis

Continuous variables are expressed as mean ± SD.

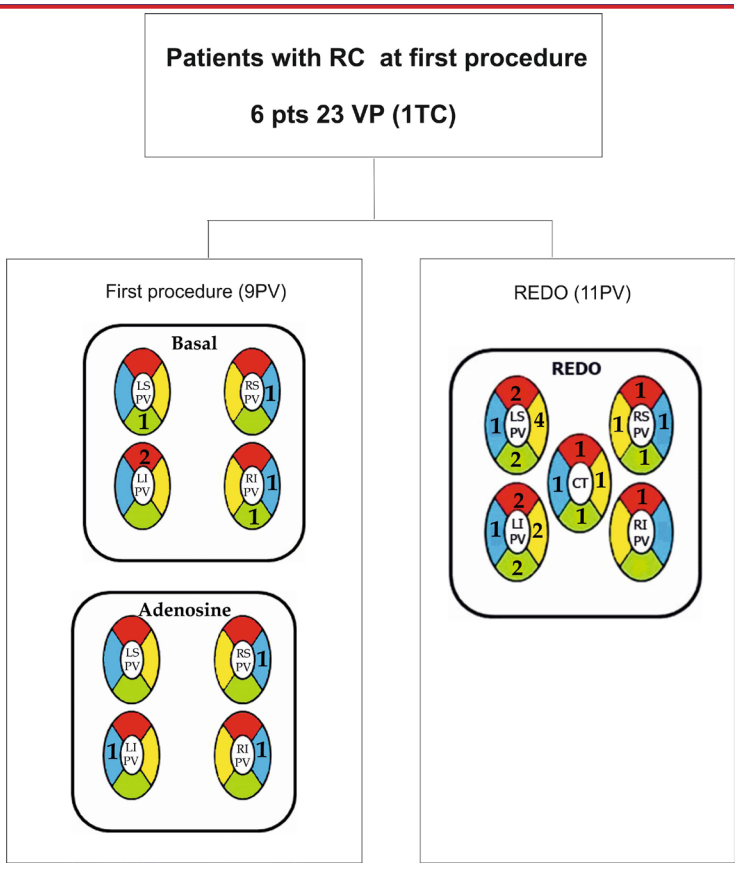


Figure 10B: Reconduction was shown at first procedure in 6 pts with 23 PV including 1 TC. Left side upper figure showed number of gaps after CB, and unmasked by AD (lower left figure), as compared to number and distribution of gaps showing at Redo (right figure) on the same pts

Categorical variables are expressed as percentages.

Study Limitations

This study has some limitations. First, this is a single center study. Second, because of the large interval of time (monthly) between holter monitoring recording on follow up, to detect arrhythmia events, along with patients whom eventually do not feeling symptoms, the success rate may have been overestimated, as none of the patient population included in the study were monitored with and implantable loop recorded.

Conclusions

The results and follow-up of our series of 128 pts treated for PAF over 7 years, allow us to conclude: 1. Cryoenergy PV applications doesn't induce a homogeneous circumferential lesion in all PV which dependents on the PV anatomy, shape, size and thickness as well as the uniform distribution of cold and temperature reached at the PV-LA junction level which is the main cause of spontaneous reconnection or incomplete lesions with dormant tissue. 2. Routine use of AD after acute CB-PVI allowed-us to identify incomplete lesions with dormant tissue in 7.8% of pts. 3. Electrically functioning EMC might be identified in 7% of pts by pacing distal vein after complete antral PVI. 4. In summary, checking for BB, AD protocol and, pacing distal vein after PVI to rule out EMC allowed-us to identified 14.8% of pts with underlying tissue substrate for potential arrhythmia recurrence. 5. All residual gaps can be eliminated by further CB shots or focal RF applications. 6. All RC gaps occurred

only with CB1 applications. 7. CB2 applications by inducing a wider and deeper lesion, minimize the RC gap appearance wich entail a lower arrhythmia recurrence rate, but involving a higher risk of damage extracardiac structures, such us PNP (9.2% CB2 vs 5.4% CB1). 8. Single CB technique is highly effective and safe for the definitive treatment of pts suffering from PAF with a 72.6% success rate, increasing up to 89.1% when this protocol is applied in a single procedure. After a second procedure performed in recurrences pts, the entire pt population group (100%), remain in sinus rhythm, free of arrhythmia, without AAD, in this very long term follow-up. 9. However, late recurrences, generates some concern about greater increased number of pts with recurrent arrhythmia over a longer course of time, especially for pts whom don't feel symptoms of the arrhythmia. 10. Patients with an estimated low ALARMEc score (≤ 1) have an excellent long term outcome. 11. Finally, to the best of our knowledge, this series includes the largest follow-up described to date, in pts treated for PAF with CB technique.

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First And Second-Generation Cryoballoon Ablation Efficacy Restoring And Maintaining Sinus Rhythm In Patients Electrically Selected And Treated For Long-Standing Persistent Atrial Fibrillation After Acute Complete Electrical Disconnection Of Pulmonary Veins From The Left Atrium Demonstrated

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Abstract

Introduction Cryoballoon ablation (CB) has proven effective to treatment of patients (pts) with atrial fibrillation (AF). However, the isolated efficacy of CB to treat pts with long-standing persistent atrial fibrillation (LSPAF) is less know. We analyzed the acute results and the long-term follow-up of our pts suffering LSPAF and initially treated with CB. Methods A cohort of 44 pts, 37 male (84%) mean age (60±10 year) suffering LSPAF were treated with first (CB1): 15pts, and second (CB2): 29 pts, generation CB. Eight pts (18.1%) had structural heart disease. Prior to CB, all pts were previously electrically cardioverted (CV) and sinus node and A-V nodal function evaluated at electrophysiological study (EP) once in sinus rhythm (SR) before antiarrhythmic drugs (AAD) load. CB ablation procedure was performed after three months waiting period on AAD following CV/EP drug testing. Result CB procedure was performed in 27 (61.4%) in AF, restoring SR in 8 (18.2%). PV isolation (PVI) was achieved in 95.2%. On follow-up of 30±39 months, 16 pts (40%) had AF recurrence. Second procedure (Redo) was performed in 7 pts. After a single procedure, 24 pts (60%) remain in SR without AAD, after Redo, 29 pts (72.5%), and when AAD added, 31 pts (77.5%) remain in SR. Phrenic nerve palsy (PNP) occurred in 9% of pts (75% with CB2). Conclusion CB technique is safe and useful tool to treat pts with LSPAF with 60% success rate maintaining SR without AAD in a long-term follow-up (30±39 months), up to 72.5% after Redo, and to 77.5% when AAD are added. In the majority of pts maintaining SR (77.5%) CB2 was used in 87% of the cases. Patients without structural heart disease along with those who SR was restored during CB showed the best result.

Introduction

The electrical disconnection of the pulmonary veins (PV) from the left atrium (LA), by CB catheter ablation, has proven effective in the definitive treatment of paroxysmal atrial fibrillation (PAF). The clinical success rate published being around 70-80% in terms of maintenance of SR, in a short-medium and long-term follow-up.[1-4] However, the single efficacy of CB alone, restoring and maintaining SR in pts with persistent atrial fibrillation in less well-known in a medium to long-term follow-up, and unknown to date for LSPAF on a long-term follow-up basis.

In the last few years a CB2 has emerged in clinical practice entailing technical modifications over the former CB1, producing a more homogenous intake and distribution of the refrigerant, resulting in a larger and more uniform zone of freezing on the balloon's surface, as the cooling zone spans over the entire distal half of its surface, minimizing the impact of balloon orientation on optimal tissue contact, which should induced deeper and more permanent tissular lesions, aiming to improve the procedural outcome in pts treated for AF.

Comparison between CB1 and CB2 showed significant differences at one- year follow-up in the general outcome of pts treated for PAF .[5] Some studies[6] having reported a success rate of CB ablation on persistent AF using CB1 in 50% of pts at a mean of 18(6-27) months

Key Words:
Cryoballoon, Long-Standing Atrial Fibrillation, Ablation.

Disclosures:
None.

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of follow-up.

However CB2 was found to have better outcomes compared to CB1 among pts with PAF and persistent AF.[7,8]

The first study to report one year follow-up outcome after CB PVI using CB2 was conducted by Metzner et al [9] with a success rate of 77% in a limited number of 14 pts with short-standing persistent AF (<3 month duration) along with 81% one year clinical success rate for PAF in the same study.

Although the first study focusing solely on persistent AF using CB2 as an index procedure has been described by Ciconte et al [10] reporting a success rate of 60.3% of pts in SR at one year follow-up. The largest survey of pts treated with CB2 for persistent AF, including one year outcome has been more recently described by Koektuerk et al [10] with 67% of pts in SR at a mean follow-up duration of 10.6 ±6.3 months.

The use of Adenosine (AD) to unmask dormant PV tissue after extensive encircling demonstration of PVI has demonstrated clinical implications after AF ablation procedures and may reduce clinical AF recurrences.[12] Some observations having shown the use of AD to guide elimination of dormant PV conduction to increase the success rate of AF ablation procedures.[13]

We aimed to assess the efficacy of CB catheter ablation in our pts treated with CB suffering LSPAF according to the latest guidelines [14] criteria and initially treated with CB1 and CB2 and elimination of residual conduction (RC) gaps unmasked by AD and guided by bidirectional LA-PV-LA conduction block as the main target end point.

Methods

Since November 2008 to November 2015, a cohort of 44 pts, 37 male (84%) mean age: 60±10 year, and 7 female (16%) mean age 64±5 years, suffering from LSPAF were treated with CB1: 15 pts (34%) and CB2: 29 pts (66%).

Clinical and demographic characteristics of the study population are provided in Table 1.

The mean time duration of stable arrhythmia was 4±3 years,(1-13)

Table 1: Clinical and demographic characteristics of the study population

Variable		Pts (n=40)
(n=40)		55±10
Male (37 pts)		60±10
Female (7 pts)		64±5
Hypertension		22(50%)
Diabetes Mellitus		2 (4.4%)
IHD		3 (6.8%)
HOCM		2
NCCM		1 (2.2%)
DCMP		2 (4.5%)
PM		5
LSPAF mean year duration		4+3 (1-13)
Follow-up time		2.8 years 30+39 months
AAD	Class IC (Flecainide)	31
	B-Blocker BtB)	36
	Amioradone	3
	Class IC+BtB	27

IHD: Ischemic heart disease. HOCM: hypertrophic obstructive cardiomyopathy. NCCM: non compaction cardiomyopathy. DCMP: dilated cardiomyopathy. PM: pacemaker

All pts were previously treated with AAD: BtB: 36pts (81.8%); class III (amiodarone): 3pts (6.8%); class 1C: 31 (70.4%), and BtB+1C: 27 pts (61.3%). Eight pts (18.1%) had structural heart disease: 2 hypertrophic obstructive cardiomyopathy (4.5%); 3 chronic ischemic heart disease (6.8%); 2 dilated cardiomyopathy (4.5%) and 1 non-compaction cardiomyopathy (2.2%). Morphological and structural pts data it's provided in table 2.

AP: anterior posterior long parasternal axis. SI: supero-inferior. LAT: lateral (transversal). LVEF: left ventricular ejection function. LCT: left common trunk.

Selection of Patients for CB-PV ablation

All pts included in the study provided informed consent prior to the procedure, which was approved by the hospital's clinical ethics committee.

1. Criteria of exclusion for pt to treat included: 1. Prior stroke or TIA.

2. Cryoglobulinemia and hematological or coagulation disorders.

3. Presence of intracavitary thrombi. 4. Significant associated comorbidity. 5. Left atrial size≥50mm. 6.Failed CV to reverse AF.

The CB ablation protocol for this group included the following approach:

All pts underwent to CV and electrophysiological study (EP) once cardioverted in SR to assess sinus node and A-V nodal function in a basal stage, and were reevaluated after intravenous load of AAD adjusted to pt body weight, mostly class I C, flecainide: 1.5 mgr /kg and calcium channel blocker verapamil: 0.15 mgr/kg for pts without structural heart disease, and class III, amiodarone and/or verapamil for pts having structural heart disease, in an attempt to estimate the sinus node and A-V nodal electrical response to the limit for better achieving early electrical stabilization of the remodeled atrium to sustained SR, allowing the pts to perform routine daily physical activity with the least adverse side effects (mostly bradycardia-related) to avoid patient/physician decision for medication to be discontinued.

Any individual pt whose SR was not restored at CV was excluded for CB ablation. Patients recovering SR were discharged from the hospital after CV/EP procedure on oral AAD including verapamil and were follow-up for the next 3 months before CB-PV ablation procedure. Oral anticoagulation with vitamin K antagonist dicumarol, when indicated, was based on CHA2DS2-VASc score targeting an international normalized ratio (INR) within the 2.0-3.0 range.

CB-PV Ablation Procedure

Previous studies and anatomical approach: CT scan 3D/high

Table 2: Morphological and structural patient population data

Structural Heart disease (n=8)				
Diameters (mm)	LA	PV (30)	LCT (2)	LVEF 61±6
AP	44±5 (34-48)	19±6 (14-28)	26±1 (25-27)	
SI	61±5 (55-65)	22±5 (16-32)	32±3 (30-35)	mean LA size (cm^2) 29±3 (24-33)
LAT	50±6 (43-60)			
Non Structural Heart disease (n=36)				
Diameters (mm)	LA	PV (136)	LCT (8)	LVEF 66%±7
AP	40±5 (33-49)	20±5 (14-30)	27±4 (25-30)	
SI	55±8 (42-70)	22±4 (9-32)	30±3 (30-35)	mean LA size (cm^2) 25±5 (14-36)
LAT	47±8 (41-66)			

AP: anterior posterior long parasternal axis. SI: supero-inferior. LAT: lateral (transversal). LVEF: left ventricular ejection function. LCT: left common trunk.

resolution /64 slide multidetector (Toshiba Aquilion 64, TSX-101A, Tokyo, Japan) as well as in some alternative cases, RMN (1.5T/ Magnetom Symphony, Siemens, Germany) were used for typification and better definition of the cardiac anatomy, morphology, number, caliber and size of PV as well as endoluminal PV analysis to assess the thickness of the interpulmonary ridge and the morphological shape and size of the PV ostium to choose the optimal CB size and the best orientation to address the balloon wedging at the LA-PV junction level in an attempt to induce the greatest cryo-lesion at the most proximal antral location including the interpulmonary ridge at the carina level in any individual PV faced for CB applications.

Transthoracic 2D echocardiogram (TTE) in addition to transesophageal echocardiogram was performed on the same day in all cases, to assess cardiac anatomy and to rule out intramural thrombi. All procedures were performed under general anesthesia with orotracheal intubation under propofol for anesthesia induction, cisatracurium for neuromuscular relaxation (only at the time of intubation), continuous perfusion of remifentanil for analgesia and mechanical ventilation maintained with sevoflurane gas.

Transeptal approach: Seldinger technique was used for all vascular access. A decapolar 6 French electrocatheter introduced through an antecubital vein, was positioned into the coronary sinus (CS) for pacing and anatomical reference purposes. Cuatripolar/6French catheter was positioned at the A-V-nodal-his bundle junction through left femoral vein, for the same anatomical reference purpose, moving later to superior vena cava (SVC) for pacing during CB applications at the right sided PV.

Through right femoral vein, an introducer and fast-cath 8.5 French sheet SLO, (Saint Jude medical, Minnesota, USA), was advanced over a 0,32 mm J typed shape guide wire to the SVC. Then, the guide wire was withdrawn, and a modified Brockenbrough needle (BRKO 71 cm beveled cut 30º/ Saint Jude Medical, MN, USA) is advance through the SLO sheet, and descending the entire transeptal assembly to embed the fossa ovalis.

After gaining left atrial access, a bolus of 10.000 IU of sodic heparin was administered, followed by continuous perfusion as needed to keep the activation clotting time ≥300-350 sec. At the end of procedure, anticoagulation is reversed with protamine and 1grm. of lysine acetylsalicylate given i.v, along with low molecular weight heparine (depending on pts body weight) given subcutaneously, in addition to flecainide (1.5 mgr/Kg) given intravenously in 10 minutes. Continuous intravenous perfusion of sodium heparine adjusted to pt's body weight is started 4 hours later after removing all catheters from the vascular bed. Twenty four hours later, oral anticoagulation with vitamin K antagonist dicumarol is started targeting an international normalized ratio (INR) within the 2.0 to 3.0 range, in addition to antiplatelet inhibition agent ASA, 100 mgr daily dose.

PV/Cartography/ Mapping: Once in the LA chamber, the long 0'32mm guide-wire is advanced into the left superior PV (LSPV) and selective PV angiogram is performed, and in the same manner for the remaining veins, Left Inferior (LIPV), Right Superior (RSPV) and Right Inferior (RIPV).

After removing the entire transeptal assembly, keeping the guide-wire in the LSPV, and steerable 15F over-the wire sheath (Flex Cath, Cryocath, Medtronic,USA) is advanced and positioned in the LA. Then basal electrical cartography of the veins is obtained with a circular duodecapolar mapping catheter with adjustable diameter (Reflexion spiral, Saint Jude Medical, MN, USA) positioned at the PV-LA junction antrum level, starting on LSPV and followed by LIPV, RSPV and RIPV respectively. After 30 minutes of CB applications all PV were mapping again to assess electrical PV-LA isolation (PVI).

Cryo-Balloon: After withdrawing the circular catheter mapping, a 28 or 23 mm double walled CB catheter (Artic Front, Medtronic, USA) is advanced over the wire up to the LA, inflated and positioned in the PV ostium of each vein and gently pushed against the PV-LA antrum to get a perfect occlusion achieved when selective contrast medium injected (50% ratio with 0.9% saline solution) is fully retained in the vein with no evidence of contrast leakage back into the atrium (grade IV) in keeping with the degree of occlusion classification proposed and used by Neumann et al [2] to grade I with poor occlusion leading to an immediate rapid outflow of contrast medium back into the LA. Until CB2 was commercially available (April, 2013) pts were treated with CB1.

Bidirectional LA-PV-LA block (BB) Protocol

Exit Block: By pacing PV from all 20 poles of the circular catheter mapping at high amplitude voltage (20 mA) with consistent 1:1 PV capture and no evidence whatsoever of any atrial response.

Entry Block: By pacing LA from the CS-catheter at three different cycle lengths (600, 500, 400 mS) with consistent 1:1 LA capture and no evidence whatsoever of any PV electrical activity in any of the 20 poles of circular-catheter mapping placed at the LA-PV junction antral level.

AD Protocol: Included bolus i.v administration of increasing doses (12-18-24… mgrs), and pacing PV/LA when A-V nodal conduction block occurred.

Extrapulmonary muscular connections (EMC)/ rule-out protocol: Included pacing distal vein from the circular catheter mapping after complete BB demonstrated at the LA-PV junction antral level and the demonstration of 1:1 PV-LA conduction reassumed.

Radiofrequency protocol: Focal RF applications were used for the elimination of RC gaps when evident after single CB application or either after checking for BB, after AD, or when EMC was demonstrated.

Sixty-second "touch-up" of focal RF was used to eliminate all residual gaps only when evident in less than 2 pairs of the circular catheter mapping. Otherwise, when more, a repeated new CB application was performed.

Phrenic nerve physiology control: Phrenic nerve physiology was monitored in all cases during right sided PV/CB applications, by placing the cuatripolar electrocatheter in SVC and pacing at 2.000 mS cycle length, checking the intensity of diaphragm contractions by intermittent fluoroscopy and tactile feedback by placing the operator's hand on the patient´s abdomen, and immediately stopping freezing when intensity of the diaphragm contraction weakens or is suddenly stopped.

Follow-up Protocol: Before hospital discharge, TTE was performed in all cases to rule out pericardial effusion, in conjunction with chest-X-ray taken in a deep breath, upright position, to confirm normal phrenic nerve physiology.

The immediate follow-up included holter monitoring at 7, 15,30,45,60 and 90 days respectively, and thorax CT-Scan at 30 and 90 days. All pts received AAD, mostly Class IC+BtB and oral anticoagulation with vitamin K antagonist dicumarol is started 1 day

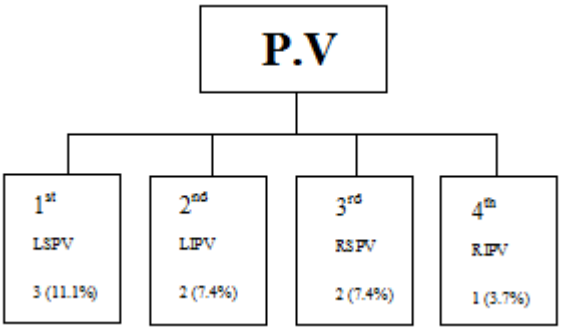

Figure 1: AF reversion/during CB application 8/27 AF pts (29.6 %)

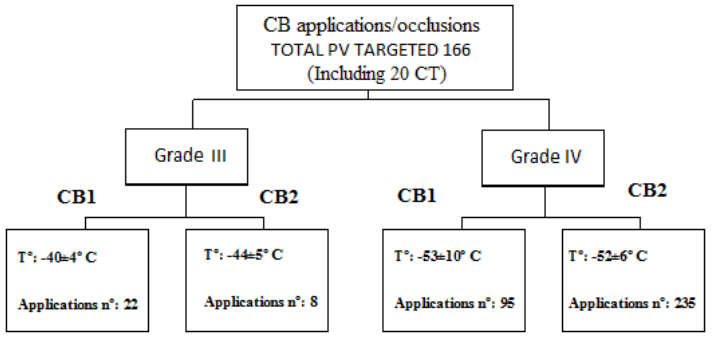

Figure 2: CB1-CB2 applications: degree of occlusions and mean nadir temperature reached

after PVI, targeting an INR within the 2.0 -3.0 range for at least three months.

After a 3 month-blanking period on medication, all AAD were discontinued, and follow-up started to count. All pts were monitored by continuous daily transtelephonic information in case of symptoms, monthly ECG holter monitoring having otherwise being routinely done over a mean follow-up of 2.8 years.

Results

Three months after CV, 17 pts (38.6%) remained in SR. The other 27 pts experienced relapses into AF (RAF). The entire group of 44 pts, were included for CB ablation procedure. At the procedure, none of the 27 RAF pts were CV before CB ablation. SR was restored in 8 pts (18.2%) during CB applications at a different PV and numbers (Figure 1).

In the other 19 of 27 RAF pts, CV was performed, and all converted in SR, allowing checking for BB.

One hundred and sixty six PV including 10 left sided common trunks, (CT) were treated with CB1, 58 PV, (35%) and 108 PV with CB2 (65%) and PVI with complete BB was demonstrated in 158 PV (95.2%).

Three of the others 8 PV, needed to be isolated with RF applications giving that the CB-PV antral anatomical wedging was difficult to approach, not allowing to achieve a complete degree IV CB-PV occlusion.

The other 5 PV showed acute reconnection due to RC gap in LSPV in the inferior segment and in the other 3PV, an extrapulmonary muscular connection (EMC) could be demonstrated. All RC and EMC were eliminated by focal RF applications. None RC were unmasked after AD.

Cryoballoon

CB1 was used to treat the first 15 pts, until CB2 become commercially available. The number of CB/PV applications, degree of occlusions and temperature reached are provided on Figure 2.

Follow-Up

Arrhythmia Recurrence And PV-LA Reconduction

After a three month blanking period on medication, AAD were discontinued and the follow-up started to count. Only 40 pts were included in the follow-up, as the other 4 were still in the blanking period.

In a mean follow-up of 30±39 months (7-84), 16 pts (40%) had recurrence of stable arrhythmia.

Among them, 7 had structural heart disease, meaning 87.5% of the total pts with structural heart disease.

In all recurrence pts, oral AAD was again reinitiated, restoring SR in 7 pts, who allowed for Redo. The other 9 recurrence pts including 7 with structural heart disease refuse Redo and continuing in AF.

Twenty six PV (including 2CT) from the 7 recurrence pts in whom SR was restored after AAD was added, were study again in Redo. In the 2 recurrence pts in whom SR was restored after AAD, all 7 PV (including 1CT) were completely electrically disconnected from the LA.

In the other 5 recurrence pts new CB-PVI was achieved with CB1 in 1pt and with CB2 in the other 4pts.

No RC was unmasked after AD.

In all pts who refused Redo and remained in AF after a single CB procedure, the type of balloon used was CB1.

In summary, in this study population in a mean follow-up of 30±39 months, 24 pts (60%) remain in SR after a single procedure without AAD. After Redo, 29 pts (72.5%) remain in SR, and when medication is added, 31 pts (77.5%) stay in SR.

Side Effects And Complications

Two pts (4.5%) had aphonia. One pt (2.2%) presented groin haematoma due to inadverted arterial puncture resulting in pseudoaneurysm requiring surgical repair. Transient PNP occurred in 4 pts (9%) during CB-RSPV application, recovering full PN function in the course of the procedure. Type of CB used along with mean nadir temperature reached when PNP occurred it's provided on Table 3.

Discussion

AF is the most disturbing and common clinical arrhythmia encountered in clinical practice with a prevalence of around 1% in developed countries, increasing the risk of heart failure and being responsible for nearly 15% of all strokes in the USA. [15]

Although it was unclear why some pts stay in PAF for decades, whereas others with the same characteristics, progress to persistent AF within a few months, the most widely-accepted theory, is based on remodeling concept, yet no fully understood to date.

Atrial stretch, shifts in autonomic tone, or depletion of high-energy phosphates it has been demonstrated do not significantly contribute to atrial electrical remodeling,[16, 17] wich is mediated by rate-induced intracellular calcium overload. The high rate of electrical activation itself provides the stimulus for the AF-induced changes in shortening the atrial effective refractory period (AERP).[18] Electrophysiological changes that contribute to sustain the arrhythmia in a self-perpetuating process supporting the concept of "AF begets AF".[19] Among many others different risk factors to build up the underlying substrate, such as age, hypertension, or structural heart disease, the common factor of tissue substrate is fibrosis wich can be an important

Table 3: Type of CB used along with mean nadir temperature reached when PNP occurred it's provided

	Transient Phrenic Nerve Palsy				
	T° C	Seconds	CB (mm)	CB Generation	
1	-62	120	28	First	Mean T ≥60 (75%)
2	-64	123	23	Second	
3	-68	103	23	Second	
4	-54	194	23	Second	CB2: 75%

factor in the maintenance and progression of AF.[20]

Many questions however still as yet unanswered on the order of explaining the multifactorial aspects involved in the atrial remodeling process and their relationship to the amount of fibrotic tissue related to the arrhythmia "phenotype" (paroxysmal, persistent and long-standing persistent).

Electroanatomic mapping studies,[21, 22] intraoperative obtained specimen analysis,[20] post-mortem autopsy findings [23] and late gadolinium delayed enhancement MRI studies [24] have demonstrated a higher mean value of fibrosis detected in pts with persistent AF vs PAF but the variability in the extend of fibrosis is always very high with part of pts with PAF having massive fibrosis an part of persistent AF pts showing mild fibrosis supporting the concept named by Kottkamp [25,26] of fibrotic atrial cardiomyopathy (FACM). According with Kottkamp editorial commentary,[27] the structural atrial disease underlying FACM typically does not present with enlarged left atria and is typically undiagnosed before the clinical advent of the first arrhythmia as AF, but a potential sub-diagnoses or disease manifestations are atrial tachycardia, sinus node and or AV node disfunction wich can be severe.

Although some studies [28] have demonstrated reverse remodeling of sinus node function after catheter ablation of AF, suggesting that prolonged sinus pauses after PAF may result from depression of sinus node function that can be eliminated by curative ablation of AF. The association of AF and sinus node disfunction, it has being known for a longtime as configuring the sinoatrial disease responsible for brady-tachycardia syndrome as well the evidence of diffuse atrial remodeling and fibrosis in sinus node disease.[29-30]

Animal experiments have shown [16-19] that AF induces shortening of the AERP resulting in an increased vulnerability for reinduction of AF, prolongs intra-atrial conduction time, shortens atrial refractoriness and perpetuates AF,[16, 17] changes that reverse gradually after termination of AF. In humans, this electrical remodeling was completely reversible within a week after CV, and presumably related to intracellular calcium overload.[31] Tachycardia-induced change of AERP in humans has been demonstrated by others [32] and the rate-dependency and effects of antiarrhythmic drugs. Yu et al [33] in this study including 70 pts with PAF without structural heart disease and EP performed after pacing-induced AF analyzing the changes on AERP pre and post AAD (class IC, BtB, amiodarone and verapamil) showed the AERP shortening was attenuated after verapamil infusion, but was unchanged after infusion of the other AAD. Furthermore, all these AAD could decrease the incidence and duration of secondary AF. The AERP shortening induced by tachycardia was a rate-dependent response, and verapamil, but no other AAD, could markedly attenuate this effect.

Reversal of atrial electrical remodeling following CV in pts with long-standing (> 6 months duration) (mean 62±36 months) range 16-132 months was demonstrated also by Yu et al [33] in 19 pts showing the AERP was gradually prolonged and its rate adaptation response improved after restoration of SR, concluding than restoration and maintenance of SR could reverse these electrophysiological changes. Additionally, the possibility of conversion and maintenance of SR was decreased as the duration of AF increases.[34] Clinical observations have demonstrated that the recurrence of AF was frequently clustered in the first month after CV.[35]

All of these data support the view that AF causes electrical remodeling wich facilitates the perpetuation of AF itself. From the clinical point of view, the early recurrence of AF after successful CV may be due to the adverse effects of electrical remodeling, and calcium-blocker might provide a beneficial effect in this situation. Conversion of AF and maintenance of SR could abolish the adverse effect of electrical remodeling. Wether the atrial remodeling process is reversible after the ablation of AF most likely depends on the degree of remodeling at the time of successful ablation.[27]

According to all the statements aforementioned, we sought to select among pts with LSPAF: Firstly, does who theoretically involved the least degree of electrical atrial remodeling able to sustain SR after CV. Secondly, among these pts selected, to try to electrically stabilized the atrium with the highest degree of drug tolerance to sustained SR, including verapamil, in an attempt to lengthen the AERP to reverse the acute-rate dependent electrophysiological changes responsible for early AF recurrence within the first week after CV.[16-19, 30-33] In fact, a pacemaker needed to be implanted in 5 pts due to impaired sinus node and A-V nodal function demonstrated after CV, before giving AAD.

After CV/EP AAD testing procedure, the entire groups of pts were discharged from hospital on AAD, including verapamil, after which a three month waiting period commenced during which the pts returned to their normal life.

We did so, on the basis of the aforementioned concepts, that conversion of AF and maintenance of SR could minimize the adverse effects of electrical remodeling, and this probable reverse atrial remodeling most likely depends on the degree of remodeling at the time of successful ablation.[27]

During this three month waiting prior to CB ablation procedure, 17 pts (38.6%) remained in SR while the rest 27 relapsed into AF, performing the CB ablation procedure being in AF.

We have not found any significant difference between the atrial size and the number of years suffering from arrhythmia in any of the different pt's group, although the mean years duration of stable arrhythmia and left atrial size was slightly higher (6±5 years) in pts who stay in AF comparing to pts whom SR was restored.

Only one pt with structural heart disease (ischemic) sustained SR on follow-up, having the lowest duration time of stable arrhythmia (1 year).

Type of CB Used/Related Findings

All PV reconduction after CB (5pts) became evident only after CB1 applications. In all 8 pts in whom AF was converted to SR, CB2 was applied in 7 (87.5%). No RC was shown after CB2 applications. All RC showed in Redo pts, the first procedure having being performed with CB1. However, CB2 showed the highest incidence rate of PNP (75% CB2 vs 25% CB1). Both CB1+CB2 totaling 9% of the incidence PNP rate in the entire group, consistent with the PNP rate found by others.[36]

On the contrary, the lower vascular access incidence complication rate (2.2%), compared to others (10%) [11] might be related to the fact

of all procedures having being performed on same operator (JMP).

Aphonia of unexplained etiology was completely spontaneously resolved within less than 72 hours.

No major complications occurred. No PV stenosis. Interestingly, in comparison to previous studies [37] and our own experience in 128 pts treated mostly with CB1, RC was unmusked by AD when using CB1 in 4.6% of PV treated,[37] and in 4% of PV when CB2 was applied.[38] By the contrary, in this study none RC were unmasked by AD when CB2 was used, most probably related with the larger and deeper cryolesions created. According with these findings, we will abandon the use of AD approach due to as the possibility of PV dormant tissue after CB2 applications it will likely being none.

Statistical Analysis

Continuous variables are expressed as mean ± SD.

Categorical variables are expressed as percentages.

Duration of Procedure

From the transeptal approach to withdrawal of LA catheters: 173±47 minutes (95-26)

Mean fluoroscopy time: 43±14 minutes (24-48).

Study Limitations

This study has several limitations. First: this is a non-randomized, single center study. Second: this study includes a small sample size. Third: the previous electrical selection of patients likely to limit the outcome that can be extended to the entire LSPAF population group. And, fourth: as a significant number of pts from this group, felt no symptoms, along with the wide interval range (30 days) in between holter ECG recording, the final outcome results might be overestimated.

Conclusions

As a result of this study, we might to conclude: 1. CB technique is a safe and useful tool for treating pts with LSPAF, with a 60% success rate in terms of maintaining SR without medication in a mean follow-up of 30±39 months after a single procedure, increasing the success rate up to 72.5% after a second procedure, and to 77.5% when ADD are added. 2. In the majority of pts maintaining SR (77.5%) (including Redo+AAD), the CB/PVI was achieved with CB2 in 87% of the cases. 3. In all pts who refused Redo (22.5%) having continued in AF, CB1 was used at first procedure. 4. CB2 is better than CB1 to restore and sustain SR after PVI in pts with LSPAF, where bigger antral lesion is needed. However, this entails a higher risk of extracardiac structures damage, mostly PNP (9%). 5. Patients without structural heart disease along with those in whom SR was restored during CB applications, showed the best results. 6. Finally, the main limitation of this study might be due to the small sample size in previously selected pts. Further larger randomized studies are needed to confirm our findings.

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Combined Diagnostic Yield of Tilt Table Test And Implantable Loop Recorder to Identify Patients Affected by Severe Clinical Presentation of Neurally-Mediated Reflex Syncope who Could Respond to Cardiac Pacing

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Abstract

In this study we wanted to verify the diagnostic value of tilt table test (TTT) to predict the efficacy of cardiac pacing (PM) for preventing recurrences of neurally mediated reflex syncope (NMS) in patients with cardioinhibitory activity (CI) documented by implantable loop recorder (ILR).

Among patients selected by ILR in the context of severe clinical presentation of NMS, we analysed those who underwent PM implantation. In this observational and retrospective study we wanted to verify the results of TTT in the groups of treated patients with and without recurrences.

We analysed 24 patients treated using a PM (10 male and 14 female, mean age 70 years). During an average follow-up period of 35 months the recurrence of syncope occurred in 7 patients (29%). 17 patients (71%) had not recurrences. TTT was negative in 15 patients out of 17 without recurrences (88%). Among the 7 patients with recurrences TTT was positive in 4 patients (57%).

In conclusion, in this selected group of patients, a positive response to TTT is more likely correlated with a higher frequency of recurrences of syncope, while a negative response seems to predict the success of the pacing therapy. Consequently, PM could be insufficient to prevent the recurrences in the group of patients with positive TTT.

Introduction

The efficacy of cardiac pacing for prevention of syncopal recurrences in patients with neurally mediated syncope was considerable controversial. It was questioned approximately 15 years ago: two important randomized, multicenter, open label studies (SYDIT[1] and VASIS[2]) showed results in favour of pacing; but in the same period other two randomized, multicenter, double-blind studies (VPS-2,[3] SYNPACE[4]) failed to demonstrate the superiority of cardiac pacing to over placebo.

ISSUE-2 Trial[5] changed the medical history in the context of severe clinical presentation of reflex syncope. ISSUE-2 Trial showed the capacity of ILR to guide the specific therapy and confirmed that there is not always a clear correlation between the results of TTT and the mechanism documented by ILR at the time of the syncope.

Three years ago, the ISSUE-3 Trial[6] (a multicenter, double blind Trial) showed that pacing is effective in reducing recurrence of syncope in patients >40 years with severe asystolic NMS documented by ILR. There was 32% absolute risk reduction and 57% relative risk reduction, with evidence of a clear, statistical difference between the two groups: Pm on and Pm off arm.

At the moment we can affirm that, according to the ESC guide-lines,[7] the pacemaker plays a role in the group of patients with frequent and invalidating recurrences of reflex syncope, selected by Implantable Loop Recorder after evidence of a documented cardioinhibitory activity, in class 2a.

Despite the efficacy of PM the ISSUE-3 Trial showed that in patients selected according to the ESC guide-lines, there is a good number of patients (25%) with recurrences during the follow-up period of 2 years.

Current knowledge about efficacy of pacing in reflex syncope is still characterized by needing further study; first of all whether in selecting patients Tilt Test-specific orthostatic stress is sufficient in identifying ideal candidates to cardiac pacing. This probably explains why the ESC Task Force for cardiac pacing is considering further research extremely important and very likely to impact future

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None.

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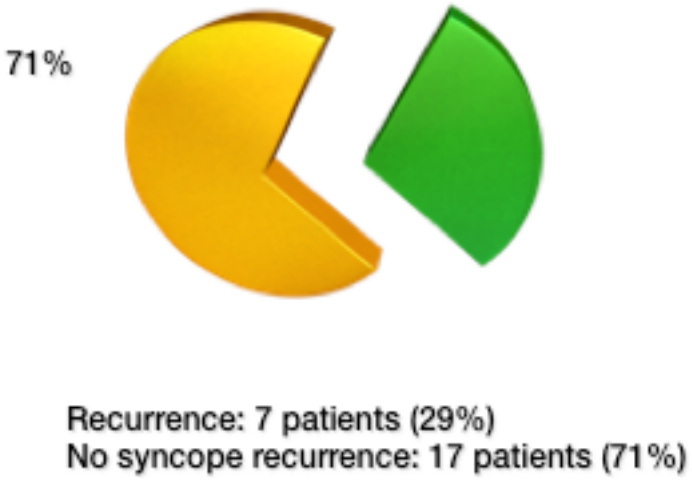

Figure 1: Recurrences in patients treated with PM

recommendations.

Aim of The Study

Among our patients who underwent a PM implantation, after a careful clinical evaluation and a diagnostic iter guided by ILR, we wanted to verify as to whether Tilt Table Test (performed in all patients during the initial evaluation) could help us to identify better responder PM patients.

Methods

The selection of patients was made according to the ISSUE-3 criteria: certain or suspected reflex syncope (except of "Carotid Sinus Syndrom" because this is an already axcepted indication for cardiac pacing), age more than 40 years, all patients had to have a severe clinical presentation to warrant a specific therapy and justify an invasive treatement like a PM implantation. The severity of the clinical presentation was based on the definition of high frequency or risk provided by guide lines: invalidated quality of life, unpredictable syncope, syncope exposing patients to risk of trauma, occurence of syncope during "high risk activity".

The exclusion of patients involved cardiac abnormalities which suggested cardiac syncope, symptomatic orthostatic hypotension, non-syncopal loss of consciousness.

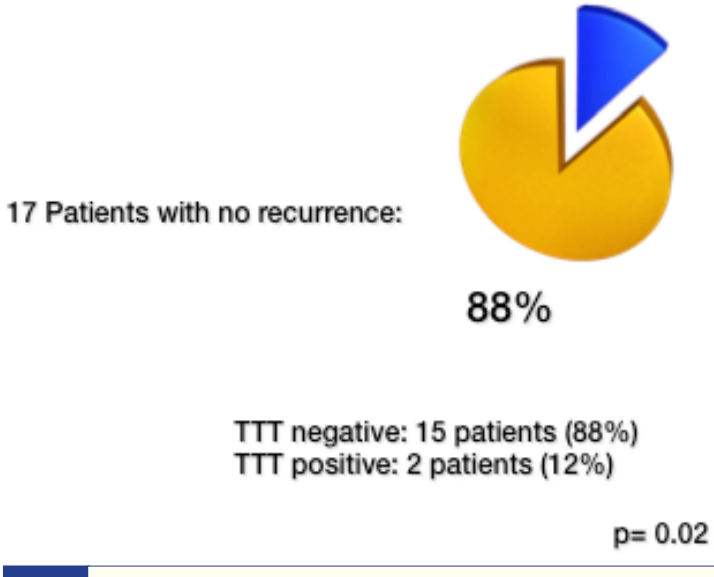

Figure 2: TTT results in patients with recurrences

During the initial evaluation in all patient a TTT was performed according to the Italian protocol.[8] It consisted in a 60-70 grades passive tilt for a duration of 20 minutes or until the occurrence of syncope; if the passive tilt phase did not induce syncope, 0,4 mg oral nitroglycerine spray was administered to the patients while the table was maintained in the same position; the test was continued for 15 minutes after pharmacological challenge. TTT positive responses were classified according to the New Vasis classification[9] in asystolic or vasis 2B form (those with an asystole > 3 s) or mixed or vasodepressor forms (all the other forms without asystole).

After a careful initial evaluation and execution of TTT, all these patients followed a diagnostic iter guided by ILR and were followed till the first documented syncopal recurrence or an occurrence of a diagnostic arrhythmic event. Events were classified according to the ISSUE classification[10] as: type 1 (asystole < 3 s), type 2 (bradycardia), type 3 (slight o no rhythm variations) and type 4 (tachycardia).

According to the ISSUE-3 Trial we implanted a dual chamber pacemaker with a specific algorithm for reflex syncope, the rate drop response (RDR), in patients with a documented asystole > 3 seconds and concomitant syncope or asystole > 6 seconds irrespective of the recurrence of syncope.

In this observational and retrospective study we wanted to observe the results of TTT in the two groups of treated patients: the group with recurrences and the one without recurrences.

Results

We treated 24 patients (10 male and 14 female, age of 70+12 years) implanting a dual chamber PM with RDR algorithm in the period between 2008 and 2012.

All patients had not a significant structural heart disease, had a presentation of likely reflex syncope, with a burden of 4+2 episodes in the index year. 10 patients had no previous medical treatment. Because of hypertension 6 patients used 1 treatment (Ca-antagonist), 8 patients received two treatments (5 patients Ca-antagonist and

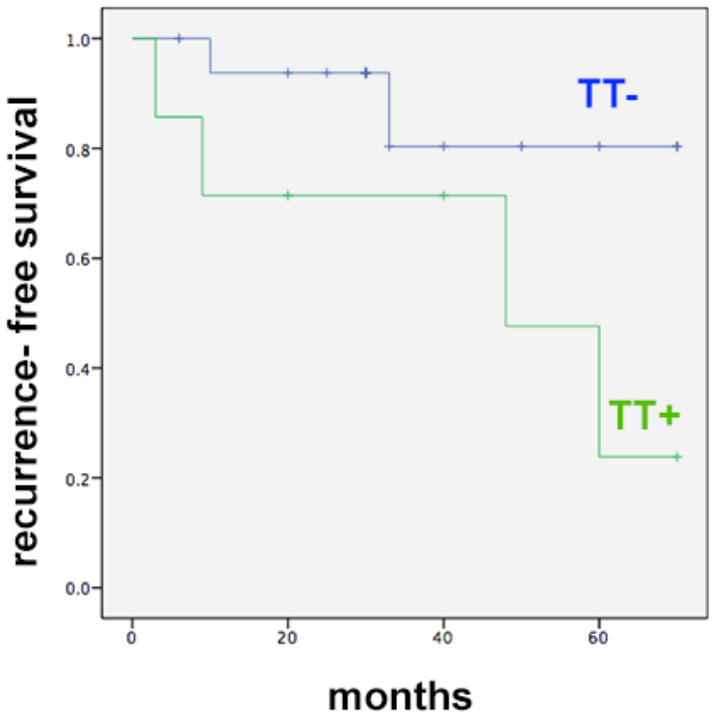

Figure 3: Recurrence-free survival of patients treated with PM and negative TTT

Ace-Inhibitor, 3 patients furosemide and Ace-Inhibitor).

During an average follow-up period of 35 months the recurrence of syncope occurred in 7 patients (29%). 17 patients (71%) had not recurrences during the follow-up (Figure 1).

The mean time to first syncope recurrence was 7 months ±7 (95% CI).

TTT was positive in 4 patients out of seven with recurrences (in two cases documented CI): 57%.

Among the 17 patients without recurrences TTT was positive only in 2 patients (12%), 15 patients had a negative TTT (88%), p= 0.02 (Figure 2).

Discussion

Considering that we are talking about well selected patients through a careful clinical evaluation, without structural heart disease and no rhythm disturbances, the common diagnostic pathway is overthrown by a small group of patients which presents with likely atypical reflex syncope.

The ours is only a small experience, which is confirmed by an important subanalysis of the ISSUE-3 Trial.[11] This substudy demonstrated that the benefit of pacemaker therapy in patients with presumed neurally-mediated syncope and documented asystole is greater when tilt test is negative. 52 Patients (26 TTT+, 26 TTT-) with asystolic ILR were treated with a PM: the recurrence of syncope occurred in 8 (31%) with TT+ and 1 (4%) with TT- patients. The unexpected and important conclusions of this subanalysis were that pacing is effective in NMS with asystole by ILR and negative TTT; there is no evidence of efficacy in positive TTT; although a positive asystolic TTT response predicts a clinical asystolic NMS, the pacing benefit is similar to that of positive non-aystolic TTT response.

Considering all that we are talking about results which could change the previous knowledge related to the historical role of TTT; in the past we implanted a PM after evidence of a significant asystolic event during the TTT, at the moment the discussion concerns the fact that just patients with positive TTT (irrespective of cardioinhibitory or vasodepressor form) are those who respond less to a PM therapy.

In perspective the somewhat surprising results of these evidences can be interpreted differently. Results are of help in selecting the best candidates to cardiac pacing. From one hand, cardiac pacing is very effective in NMS patients who have the documentation of an asystolic event and a negative TTT. In the ISSUE-3 substudy the observed 5% recurrence rate with pacing at 21 months is similar to that observed in the DANPACE Trial, in patients paced for cardiac intrinsic bradycardia.[12] thus, pacemaker therapy could be offered to these patients with the same confidence than that used for indications in patients with sick sinus syndrome or AV block. These patients could be reassured that, after pacemaker implantation, they will likely be free of recurrence of syncope. On the other hand, caution should be exercised before offering such therapy to patients with a positive TTT even if they have had an asystolic response during TTT and the documentation of an asystole during spontaneous event by ILR. Even if some benefit could be still possible in terms of reduced burden of syncope, the patients should be informed that they will likely have some recurrence of syncope despite cardiac pacing. This is the reason why this group of patients could take advantage from a supplementary therapy like the "isometric counterpressure manouvres" (ICM), in a sort of hybrid therapy: PM plus ICM.[13]

Recently the SUP-2 Study[14,15] has been completed; it is a multicenter, prospective, observational study which wanted to verify the utility of a standardized algorithm for cardiac pacing in older patients affected by severe unpredictable reflex syncope. The Syncope Unit Project 2 (SUP 2) showed the benefit of cardiac pacing at 3 years in patients selected according to the ESC-guide lines: carotid sinus massage (CSM) , followed by Tilting Table Test (TTT) if CSM was negative, followed by implantation of an Implantable Loop Recorder (ILR), if TTT was negative; those who had an asystolic response to one of these tests received a dual-chamber pacemaker. The 3-years recurrence of syncope was 20% and was significantly lower than the group of patients who did not receive the pacemaker and were observed by ILR. The 3-year recurrence was not different among the subgroups (CSM, TTT and ILR) used to select patients to undergo pacemaker implantation, whereas it was lower in patients with negative TTT than patients with positive TTT.

Considering the recent scientific literature concerning the use of a pacemaker as first line treatment in the context of neurally mediated syncope we can affirm that:

1. the most important point is the accuracy in the selection of patients after a careful initial evaluation
2. ISSUE-3 (double blind study) demonstrated the efficacy of pacemaker in this group of patients selected by ILR, but first of all in patients who had a negative TTT (subanalysis)
3. SUP-2 (observational study) showed that TTT is also efficient to identify patients who could respond to the cardiac pacing but, once more, PM seems to be mostly effective in patients with negative TTT
4. in these studies we have used in most cases a dual chamber pacemaker with a specific algorithm, the rate drop response (RDR). It is necessary to remember that we do not have studies of comparison between a pacemaker with and without the RDR, as there are no studies of comparison involving devices with different algorithms.

At the moment there are two points to investigate further: the capacity of TTT to identify patients to undergo a pacemaker and the opportunity to verify other pacing algorithms in the context of a selected group of patients affected by NMS. Further important information will be given from the BIOsync Trial: an international, randomized, double-blind parallel trial, which aims to verify the benefit of dual-chamber pacing with closed loop stimulation (CLS) in tilt-induced (tilt positive) cardioinhibitory reflex syncope.[16,17,18,19]

Conclusions

These results show that a positive TTT seems to be more likely correlated with a higher frequency of recurrences of syncope in patients treated using a PM, while a negative response seems to predict the success of the pacing therapy.

The rationale could be that TTT is able to highlight the importance of a concomitant hypotensive reflex response or that the orthostatic stress (for example during prolonged standing) as trigger of reflex syncope (investigated by TTT) produces an important reduction in the central venous volume, as consequence the compensative chronotropic pacing in an empty heart is not able to prevent the syncope.

Anyhow PM could be insufficient in a group of patients with positive TT response.

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Cardiac Rhythm Device Threshold Testing Via Pulse Oxymetry

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Abstract

Threshold testing of cardiac rhythm devices is essential to monitoring the proper functioning of such devices (1). However, the currently method of applying multiple ECG leads to the patient is burdensome and time consuming (2). We are presenting a completely new way to perform cardiac rhythm device threshold testing using pulse oximetry.

Twenty patients, with varying cardiac rhythm devices and pacing modes, were enrolled and had their atrial and ventricular thresholds tested. A comparison was made between simultaneous threshold determinations via the standard EGM based method and the new pulse oximetry based method. 75% of the ventricular threshold tested and 58% of the atrial thresholds tested were the same with the two testing methods. The remainder of the tests (25% of ventricular threshold and 42% of the atrial threshold tests) varied by +0.25 V.

This study shows that pulse oximetry based testing is an accurate, reliable, and easy way to perform cardiac rhythm device threshold testing and may complement traditional methods to perform such tests in the future.

Introduction

Monitoring of cardiac rhythm devices is key to preventing, identifying and solving problems with the devices.[1] A standard interrogation includes sensitivity, impedance, and threshold testing. While sensitivity and impedance testing are fairly quick and easy to do, threshold testing is fairly labor intensive and uncomfortable to the patient.[2]

Currently threshold testing procedures involve placing multiple ECG leads on the patient and using the interrogator to slowly lower the pacing Voltage outputs while monitoring when devices loses capture. This usually involves undressing the patient and applying ECG leads and electrodes to the patient. This is further complicated if the patient has applied lotion to the skin, or has a lot of hair, making the ECG signal much less accurate. New algorithms have allowed for simpler threshold testing, but the new interrogator based tests still require accurate interpretation of ECG and/or EGM interpretation.

We have discovered a new way of performing threshold testing for cardiac rhythm devices, which is based on pulse oximetry. This new process uses the principle of plethysmography, which is a process of determining changes in volume based on the physical relationship between pressure and volume. A photoplethysmogram, such as a pulse oximeter, is an optically obtained plethysmogram, and relies on an optical source to detect changes in volume of body fluids as a result of pressure waves.[3,4] Pulse oximeters emit light and are able to measure the change in light absorbance and reflection, and correlate it to the change in volume of blood within a pulse pressure wave.[3,4] This then creates a fairly accurate and reliable graph of the increase and decrease of blood volume in a specific body part, which is then indicative of the actual cardiac pulse in the body.

The new threshold testing protocol proposed here relies on pulse oximetry. A standard pulse oximeter, which is able to procedure a plethysmographic curve on a display, is placed on the digit of a patient. Once a clear plethysmographic curve is produced, standard technique of decreasing output voltage of the cardiac rhythm device is used to determine when the capture is lost. At the point of loss of capture, a cardiac pulse would not be produced, and a loss of the pulse pressure would result in a reduction or loss of the change in blood volume in the measured digit. This curve would then resume its normal volume change recording once a pulse is reestablished, which would be a result of either pacing at higher output voltage or the resumption of patient's natural heart beat.

Methods

Twenty consecutive patients with cardiac rhythm devices (biventricular devices were excluded) were enrolled in the study from a busy cardiac rhythm device clinic in Brooklyn, NY. Standard

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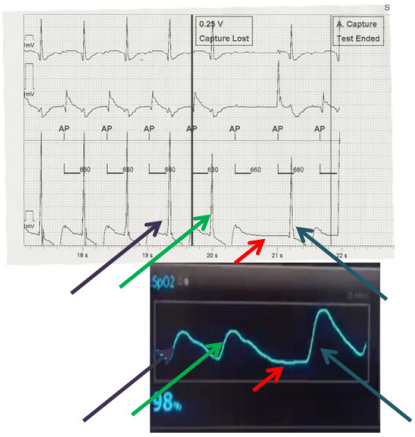

Figure 1: Simultaneous EGM (top) and pulse oximetry (bottom) displays during atrial threshold testing in AAI format. Purple and green arrows represent captured beats during threshold testing, red arrows show the missed capture beat, and the blue arrows shows the beat after resumption of normal pacing

informed consent protocols were followed with all of the enrolled patients.

A standard deluxe handheld pulse oximeter, Model CCI-300M, was used for the study. The pulse oximeter was placed on the index finger of all patients (patients would chose which arm they preferred). One patient was on hemodialysis, and had a AV graft on the right side, forcing us to use the left arm for the study analysis.

Once a good plethysmographic curve was established, the threshold testing would begin. Two board certified physicians were involved with the testing of each patient. One of the physicians was placed at the interrogator and was managing the threshold testing protocol using a standard algorithm (start at 2.0 V, and decrease the voltage by 0.25 V on every third beat). All threshold testing was done at 0.4 msec. This physician would state out loud every time the output was lowered and to what voltage. This physician would also record on a piece of paper (without announcing the value) the threshold result based on the ECG and EGM monitoring of the interrogator machine. The second physician was placed near the patient and had a clear view of the pulse oximeter plethysmographic output curve. The second physician did not have the ability to see the interrogator screen or any documentation by the first physician. The job of the second physician was to monitor the plethymosgraphic curve, and listen to the voltage readings by the first physician. Once the second physician saw that the pacing threshold was reached, the physician would record the threshold value for comparison.

For ventricular threshold testing, all tests were done in VVI mode at a rate of 90 bpm. For atrial threshold testing, tests were done either in AAI mode (if possible based on the state of patient's conduction system) or DDD mode at 90 bpm. If the patient's native heart rate was noted to be above 85 bpm, the testing was performed at 10 bpm higher than the patient's native heart rate.

If the loss of capture (atrial or ventricular) occurred at >1.5 V, the threshold testing would be repeated starting at 4V. If the loss of capture occurred at >3.5 V, that patient was excluded from this study.

For every patient, the threshold results of the two physicians were analyzed and compared. For clinical purposes, the result obtained by the ECG/EGM method was used for cardiac rhythm device management and adjustment.

Results

All together, twenty patients were selected consecutively for this study. Out of the twenty selected, all twenty agreed to participate in the study.

Out of the twenty patients, five were set in VVI mode and pacemaker dependent, three were set in VVI mode and were not pacemaker dependent, five were set in DDD mode and were pacemaker dependent (either atrial, ventricular, or both) and seven were set in DDD mode and were not pacemaker dependent. No patient had a resting heart rate above 85 bpm. There were no patients who had generators at ERI or EOL.

All threshold tests were performed only once. There were twenty ventricular threshold tests performed and twelve atrial threshold tests performed.

Figure 1 shows the EGM (above) and pulse oximetry (below) based displays while conducting atrial threshold testing. This was recorded simultaneously in a patient who was atrial pacing dependent, but did not have AV block. As such, atrial threshold testing was performed in AAI mode. Arrows of the same color represent the corresponding beats in the two sets of displays. Purple arrows represent the beat prior to the threshold setting beat. The green arrows represent the beat that is the threshold beat. The red arrows represent a failure to capture beat, and the blue arrows represent the resumption of normal atrial pacing in this patient. Nicely illustrated here in the pulse oximetry curve is the concept that a beat after a pause produces a stronger contraction than prior beats (the blue arrow beat has a much higher amplitude than purple and green arrow beats).

Out of the twelve atrial threshold tests performed, seven (58%) had the same threshold results between the two physicians involved in the tests. The other 42% had differences of no more than 0.25 V.

Figure 2 shows the EGM and pulse oximetry based displays in ventricular threshold testing. This was conducted in a patient who was not pacemaker dependent, in VVI format. These were recorded simultaneously. Yellow and green arrow beats are prior to the missed capture beats, with the green arrow representing the threshold setting beat. The red arrow represents the missed capture beat, and the blue arrow representing the patient's native beat after threshold has been reached. As in Figure 1, the amplitude of the post pause beat is higher than the pre-pause beats. However, in this case the post pause beat is a patient's native beat, and not a paced beat.

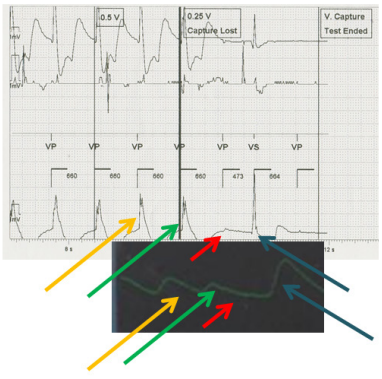

Figure 1: Simultaneous EGM (top) and pulse oximetry (bottom) displays during ventricular threshold testing in VVI format. Yellow and green arrows represent captured beats during threshold testing, red arrows show the missed capture beat, and the blue arrows shows the resumption of native beating

Out of the twenty ventricular threshold tests, fifteen (75%) had the same threshold as recorded by the two physicians involved in the tests. The other 25% of the tests had a difference of 0.25 V between the two recorded thresholds. There were no difference above 0.25 V in any of the performed ventricular threshold tests.

Figure 3 shows the pulse oximetry recording in a single patient who is not pacemaker dependent. The patient's native heart rate was 70 bpm. On the left side of the figure (green arrow) there is a beat recorded while the patient is being paced at VVI 75 bpm (pacing is doen at 2 V @0.4 msec, which is higher than the patient's ventricular threshold of 0.75 V @0.4 msec). On the right side of the figure (red arrow) there is a patient's native beat recorded. The amplitude of the patient's native beat is much higher than the patient's ventricular paced beat. Although this amplitude difference can be caused by the higher pulse during pacing, we set the difference in heart rate as small as possible between native and paced beats, and believe that it should not account for such a large difference in amplitude between the two beats.

Discussion

The use of pulse oximetry is a reliable and accurate method to determine the atrial and ventricular thresholds of cardiac rhythm devices. In this study, we have shown as proof of concept the successful determination of atrial and ventricular thresholds using pulxe oximetry.

The use of EGM/ECG based algorithms to determine thresholds is complicated, labor intensive, and patient effort intensive, which is not ideal for routine cardiac rhythm device maintenance testing. Pulse oximetry is much less labor intensive and involves almost no discomfort to the patient. The patient just notices that the pulse oximeter has been applied to his/her finger during the test. There is no need for undressing, application of ecg leads, or shaving of hair.

We did observe, as expected, a higher incongruence rate with atrial threshold testing than ventricular threshold testing: 42% vs. 25% error rate respectively. We believe this to be acceptable as there was no deviation between the methods of testing by more than 0.25V in any of the cases, which is unlikely to be clinically significant. Atrial threshold testing was expected to be more difficult and less congruent since EGM and pulse oximetry based threshold testing rely heavily on the display of the effects of ventricular contraction, and it becomes necessary to account for differences in atrio-ventricular conduction. Furthermore, atrial threshold testing in patients who are pacemaker dependent may not be feasible with our method, or be technically very challenging, since it would be based on detection of subtle differences in the waveform shape, related to loss of atrial contribution to the cardiac output.

Our exploratory study suggests that pulse oximetry may be a safe, accurate, and reliable guide for the performance of threshold testing in cardiac rhythm devices. Further research needs to be performed to clarify the benefits and pitfalls of this new technique. However, with its promise of much less patient discomfort and much less labor intensive threshold testing, pulse oximetry may become a useful, alternative method of conducting cardiac rhythm device threshold testing.

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Hyperacute And Chronic Changes In Cerebral Magnetic Resonance Images After Pvac, nmarq And Epicardial Thoracoscopic Surgical Ablation For Paroxysmal Atrial Fibrillation

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Abstract

Threshold testing of cardiac rhythm devices is essential to monitoring the proper functioning of such devices (1). However, the currently method of applying multiple ECG leads to the patient is burdensome and time consuming (2). We are presenting a completely new way to perform cardiac rhythm device threshold testing using pulse oximetry.

Twenty patients, with varying cardiac rhythm devices and pacing modes, were enrolled and had their atrial and ventricular thresholds tested. A comparison was made between simultaneous threshold determinations via the standard EGM based method and the new pulse oximetry based method. 75% of the ventricular threshold tested and 58% of the atrial thresholds tested were the same with the two testing methods. The remainder of the tests (25% of ventricular threshold and 42% of the atrial threshold tests) varied by +0.25 V.

This study shows that pulse oximetry based testing is an accurate, reliable, and easy way to perform cardiac rhythm device threshold testing and may complement traditional methods to perform such tests in the future.

Introduction

Patients with atrial fibrillation (AF) are at increased risk of symptomatic cerebral ischaemic events.[1] Cerebral magnetic resonance imaging (MRI), especially using Diffusion Weighted Imaging (DWI), is the current gold standard for detection of acute cerebral ischaemia[2] in clinical practice. Asymptomatic cerebral events (ACE), defined as changes on DW-MRI without detectable neurological symptoms, have been described in the setting of invasive neurovascular[3, 4] and cardiac[5] procedures. However, since the first report of ACEs in the setting of AF ablation.[6] a number of studies have reported an incidence of ablation-related ACE of between 2% and 41%.[7–16] ACEs have recently been subdivided into either silent cerebral events (SCE) or silent cerebral lesions (SCL) based on MRI criteria.[17]

Attention has been focused on the platinum-tipped electrode pulmonary vein ablation catheter (PVAC, Medtronic Inc., Carlsbad, CA, USA). In initial reports, this decapolar non-irrigated duty-cycled radiofrequency ablation system was associated with the highest rates of ablation-related ACE. However, the PVAC system has been shown to have similar antiarrhythmic efficacy to conventional ablation,[18, 19] and modifications to the ablation procedure have resulted in an apparent ACE rate comparable to other techniques.[7]

nMARQ (Biosense Webster, Diamond Bar, CA, USA), like PVAC, is a 'single-shot' multipolar pulmonary vein mapping and ablation system.[20] A key difference is that all electrodes on the nMARQ catheter are continuously irrigated. Irrigation is thought to reduce the risk of thrombus formation and microbubble cavitation,[21] and consequently the incidence of cerebral microembolism.[22]

Minimally invasive thoracoscopic epicardial surgical AF ablation, an evolution of conventional open surgical AF ablation,[23] appears highly effective.[24] There is evidence to suggest that epicardial ablation causes fewer cerebral emboli than endocardial ablation.[25]

This is the first prospective randomised controlled study comparing the incidence of SCE after PVAC using modified techniques, the nMARQ system and thoracoscopic surgical AF ablation.

Key Words:
Silent Cerebral Event, Atrial Filbrillation Ablation, Thoracoscopic Epicardial Surgical AF Ablation.

Disclosures:
None.

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Material and Methods

Study Population and Protocol

A prospective randomised study was conducted in a single tertiary arrhythmia referral centre between May 2012 and September 2014. Patients with symptomatic paroxysmal AF were randomised 1:1:1 to PVAC ablation, nMARQ ablation and surgical AF ablation. The

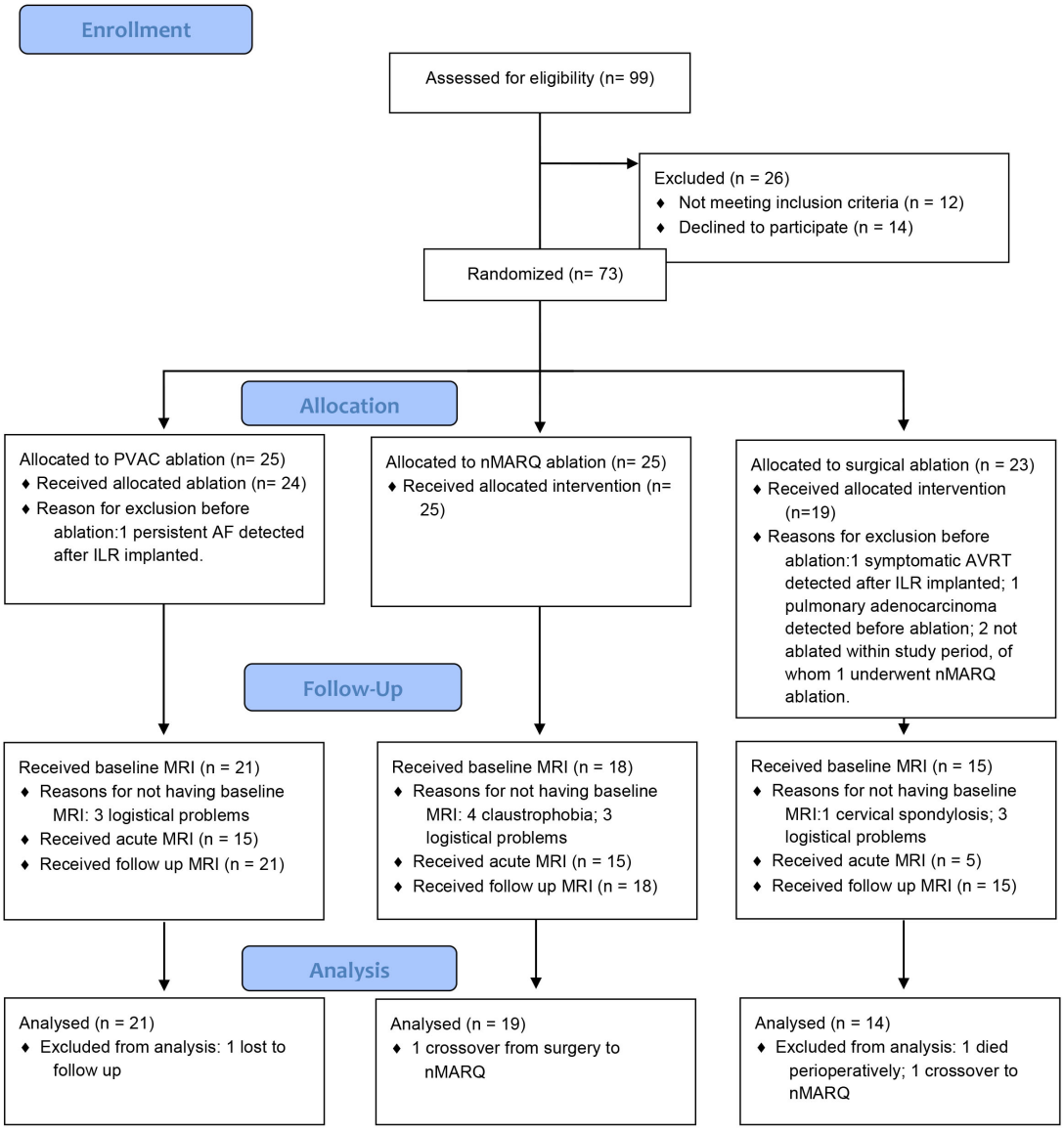

Figure 1: **Study flow diagram**

study protocol was developed by the investigators and was approved by the institutional review board and national ethics committee. All patients gave written informed consent. Inclusion criteria were age over 18 and symptomatic paroxysmal AF suitable for AF ablation. Exclusion criteria were: prior cardiac or thoracic surgery, inability to undergo general anaesthesia for AF ablation, pregnancy, the presence of pre-existing permanent pacemakers or implantable loop recorders that did not allow for continuous monitoring for AF occurrence, or were not MRI-safe, and cardiac rhythm disorders other than AF. Patients who had atrial flutter induced during the ablation procedure were not excluded. All patients were offered pre-procedural cerebral MRI (baseline), followed by MRIs as soon as possible after ablation (acute) and 3 months after ablation (follow up).

In total, 73 patients were recruited. 10 of 64 patients who were ablated did not undergo pre-procedural cerebral MRI (see Fig 1). 54 patients had both baseline and follow up scans. 12 patients (predominantly patients allocated to surgical ablation) were unable to have an acute scan, all because they were not stable enough to undergo MRI. One patient allocated to surgical ablation crossed over to nMARQ ablation.

Cerebral MRI

Cerebral MRI was performed using a 1.5T scanner (Signa HDXT, GE Medical Systems, Milwaukee, WI, USA). Coronal T1 and axial T2, fluid-attenuated inversion recovery (FLAIR) and DWI sequences were acquired, and apparent diffusion coefficient (ADC) maps constructed. Slice thickness was 4-5mm (1mm spacing) for T1, FLAIR and T2 sequences, and 5mm (no spacing) for DWI sequences.

As per the prospectively-defined analysis plan, cerebral infarction (CI) and white matter change (WMC) were defined as a focal lesion (>3mm in any axis) with associated T2 and FLAIR hyperintensity in any part of the lesion. CI was distinguished from WMC if there was corresponding T1 hypointensity within the lesion such that any part of the lesion appeared isointense to cerebrospinal fluid. Acute lesions (AL) were defined as a focal or wedge-shaped hyperintense lesion seen on DWI, with a hypointense signal in the corresponding region on the ADC map. No FLAIR criterion was used to evaluate AL, i.e. asymptomatic ALs are equivalent to silent cerebral events (SCEs).

Table 1: Baseline demographics of per protocol study population. TIA: transient ischaemic attack; IQR: interquartile range. No patients had prior documented stroke or congestive cardiac failure

	PVAC	nMARQ	Surgery	Total
n	21	19	14	54
Mean age (years)	66	67	62	65
Gender (female)	12 (57%)	13 (68%)	7 (50%)	32 (59%)
Prior AF ablation	3 (14%)	3 (16%)	2 (14%)	8 (15%)
Prior TIA	3 (14%)	0 (0%)	0 (0%)	3 (6%)
Hypertension	11 (52%)	11 (58%)	6 (43%)	28 (52%)
Hyperlipidaemia	7 (33%)	5 (26%)	4 (29%)	16 (30%)
Coronary artery disease	3 (14%)	4 (21%)	2 (14%)	9 (17%)
Diabetes	4 (19%)	1 (5%)	1 (7%)	6 (11%)
Median CHA2DS2Vasc score (IQR)	2 (1 to 3)	3 (1 to 3.5)	1 (1 to 2)	2 (1 to 3)
Median CHADS2 score (IQR)	1 (0 to 2)	1 (0 to 1)	0.5 (0 to 1)	1 (0 to 1)

The location and temporal resolution of lesions were analysed. Three blinded consultant radiologists independently analysed all MRI images. Lesions were considered present if independently reported by at least two of the three blinded radiologists.

All scans were anonymised, and the radiologists were blinded to the treatment assignments throughout. Scans were reported by the radiologists in three phases. In the first phase, radiologists were not aware whether a scan was the first, second or last scan performed. Scans were examined for the presence or absence of CI, WMC or AL without reference to any other study. In the second phase, scans were re-anonymised, and the radiologists examined the 3 month post-ablation MRI in comparison to the baseline MRI. Radiologists assessed whether there was new or increasing CI or WMC. Finally, in the third phase radiologists examined all three scans in patients who had an apparent ablation-related AL (i.e. an acute lesion appearing on the post-ablation scan). Radiologists assessed whether the lesion was new (i.e. not present in the baseline scan), and whether it had resolved (i.e. whether it was detectable on the 3 month MRI).

Cognitive Function Tests

All patients underwent the Mini Mental State Examination (MMSE) and Montreal Cognitive Assessment (MoCA) cognitive function tests immediately before ablation, 6 weeks post ablation and 3 months post ablation.

Table 2: Procedural factors relevant to the risk of periprocedural embolic events. SD: Standard deviation; IQR: Interquartile range; NA: Not applicable

	PVAC	nMARQ	Surgery	Total
N	21	19	14	54
Mean procedure time in minutes (SD)	87 (21)	77 (23)	284 (50)	124 (87)
Preprocedural Warfarin (%)	19 (90.5%)	14 (73.7%)	9 (64.3%)	42 (77.8%)
Preprocedural Dabigatran (%)	1 (4.8%)	4 (21.1%)	5 (35.7%)	10 (18.5%)
Preprocedural Rivaroxaban (%)	1 (4.8%)	1 (5.3%)	0 (0%)	2 (3.7%)
Median days prior to procedure anticoagulant stopped (IQR)	0	0	3 (2 to 4)	
Mean preprocedural INR for patients on Warfarin (SD)	2.3 (0.4)	2.2 (0.3)	NA	
Mean heparin dose given (SD)	9,632 units (2,290)	10,412 units (2,293)	NA	
Mean ACT during procedure (SD)	300 seconds (56)	313 seconds (54)	NA	

Table 3: Outcome of blinded assessment of all MRIs by treatment group. CI: Cerebral infarction; WMC: White matter change; AL: Acute lesion

Baseline	PVAC	nMARQ	Surgery	Total	p-value
N	21	19	14	54	
CI	4 (19.0%)	5 (26.3%)	0 (0.0%)	9 (16.7%)	0.12
WMC	18 (85.7%)	16 (84.2%)	14 (100.0%)	48 (88.9%)	0.31
AL	1 (4.8%)	2 (10.5%)	0 (0.0%)	3 (5.6%)	0.41
Mean Fazekas score	1.1	1.0	1.3	1.1	0.41
After ablation	**PVAC**	**nMARQ**	**Surgery**	**Total**	**p-value**
N	15	15	5	35	
CI	1	3	1	5	0.54
WMC	13 (86.7%)	13 (86.7%)	4 (80.0%)	30 (85.7%)	0.93
AL	3 (20.0%)	2 (13.3%)	0 (0.0%)	5 (0.0%)	0.54
Mean Fazekas score	1.1	0.9	1.3	1.1	0.36
3 months post ablation	**PVAC**	**nMARQ**	**Surgery**	**Total**	**p-value**
N	21	19	14	54	
CI	4 (19.0%)	4 (21.1%)	2 (14.3%)	10 (18.5%)	0.82
WMC	19	16	12	47	0.80
AL	1 (4.8%)	1 (5.3%)	0 (0.0%)	2 (3.7%)	0.70
Mean Fazekas score	1.2	1.0	1.2	1.1	0.68

PVAC Ablation

All patients were therapeutically anticoagulated preprocedurally, and anticoagulation (including with Dabigatran or Rivaroxaban) was continued through the procedure. No routine pre-procedural imaging (e.g. transoesophageal echocardiography) was performed. Through femoral venous access, a decapolar catheter was placed in the coronary sinus. A deflectable trans-septal sheath was used to perform a single trans-septal puncture, after which a bolus of unfractionated Heparin (approximately 70 units per kg of body weight) was injected intravenously. Thereafter, unfractionated Heparin was administered to maintain the activated clotting time (ACT) above 300 seconds whilst the left atrium (LA) was instrumented. Pulmonary vein (PV) anatomy was determined fluoroscopically using the PVAC catheter and guide wire, i.e. without routine left atrial angiography. The PVAC catheter was used to perform PV ablation using the GENius generator Version 15.1, which did not allow simultaneous ablation through the proximal and distal ablation electrodes. PV isolation was tested using the PVAC catheter. Inducibility of arrhythmia was tested with incremental atrial pacing and isoprenaline infusion. PV isolation was rechecked during isoprenaline infusion. A cavotriscuspid isthmus (CTI) line using a standard non-irrigated 8mm ablation catheter was performed if there was prior evidence of atrial flutter or it was induced during the case. Immediately following removal of the left atrial catheter, 25mg to 50mg of Protamine was injected intravenously.

nMARQ Ablation

nMARQ irrigated ablation was performed in a similar manner to PVAC ablation. Differences included use of a CARTO geometry created using the nMARQ catheter. The nMARQ catheter is not an over-the-wire system, and the nMARQ ablation system displayed

Table 4: Outcome of analysis of MRIs in temporal sequence. AL: Acute lesion; SCE: Silent Cerebral Event

	PVAC	nMARQ	Surgery	Total	p-value
N	21	19	14	54	
Number with evidence of progressive white matter change at 3 month MRI (%)	5 (24%)	4 (21%)	2 (14%)	11 (14%)	0.79
Number of acute scans with AL evident (%)	3	2	0	5	0.35
Number of apparent ablation-related SCE reclassified as pre-existing on comparison with baseline scan	1	1	0	2	0.69
Number of ablation-related SCE	2 (10%)	1 (5%)	0 (0%)	3	0.48 (6%)

live data from Tissue Connect, an impedence-based tissue contact algorithm, onto the CARTO geometry. nMARQ ablations were performed prior to changes in energy settings and algorithms were recommended. Hence the maximum bipolar power delivered was 25W. Otherwise, all other aspects of the procedure were similar to the PVAC ablation.

Surgical Ablation

Patients were all anticoagulated for at least 6 weeks prior to ablation, and stopped anticoagulants pre-procedurally without any bridging anticoagulation. Patients underwent general anaesthesia with double-lumen endobronchial intubation. Central venous and radial arterial access was routinely attained. A transoesophageal echocardiogram was performed after intubation but before surgery commenced. Thereafter, surgical ablation was performed as previously described.[23] Briefly, PV isolation was achieved by epicardial ablation using a bipolar radiofrequency clamp (AtriCure Inc, Cincinnati, Ohio, USA). Empiric ganglionated plexi ablation, as well as an anterior right atrial line, posterior left atrial roof line and left atrial appendage excision or clipping was routinely performed. Oral anticoagulation was reinstated immediately after the procedure.

Statistical Analysis

Data analysis was performed using SPSS statistical software (version 22, IBM Corp, New York, USA). Baseline characteristics of all randomised subjects were summarised. Categorical variables are reported as observed number of patients (percentage). A p-value of less than 0.05 was considered significant. Categorical variables were compared using the chi-squared test, ordinal data compared using the Kruskal-Wallis test, and continuous variables compared using ANOVA. Repeated measures were compared using the Wilcoxon signed-rank test.

Results

54 patients were included in a per-protocol analysis of patients ablated with either PVAC, nMARQ, or surgical ablations. Baseline demographic data are displayed in Table 1. There were no significant differences between groups, including in their CHADS2 and CHA2DS2Vasc scores. No patients had congestive cardiac failure or prior documented stroke. Procedural factors relevant to the risk of periprocedural cerebrovascular events are shown in Table 2.

Blinded Assessment Of All Scans

The outcome of the first blinded assessment of all scans is displayed in Table 3. There was a high rate of prevalent cerebrovascular disease on the baseline MRIs, despite the fact that no patient had any prior history of clinical cerebrovascular accident. Similarly there was a high rate of prevalent DWI-positive acute lesions seen both on the baseline and 3-month post ablation scans. None of these lesions can be attributable to the AF ablations. Pre-existing SCEs were no more likely in the patients who had had prior AF ablation (p = 0.33).

Table 5: Baseline and post-ablation cognitive function test results. MMSE: Mini Mental State Examination; MoCA: Montreal Cognitive Assessment; IQR: Interquartile range

	PVAC	nMARQ	Surgery	Total
Median baseline MMSE score (IQR)	100% (97 to 100%)	100% (97 to 100%)	97% (97 to 99%)	97% (97 to 100%)
Median post ablation MMSE score (IQR)	98% (98 to 100%)	100% (97 to 100%)	98% (95 to 100%)	99% (97 to 100%)
Median baseline MoCA score (IQR)	93% (87 to 97%)	90% (86 to 93%)	87% (84 to 93%)	90% (86 to 94%)
Median post ablation MoCA score (IQR)	97% (93 to 98%)	93% (88 to 97%)	95% (91 to 97%)	94% (90 to 97%)

Overall, there were no significant differences observed between the three ablation groups in the rate of CI, WMC or AL at any time point. However, only five patients who underwent surgical AF ablation were able to have MRI scans in the early post-ablation period. Whereas the median time from ablation to the post-ablation scan was 1 day for both the nMARQ and PVAC groups, the median delay to MRI scan for these five surgical patients was significantly longer (3 days, p=0.003).

Blinded Comparison Of Baseline And 3 Month Post-Ablation Scans

The baseline and 3 month post-ablation scans were compared and examined for evidence of new CI or WMC. No new CI were reported at all, however 20% of patients showed evidence of progressive WMC disease (Table 4). The extent of the progression in WMC was not great. All progressive WMC lesions were reported in the cerebrum supplied by the anterior circulation. No patient had more than one de novo WMC lesion (maximum diameter 5mm) and one existing WMC which increased in size (from 3 to 5mm in length measured at maximal dimension). There was no significant difference seen in the rate of progressive WMC disease between the ablation methods.

Blinded Comparison Of All Scans In Temporal Sequence

Five scans where an AL had been reported on the acute scan were compared with the baseline and 3 month post ablation scans. Two of five (40%) scans with an apparent ablation-related SCE were shown to be pre-existing, i.e. the DWI hyperintense lesion was already apparent on the pre-ablation scan. In total, only three patients had new ALs when baseline and the acute scans were compared: two after PVAC ablation and one after nMARQ ablation. In the nMARQ case, there was a new 3mm AL detected in the right frontal lobe, with no residual MRI abnormality in the corresponding region at 3 months. In one of the PVAC cases, there were a total of three new ALs detected: one 18x2mm left cerebellar, one 4mm left frontal and one 3mm left occipital AL. All three ALs had completely resolved with no MRI abnormality at 3 months. However, in the remaining PVAC ablation, there was a new 5mm right frontal lobe AL, with a corresponding 3.5mm new WMC lesion at that site 3 months after the ablation. Selected images are presented in the Supplementary Appendix.

Overall, there was no significant difference in the rate of ablation-related SCE observed between the three types of AF ablation.

Cognitive Function Tests

Overall, baseline cognitive function assessed by the MMSE and MoCA tests were normal across all three groups (Table 5). There were no significant differences between groups at before or after ablation. On repeated measures analysis, there were no significant

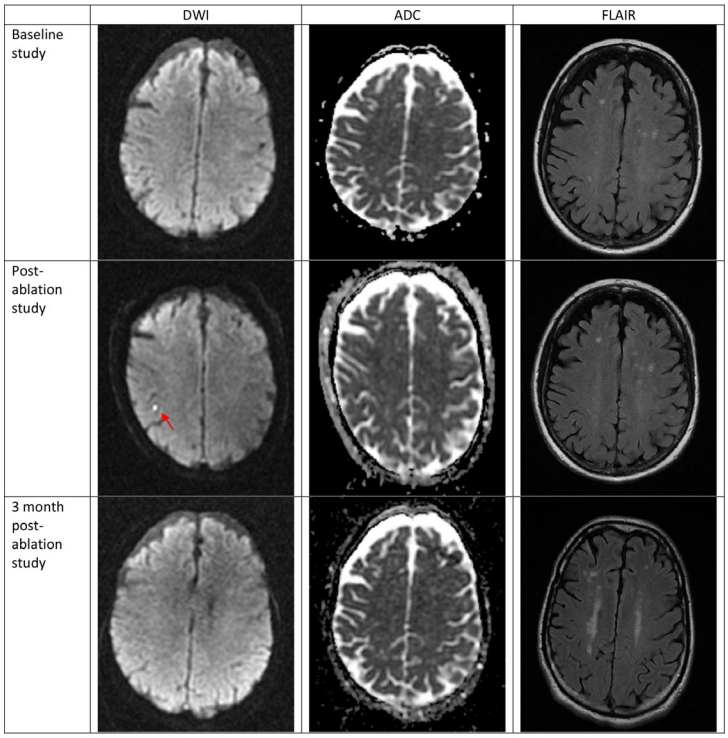

Figure 2: **Silent cerebral event (SCE) after nMARQ ablation**
This patient with a CHA2DS2Vasc score of 2 underwent nMARQ ablation. Baseline MRI shows multiple areas of cerebral white matter change on the FLAIR sequence. A new DWI hyperintense, ADC hypointense lesion is seen on the post ablation study. 3 months after ablation, the lesion is no longer present

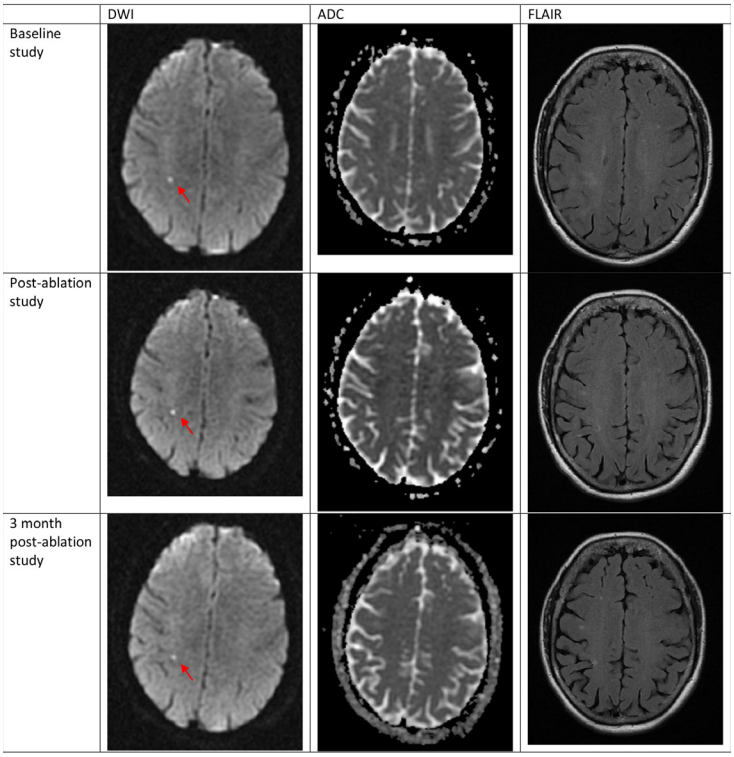

Figure 3: **DWI positive lesion present before nMARQ ablation**
This patient with a CHA2DS2Vasc score of 4 underwent nMARQ ablation. Examination of the post-ablation MRI demonstrates a clear DWI hyperintense, ADC hypointense lesion. If there were no symptoms, this would fit the criteria for a silent cerebral event (SCE). However, this lesion is evident on the pre-ablation study, demonstrating that it is not ablation-related

changes seen in cognitive function test scores. At no point within study follow up was there any change in neurological status including any new clinical signs.

Discussion

In this prospective randomised controlled trial of three different AF ablation techniques in paroxysmal AF, we performed serial cerebral MRI assessments up to 3 months post-ablation. The platinum-tipped PVAC catheter has previously been reported to have a very high rate of ACE, Non-randomised studies have suggested that with some procedural modifications, the apparent ACE rate can be reduced. Consequently the reported rate of PVAC-related ACE has varied between 39%[16]and 2%.[7] The nMARQ ablation system has similarities to the PVAC system, but with the difference that all ablation electrodes are continuously irrigated. Non-randomised studies have suggested varying rates of ACE,[20, 26] but this is the first randomised study examining this technique. Finally, there are few published data describing minimally invasive thoracoscopic surgical AF ablation, an entirely epicardial procedure. This is the first study to ever report cerebral MRI changes associated with stand-alone surgical AF ablation.

Ablation-Related Silent Cerebral Events (SCE)

The main finding of this study was that in 54 patients undergoing different types of AF ablation, there were only 3 ablation-related SCEs detected. Overall, there were no significant differences seen in the rate of ablation-related SCE seen between the three ablation strategies. However, a major limitation of this study was that a number of patients, disproportionately those who underwent surgical ablation, did not receive an early MRI. No surgically ablated patient was found to have an ablation-related SCE, but it is possible that undetected SCE occurred in some patients who could not receive an early MRI scan. In practice, it proved very challenging to perform cerebral MRIs in patients recovering from surgical ablation. With improvements in post-operative recovery after surgical ablation, this may become feasible in the future.

Comparison of the PVAC and nMARQ patients showed that the ablation-related SCE rate was similar between the groups, and is within the range described in other studies.[7–16] Although it is not possible to draw conclusions from such few events, we did observe a numerically higher number of ablation-related SCE in the PVAC group, and the only patient with an SCE which did not resolve at 3 months had had a PVAC ablation.

An unexpected finding was the high rate of background DWI-hypertense acute lesions (AL) seen at baseline (5.1%) and at 3 months (3.3%), which has not been reported elsewhere. The study design meant that all ALs were reported without the potential bias of radiologists knowing the order in which scans were undertaken. This revealed a surprising number of SCEs which could not be related to any ablation. All patients were therapeutically anticoagulated throughout the study, and the median CHA2D¬S2-Vasc was only 2. The high background rate of asymptomatic lesions in this population raises further questions as to the clinical relevance of post-ablation SCE defined by DW-MRI signal abnormality.

High Background Prevalence Of MRI-Detected Cerebrovascular Disease

In addition to the unexpectedly high baseline rate of AL (5.1%),

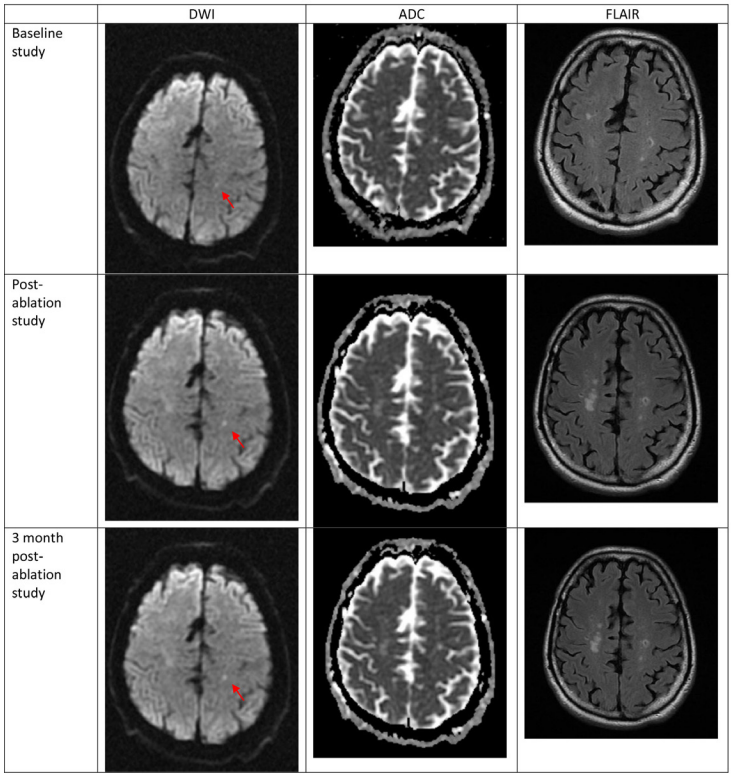

Figure 4: DWI positive lesion present before PVAC ablation
This patient, with a CHA2DS2Vasc score of 5, underwent PVAC ablation. As with the previous case, the DWI hyperintense lesion is present prior to ablation

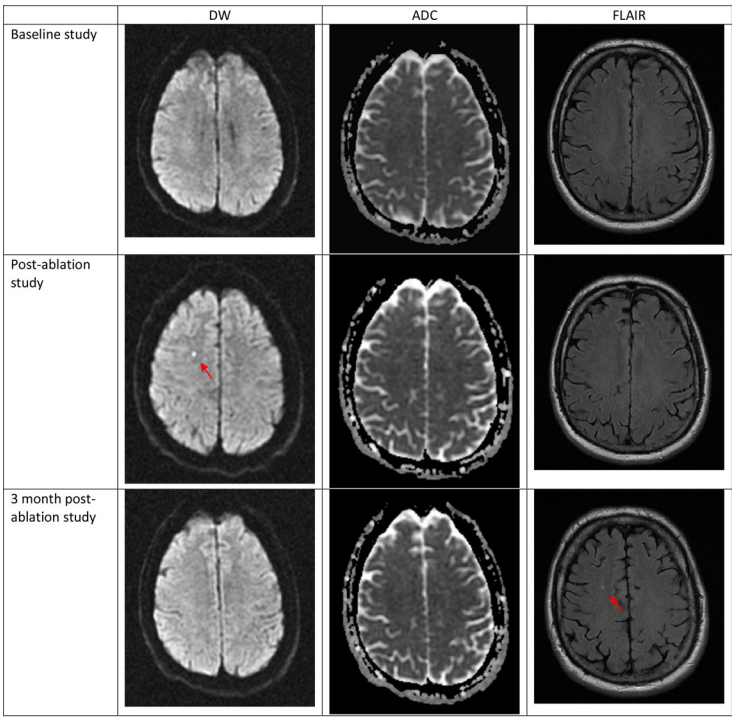

Figure 5: Silent cerebral event after PVAC ablation with residual white matter change at 3 months
This patient (CHA2DS2Vasc score of 2) underwent PVAC ablation. A new SCE (asymptomatic DWI hyperintense, ADC hypointense lesion) is evident in the right frontal lobe. At 3 months, there is a FLAIR hyperintensity in the same region, consistent with cerebral white matter change (WMC)

there was a high rate of established cerebral infarction (15.1%) and white matter change (90.0%). This is particularly remarkable given the low prevalence of clinical cerebrovascular disease, and the low CHA2D¬S2-Vasc scores. The patients within this study had a much higher rate of existing cerebral lesions than have ever been reported before in any other similar study.[7, 8, 14, 27] However, the overall burden of white matter change as indicated by the Fazekas score was appropriate to this age group. Given the highly selected nature of most studies examining the cerebral MRI effects of AF ablation, this study provides further insight into the prevalence of MRI abnormalities in typical AF ablation patients.

The effect of pre-existing MRI abnormalities on the detection rate for new lesions should be considered. It is feasible that embolism to vessels supplying already abnormal cerebral tissue may not result in radiographically detectable new MRI changes. There are little existing data validating the accuracy of DWI in detecting small new lesions in patients with established cerebral infarction or white matter change.

High Rate Of Progressive Cerebral MRI Change

The uncertain validity of DWI for detecting acute lesions in patients with pre-existing cerebral MRI abnormalities was a key reason we prospectively planned to compare baseline and 3 month scans for evidence of progressive disease. To our knowledge, this was the first study to use this methodology. As a consequence of this approach, all studied patients, even those who could not have an acute MRI, could be analysed.

Although there was no evidence of new ablation-related cerebral infarction, there was a high incidence of new cerebral white matter change. In the absence of a comparator group of patients who did not undergo ablation, it is not possible to know if the rate of progressive cerebral disease was higher or lower than expected for this population. However, at least one instance of progressive WMC was directly attributable to an ablation-related SCE, implying that the ablation procedures had at least a partial causal role in progressive cerebral MRI abnormality.

The methodology of comparing all pre-ablation to 3 month post-ablation scans was straightforward for patients and investigators. More new events were detected than with the DWI-based method, including several in patients who had apparently unchanged MRI appearances in the early post-ablation scans. The clinical significance of SCE and asymptomatic new WMC is not certain. However, most SCEs appear to completely resolve whilst new WMC appears to persist. It may be that progressive new WMC is a more clinically relevant MRI end-point than SCE.

Although the overall incidence of new chronic MRI changes was alarmingly high, the number and extent of progressive WMC was limited. Furthermore, it should be noted that no patient had any adverse clinical neurological event at any time and there was no evidence of any ablation-related cognitive deficit at any time. It is feasible that AF ablation may demonstrate protective effects on progressive cerebrovascular disease if assessed at other time-points than 3 months post ablation. At present, there are insufficient data to draw strong conclusions about the interaction between AF ablation and progressive cerebral MRI abnormalities.

Study Limitations

The major limitation of this study is that a low number of patients undergoing surgical ablation were able to have an early post-ablation MRI. However, all patients had baseline and 3 month post ablation

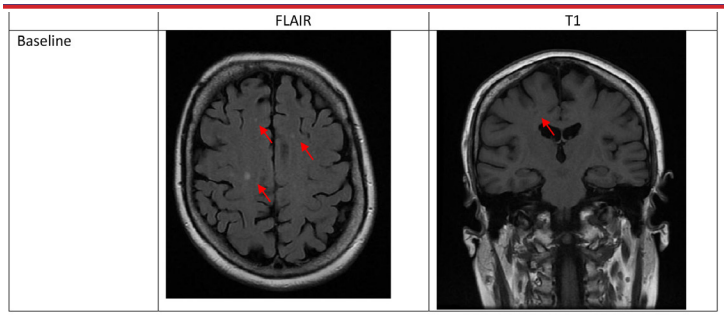

Figure 6: **Pre-existing asymptomatic cerebral infarction**
This patient with CHA2DS2Vasc score of 1 underwent cerebral MRI prior to ablation. There was no prior history of cerebrovascular disease. This demonstrated several areas of white matter change (WMC), with one area of cerebral infarction (FLAIR hyperintense, T1 hypointense)

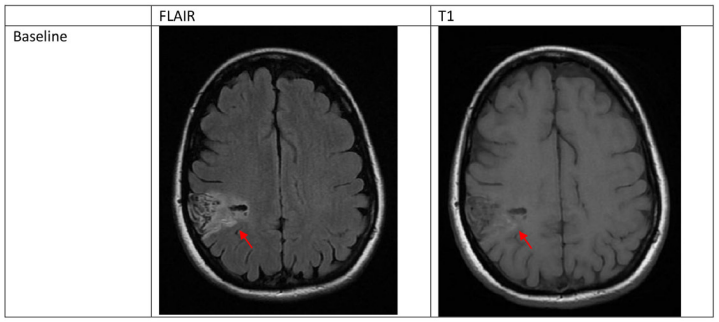

Figure 7: **A similar finding is evident in this patient, also with a CHA2DS2Vasc score of 1. A large pre-existing cerebral infarction is seen. The patient underwent further cerebral imaging after this study, and was reviewed by independent neuroradiologists and neurologists. They concurred that the patient had suffered a prior asymptomatic cerebrovascular accident**

MRIs. The study was not powered to detect small differences in the rate of cerebral MRI abnormality. Nevertheless, the prospectively defined analysis plan maximised the use of the available data, and demonstrated several new hypothesis-generating findings. Furthermore, the overall event rates for new ablation-related SCE were consistent with other published studies.[7–16]

The boundaries used to define established cerebral infarction are consistent with the major published work in this field.[28,29] However, the requirement for FLAIR hyperintensity meant that some cerebral infarctions (especially lacunar infarctions) were not counted within this scheme. Hence the prevalence of underlying silent cerebral infarction is likely to be underestimated. Nevertheless, the FLAIR criterion acted as an effective way of excluding incidental enhancing periventricular (Virchow-Robin) spaces.[30] Furthermore, the aim of this study was to look for the presence of ablation-related cerebral infarction on the 3 month scan. FLAIR hyperintensity consistently occurs within hours of a cerebral infarction,[31] and is known to persist for at least 3 months, supporting the use of a FLAIR criterion for detection of ablation-related events.

Conclusions

This study population had the highest rate of prevalent cerebral MRI abnormality so far reported. They, however, represent a clinically relevant group of patients. The overall rate of ablation-related SCE was consistent with other published data, but was overshadowed by a high background rate of SCE which was not ablation-related. The prevalence of spontaneous SCE in this population undermines the clinical significance of asymptomatic acute ablation-related cerebral MRI changes based on DWI.

When pre- and 3 month post-ablation MRIs were compared, 1 in 5 patients had detectable new cerebral white matter change. The volume and number of lesions were low, but the high incidence of these lesions within a short time-frame is alarming. There was no evidence that nMARQ, PVAC or surgical ablation resulted in a difference in the rate of progressive WMC, and no patients were found to have any adverse neurological sequelae or change in cognitive function at any time.

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Antiarrhythmic Effect Of Antioxidants In Patients With Atrial Fibrillation

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Abstract

Resume In accordance with modern concepts, one of the leading roles in the development of paroxysmal atrial fibrillation and flutter, belongs - the restructuring of the myocardium, in second place - sick sinus syndrome and in third place - the presence of accessory pathways and hormonal disorders. The development of atrial fibrillation and flutter in the structural pathology, primarily begins with of drugs if it does not work, we have to carry out ablation. Providing proper, effective and important combination therapy - is the main challenge in cardiology.

Introduction

Fibrillation and atrial flutter (AF) - one of the most common heart rhythm disturbance. In the population of their frequency is 1-2%. According to data presented in the recommendations of the European Society of Cardiology, about 6 million people in Europe suffer from AF, and in the next 50 years, their number at least double. AF can significantly reduce the quality of life of patients.[7] All this makes it necessary to find effective methods of treatment and prevention of cardiac electrical instability (CEI).

Antiarrhythmic drugs have limited efficacy in the treatment and prevention of AF and do not modify the structural substrate in AF. Currently, few controlled clinical studies on the choice of anti-arrhythmic drug, taking into account a variety of mechanisms and causes of AF. Therefore, modern algorithms for medical treatment of AF should include the combined use of anti-arrhythmic and anti-arrhythmic drugs, in order to address the complex causal interaction, forming a vicious circle and put increased difficulties in treating this rhythm disturbance over time.[2]

Promising reasons and mechanisms of AF can assume the existence of an antioxidant barrier, which can be damaged by structural heart disease. Under normal conditions, there is a distinction between the myocardium and the ectopic nodes located along the pathways of the heart. In the myocardium, intercellular fluid contains large amounts of Na^+ ions and Cl-, especially during hypoxia and acidosis, i.e. there prevails acidic environment, and in ectopic sites and conductive paths heart predominant acidic environment. In order to prevent any oxidation of the proximal and middle conductive paths ectopic sites, there is the antioxidant barrier in the form of connective tissue adhesive coating. A distal Purkinje fibers, antioxidant barrier moves into T-cells, which differentiate B cells (Purkinje cells), and the myocardium itself. It is this antioxidant barrier, often damaged by structural heart disease, which leads to the development of atrial or ventricular fibrillation.[4]

Accordingly, if hypothetically assume that there is a damage of the antioxidant barrier, and treatment should be combined to work on all parts of AF: antiarimicheskoe, antioxidant and reparantnoe. Research in this area has not yet been carried out in the world, the very reason for the oxidation of ectopic sites at various anatomical levels of the heart, is an innovative, so references to the use of the described combination treatment of atrial fibrillation and flutter of the heart in the literature. Nevertheless, we refer to the use of some authors in the studies undertaken.

In this study, TA Zaynutdinova (2008.), It is noted that the beats I-III functional class Qudesan at course at a dose of 2 mg / kg / day in the complex therapy is the overall antiarrhythmic effect in 50% of children, causing half of them complete suppression of arrhythmias and improving the results of the basic treatment of 10%.[1]

In a study conducted Shubik Y. (1998.), Argues that solkoseril proved to be quite effective antiarrhythmic agent in the treatment of ventricular arrhythmias high grading B. Lown. effect which is realized by means of membrane and antihypoxic effect on cells including - myocardial cells.[5]

Key Words:
Atrial Fibrillation, Structural Heart Disease, Electrical Instability Of The Heart.

Disclosures:
None.

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The aim of our study was to evaluate the efficacy and safety of antiarrhythmic action Qudesan and solcoseryl in patients with atrial flutter and atrial fibrillation.

Materials And Methods

The study met the requirements Helsenskoy diklaratsii. All patients provided written consent to participate in a clinical trial. The study protocol was approved by the Ethical Committee of the SEI HPE "Dagestan State Medical Academy" MoH.

Randomezirovannoe open prospective comparative study included 53 patients with new-onset paroxysmal AF or TA. Patients were treated in the cardiology department of the Republican Hospital №2 TSSEMP MOH RD (Makhachkala) in the period 2012-2013. Inpatient treatment lasted 7 days after discharge outpatient supervision and treatment continued - the total duration of the study was one month.

Criteria For Inclusion

1) hemodynamically stable episodes of AF with no more than 7 days;
2) informed consent to participate in the study;
3) age from 18 to 75 years.

Exclusion Criteria Were

1) Unstable Angina
2) a permanent form of atrial flutter or atrial fibrillation;
3) artificial pacemaker;
4) the inability of prospective study;
5) participation in any other study.

Criteria For Early Retirement From The Study

1) the emergence of side effects of drugs;
2) failure to continue to research and treatment;
3) non-compliance to medication.

On admission, patients were randomized by random numbers into two groups matched for sex and age, the level of blood pressure, body mass index. The ratio of male to female ratio was 44 (83.0%) and 9 (17.0%), respectively (Table 1).

For all these measures groups were not significantly different from each other (p> 0.05).

Patients in both groups had a variety of related heart disease: coronary heart disease, hypertension, cardiomyopathy, myocarditis, atherosclerosis, etc. (Table 2).

In the 1st group included (n = 28) patients undergoing therapy following:

1 Cordarone (Sanofi-Aventis / France) - 600 mg / day in the 1st day, the 2nd day to 400 mg / day., On the third and subsequent days, 200 mg / day., Within 7 days , followed by the transition to B-blocker - Concor (Merck / Germany) - 5 mg per day.

For all these measures groups were not significantly different from each other (p> 0.05).

Table 1: Baseline demographic and clinical and laboratory characteristic groups

ndicators	group 1 (n = 28)	group 2 (n = 25)
Men, n %	67,9	74,4
Average age	57,8±7,3	56,5±7,0
BMI: + 25–30 кг/м2, n (%) > 30 кг/м2, n (%)	20 32	23 29
Physical inactivity, n (%)	47	51
Smoking, n (%)	32	26
Leukocytes thousand. 1 ml.	4,8±2,5	9,2±3,2

Table 2: Characteristics of the groups on the main and additional diseases

Indicators	group 1 (n = 28)	group 2 (n = 25)
Duration of paroxysmal atrial tachycardia, days (M±m)	3,7±0,6	4,1±2,9
Duration of ischemic heart disease, years (M±m)	4,2±1,5	3,7±1,3
Myocardial infarction, n (%)	38	29
Myocarditis, n (%)	2	0
Cardiomyopathy, n (%)	8	4
Hypertension, n (%)	33	37
Diabetes mellitus type 2, n (%)	12	9
Hypercholesterolemia, n (%)	42	40
Ventricular premature beats, n (%)	14	11
Supraventricular arrhythmias, n (%)	8	7

2 From the moment of admission, administered one-time 4% sodium hydrogen carbonate - 200 ml / drip, with subsequent transition to kudesan Q10 (Akvion / Russia) - 10 drops (0.5 ml) 2 times a day with meals for 1 month. previously dissolved in a small amount of water.

3 Solkoseril (Solco Basel / Poland) - the drug was administered at 2 ml / drip (previously diluted in 250 ml 0.9% sodium chloride) for 5 days.

4 Dabigatran (prodaksa), Boehringer Ingelheim Pharma GmbH & Co. KG (Germany) - 150 mg, 1 time a day.

The 2nd group included (n = 25) of patients.

1 Cordarone (Sanofi-Aventis / France) - 600 mg / day in the 1st day, the 2nd day to 400 mg / day., On the third and subsequent days, 200 mg / day., Within 7 days , followed by the transition to B-blocker - Concor (Merck / Germany) - 5 mg per day.

2 Dabigatran (prodaksa), Boehringer Ingelheim Pharma GmbH & Co. KG (Germany) - 150 mg, 1 time a day.

In addition to the results of clinical and laboratory studies (clinical analysis of blood and urine, total cholesterol), patients in both groups was carried out daily, three-time ECG examination.

On the 2nd day, and a month later, all patients underwent ECG monitoring (CM ECG).

ECG study was conducted using a computer program of "Poly - spectrum" Neurosoft (Ivanovo). SM ECG Holter was performed using the computer program «DiaCard» CJSC "Medic" (Moscow).

Statistical Treatment Of Results Of Research

Statistical analysis of the results of research carried out using the software package STATISTICA 6.0 (StatSoft Inc, USA).

Analysis of normality studied traits analyzed using the Shapiro-Wilk test. Quantitative data are presented as mean values and standard deviations (M ± SD). Statistical significance of differences was assessed by Student t-test for dependent and independent samples, with uneven distribution using nonparametric Wilcoxon (x2). Statistical significance of differences or shear effect due to treatment was assessed at the level of $p \leq 0.05$.

Results

According to the results of the ECG in the 1st study group, sinus rhythm was restored in 19 (67.8%) patients after 6 hours from the beginning of hospitalization and treatment. More in 5 (17.8%) of the patients heart rhythm was restored after 48 hours from the moment of admission to the hospital, and after 7 days of heart rhythm was

Table 3: Results SM ECG in the 1st study group (M±SD)

Performance	After 48 h (1)	After 1 month (2)	Growth rate,% (48 h-1 month)
Number of episodes of painful ischemia	3,42±2,68	0,71±1,61	-79,2 P1-2= 0,000009
Number of episodes of silent ischemia	4,80±3,45	0,90±2,05	-81,2 P1-2= 0,000001
The average duration of episodes of paroxysmal AF or TA min	18,53±3,85	0,00	-100,0 P1-2= 0,000004
Ventricular premature beats, n	11	11	(1-2) (χ2=16,0 p=0,00)
Supraventricular extrasystoles, n	7	5	(1-2) (χ2=12,0 p=0,009)

Note: The statistical significance of inter-group differences in the t-test for dependent data (r1-2-between the 1st and 2nd stages), n-number of patients with arrhythmia and □u 2 before and after by Wilcoxon, step by step.

Table 4: Results SM ECG 2nd study group (M±SD)

Performance	After 48 h (1)	Within 1 month (2)	Growth rate,% (48 h-1 month)
Number of episodes of painful ischemia	3,38±2,95	0,86±1,62	-74,5 P1-2= 0,0003
Number of episodes of silent ischemia	4,52±3,37	1,00±1,94	-77,8 P1-2= 0,0002
The average duration of episodes of paroxysmal AF or TA min	15,36±4,22	3,17±2,25	-78,1 P1-2= 0,0003
Ventricular premature beats, n	14	10	(1-2) (χ2=20,9 p=0,00)
Supraventricular extrasystoles, n	8	4	(1-2) (χ2=8,9 p=0,038)

Note: The statistical significance of inter-group differences in the t-test for dependent data (r1-2-between the 1st and 2nd stages), n-number of patients with arrhythmia and □u 2 before and after by Wilcoxon, step by step.

restored in the remaining 4 (14.2%) patients, respectively, in all 28 patients. Statistically significant reduction from baseline (P <0.001).

According to the results (see ECG) - on the 2nd day of AF paroxysms were observed in 13 (46.4%) patients after 1 month none of the patients (P <0.05) (Table. 3).

According to the results of the ECG in the 2nd - group, sinus rhythm was restored in 13 (48.0%) patients after 6 hours from the beginning of hospitalization and treatment. More in 7 (32.0%) patients of CP recovered after 48 hours of admission to the hospital. 7 days - AF was observed in 5 (20%) patients, respectively, heart rhythm they never recovered. Statistical reduction from baseline (P <0.001).

According to the results (see ECG) on the 2nd day, paroxysms of AF were observed in 15 (60.0%) patients, and 1 month in 7 (20.0%) patients (P <0.05) (Table . four).

Discussion

The study revealed significant differences in the dynamics of the electrocardiogram and daily ECG monitoring in the two groups.

In group 1, with the appointment of a comprehensive treatment of a statistically significant reduction in the number of patients with paroxysmal AF, six hours after admission to the hospital with n = 19 of 28 Much of this effect is due to the appointment of Cordarone with sodium bicarbonate. In the following 48 hours of complex treatment kordaronom, kudesanom and solkoserilom, sinus rhythm was restored in 5 patients, and after 7 days, the remaining four (P <0.001). Further comprehensive antioxidant treatment on an outpatient basis, a control examination CM ECG one month showed that relapse paroxysm AF are not revealed in the examined patients of group 1 (P <0.05).

According to the results (see ECG) - the second day of paroxysms of AF in group 1 were observed in 13 (46.4%) patients, and 1 month later episodes of paroxysmal absent in all patients (P <0.05). (Fig. one).

In group 2, the subjects with the main purpose of Cordarone without antioxidant therapy and reparant, just decreased the number of patients with paroxysmal AF (P <0.001). After 6 hours, the sinus rhythm was restored in 13 of the 25 patients from the start of admission and early treatment, and even at n = 7 for 48 hours. In 4 patients, paroxysmal atrial fibrillation and atrial flutter 1 turned into a permanent form (P> 0.05).

According to the results (see ECG) on the 2nd day, paroxysms of AF were observed in 15 (60.0%) patients, and 1 month in 7 (20.0%) patients (P <0.05). (Figure 1).

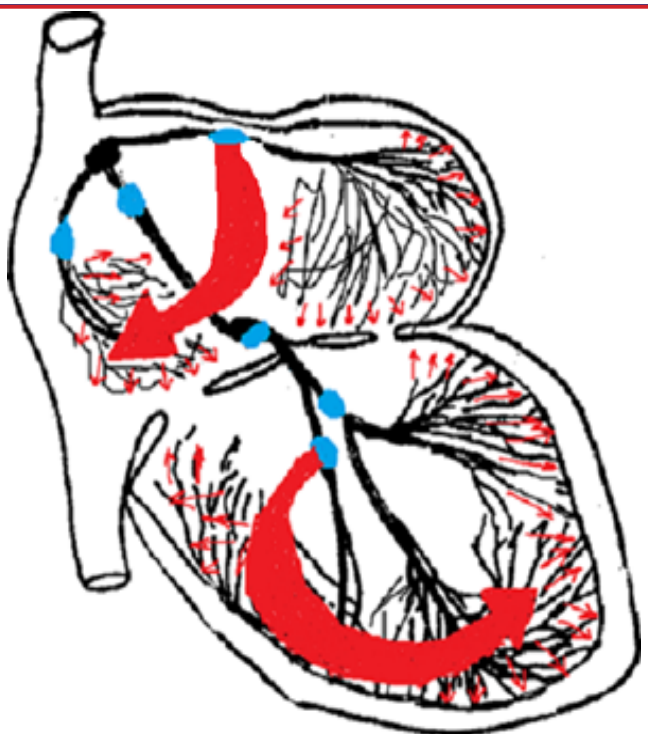
Thus, it can be noted that a comprehensive treatment kordaronom, sodium hydrogen carbonate and kudesanom contributed to the creation of anesthesia and antioxidant protection for ectopic sites, and solkoseril restored antioxidant barrier along the pathways of the atria. This has led to excellent results in group 1 had completely disappeared paroxysms of AF, and in the 2nd group of five patients with atrial fibrillation and moved into a permanent form, and still remained in seven episodes of paroxysmal. As we can see, the use as a basic drug Cordarone only, not as effective. Probably, it leads only to a temporary anesthetic stabilization of ectopic foci, followed by the inclusion of compensatory abilities of the body to restore the antioxidant barrier. But the ability of the organism are not unlimited, especially in the age of patients, and for this you need to carry out a comprehensive treatment with the additional use reparants and antioxidant drugs.

In both groups, there was no side effects from the therapy, all patients comply with their assigned mode of treatment failures and drop-outs were not.

In the chapter "Introduction", we described the cause of atrial fibrillation, and heart, and in the discussion of the topic, we want to offer you the mechanism of their development. If you can analyze these mechanisms, then you will understand that we are not trying to go to the section of the existing scientific data, we are only their orderable.

One may wonder why the proposed mechanism of atrial right? The fact that the most powerful source of ectopic supraventricular paroxysmal tachycardia and atrial flutter is in the atria (atrial fibrillation does not count, it is due to multiple ectopic), but ECG is observed different picture, why? Because supraventricular paroxysmal tachycardia electrical impulses to overcome obstacles, passing through many small pathways and ectopic sites in the atria, and then he goes to the myocardium is not as powerful impetus, as in macro - re-entry. A atrial flutter on the myocardium smoothly sees powerful wave electric pulse (macro - re-entry), connective tissue damage through the insulation shell (Figure 2).

Figure 2: The figure of the heart can be seen, the formation of a powerful wave of macro - re-entry at damage to the connective tissue adhesive coating pathways in heart atria and ventricles (large red arrow). The simultaneous excitation of the myocardium through Purkinje fibers (small red arrows). Blue dots indicate the likely fault locations connective insulation shell with structural heart disease, as well as, the approximate anatomical location of the proximal ectopic sites in the atria and the ventricles, which are able to run as



paroxysmal tachycardia, and flutter.

This mechanism can be compared with the syndrome WPW, only in this case, a large part of the wave of electrical excitation (wave macro - re-entry), vomited through the damaged connective insulation shell covers less passed through the pathways of the heart, and the F-wave flutter - a delta wave pre-excitation infarction.

Oxidation and irritation of the proximal ectopic focus in damage connective insulation shell with free discharge of electricity in the atrial myocardium, contributes to a more rapid reduction in the power voltage in the pathways and ectopic foci. This shortens the refractory period, which leads to higher frequency rate during atrial flutter, paroxysmal supraventricular than tachycardia. Accordingly, in the interruption of atrial fibrillation and restoring sinus rhythm, the ECG will be celebrated only broad P wave (more than 0.13 sec.). Moreover, F delta wave macro - re-entry will be present, but it will merge with P tooth and become invisible due to the fact that the source of rhythm shift to the sinus node and the electricity goes in three ways: Wenckebach, Bachman and Toreli.

In the book written by Genco of the existence of two theories of flutter, increased ectopic activity or development of a powerful wave (macro - re-entry).[3] This study and the described mechanism does not refute any of the theories, and combines them into a single mechanism of flutter.

Fibrillation, most often damaged connective insulating sheaths distal portions of the conductive paths of the heart (atrial or ventricular branch) or multiple damage transition of T cells. This leads to the oxidation of not one but several less powerful ectopic foci and the development of atrial fibrillation with the mechanism of micro - re-entry.

In the assumed cause of AF, it is clear that the damage antioxidant barriers pathways of the heart and along these ectopic sites, leading to a rapid oxidation process with the development of AF. The longer the oxidation process continues, the greater will be deposited calcium salts around ectopic sites to form calcific capsules, respectively, such oxidation will never recover sinus rhythm of the heart, without cauterization of ectopic foci (ablation).

Analysis of the literature indicates that in many studies, structural and pathological condition of the heart is the source of a life-threatening arrhythmias:

1. is a prerequisite for the emergence of life-threatening arrhythmias is the presence of structural heart disease, which leads to the formation of an unstable substrate under the influence of various functional factors. As these structural changes that underpin the development of LTA can be: marked hypertrophy, dilatation, aneurysm, heart, necrotic and sclerotic processes myocardial inflammation with swelling of the myocardial tissue, etc. These changes, according to many researchers, are anatomic substrate with different mechanisms of occurrence of LTA.[6]

2. for the appearance of LTA requires a combination of several factors predisposing to CEI: the presence of a substrate (structural heart disease), the modulation of the autonomic nervous system dysfunction and triggering factors LTA. Morphological substrate that creates inhomogeneity impulse conduction after a myocardial infarction, is the border with necrotic tissue infarction zone formed of intertwined islands of viable myocardial fibers and connective tissue. At this point, the path of the pulse is lengthened due to the fact that the connective tissue islets become barriers to excitation wavelength, and the speed is slowed down as a result of violation of a parallel orientation of the muscle fibers. Thus, the area of myocardium with delayed ventricular depolarization may represent the anatomical and physiological substrate for re-entry - the main mechanism of LTA.[8]

Conclusions

The study showed that the complex pharmacological effect on the causes of atrial fibrillation and flutter of the heart, leading to a more significant effect than just an anti-arrhythmic. This effect is achieved due to the impact on all parts of structural heart disease in the development of atrial fibrillation and flutter. Integrated use of Cordarone with antioxidant drugs - sodium bicarbonate and kudesan (Q10), as well as reparants - solkoseril, just contributes to the stabilization of electrical processes of the heart.

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A Comparison Between Dabigatran and Warfarin on Time to Elective Cardioversion

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Abstract

Objective: To evaluate the use of dabigatran versus warfarin on time to elective direct current cardioversion (DCCV).

Methodology: This retrospective observational study was conducted at a single Veterans Affairs hospital in the Southwestern region of the U.S. Patients with atrial fibrillation or atrial flutter who were initiated on either warfarin or dabigatran prior to DCCV were reviewed. The time to cardioversion was compared between warfarin and dabigatran, as well as costs of therapy, rescheduling rates, and adverse events.

Results: Out of 258 patients reviewed, a total of 68 patients were included in the study. All patients were male with an average age of 68 years (SD=8.6). A total of 38 patients (56%) received dabigatran and 30 patients (44%) received warfarin. Patients in both groups had a median $CHADS_2$ and HASBLED score of 2. The median number of days to cardioversion was 34.5 (range=22-148) for dabigatran compared to 66.5 (range=32-183) for warfarin ($p<0.01$). Total costs of anticoagulation for warfarin averaged $183.50 (SD=95.02) from initiation of anticoagulation to the end of the required four week period following cardioversion, whereas dabigatran costs averaged $193.20 (SD=59.38). Three patients (10%) in the warfarin group had DCCV rescheduled compared to none in the dabigatran group. There was one bleeding event in the warfarin group and no thromboembolic events in either group.

Conclusion: The use of dabigatran prior to elective DCCV results in a significant decrease in number of days from initiation of anticoagulation to cardioversion as compared to warfarin, with a minor increase in total costs.

Background

Rhythm control with direct current cardioversion (DCCV) is a commonly used strategy in the treatment of atrial fibrillation (AF). Factors favoring rhythm control include young age, first episode of AF, difficulty in achieving rate control, persistent symptoms despite rate control, tachycardia induced cardiomyopathy, and patient preference. Both the current CHEST and AHA/ACC/HRS guidelines recommend therapeutic anticoagulation for a minimum of three weeks before and four weeks after cardioversion for patients with AF or atrial flutter.[1,2] In studies with warfarin, the risk of thromboembolic events following DCCV was significantly reduced with appropriate anticoagulation .[3,4] However, interactions with diet and other drugs, frequent blood tests for monitoring, and INRs outside of therapeutic range can result in rescheduling and delay DCCV, making warfarin less desirable to use. A meta-analysis to assess the quality of warfarin control in atrial fibrillation patients found INRs within therapeutic range only 55% of the time.[5] The approval of new agents in the class of direct oral anticoagulants (DOACs) in recent years has expanded options for patients undergoing cardioversion. Dabigatran (Pradaxa®) was the first DOAC approved in 2010 for stroke prophylaxis in patients with non-valvular atrial fibrillation. DOACs are an attractive option overcoming the limitations of warfarin as they do not require INR monitoring.

There is limited literature comparing the use of warfarin to dabigatran for anticoagulation associated with cardioversion, although the 2012 CHEST guidelines recommend dabigatran as an option for anticoagulation prior to DCCV.[1] The Veterans Affairs (VA) criteria for dabigatran use, last updated in December 2014, lists warfarin as the standard of care for anticoagulation associated with cardioversion. This study intended to evaluate if dabigatran reduces the number of days from start of anticoagulation to cardioversion in our veteran population. Additionally, this study sought to observe rescheduling rates, adverse outcomes such as thromboembolic and bleeding events, and compare costs of anticoagulation between the two groups.

Key Words:
Cardioversion, DCCV, Dabigatran, Warfarin, Anticoagulation.

Disclosures:
None.

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Table 1: Patients undergoing elective direct current cardioversion receiving either warfarin or dabigatran

	Total Sample (N=68) mean (SD) median (min-max)	Warfarin (N=30, 44.1%) mean (SD) median (min-max)	Dabigatran (N=38, 55.9%) mean (SD) median (min-max)	P-value
Age	67.5 (8.6) 68.0 (41-89)	69.3 (7.5) 68.5 (59-89)	66.1 (9.2) 68.0 (41-83)	0.43
CHADS2	1.72 (0.98) 2 (0-4)	1.67 (1.03) 2 (0-3)	1.76 (0.94) 2 (0-4)	0.80
HASBLED	2.16 (0.94) 2 (0-4)	2.03 (0.93) 2 (0-4)	2.26 (0.95) 2 (1-4)	0.35
Time to cardioversion (days)	58.0 (37.6) 43.5 (22-183)	78.8 (40.4) 66.5 (32-183)	41.6 (25.6) 34.5 (22-148)	<0.01

Methods

Study Design

This retrospective observational study was approved by the local institutional review board at the Central Texas Veterans Health Care System. Data was collected by retrospective chart review. Patients were included if they received DCCV between January 2010 through January 2015, were started on warfarin or dabigatran with a plan for elective cardioversion, and were between 18-89 years old. Patients were excluded if they underwent pharmacologic cardioversion, emergent cardioversion, or early transesophageal echocardiogram (TEE) based cardioversion.

Anticoagulation

Anticoagulation was initiated by physicians, and follow-up was monitored through an anticoagulation service managed by clinical pharmacists and clinical pharmacy technicians. For warfarin patients, clinical pharmacists conducted the initial visits and reviewed all subsequent INRs. Patients were responsible for arriving to the nearest laboratory when requested by the anticoagulation clinic and were contacted by telephone if an INR was above or below goal range. For dabigatran patients, pharmacists did the initial medication counseling, and clinical pharmacy technicians provided telephone follow-up at approximately two weeks and one month after initiation. Pharmacy encounters were documented in 15-minute increments which were used to calculate the cost of clinical time associated with monitoring anticoagulation. In addition, lab assay costs, lab technician costs, and medication costs were factored in the total cost of anticoagulation. Data used for the cost analysis was collected from the start of anticoagulation to the end of the required four-week period following cardioversion.

Statistical Methods

Descriptive statistics were calculated for age, $CHADS_2$ and HASBLED scores, and the number of days to cardioversion. Bivariate analyses were used to assess underlying differences among patients receiving the two anticoagulants. Two-sample independent T-tests were used for total cost, and the nonparametric Wilcoxon rank-sum test was used for other continuous measures. Fisher's exact test was employed to compare categorical outcomes due to small expected cell counts (less than 5). A type I error of $\alpha = 0.05$ was assumed for all tests. All analyses were performed using SAS, Version 9.2 (Cary, NC).

Results

Out of 258 patients reviewed, a total of 68 patients fulfilled the inclusion criteria and were included in the analysis. Patients were all male with a median age of 68 years (Table 1). The median $CHADS_2$ score was 2 and the median HASBLED score was 2. The median time from initiation of anticoagulation to cardioversion for all patients was 44 days.

A total of 30 patients (44%) received warfarin and 38 patients (56%) received dabigatran. In the warfarin group, the time from initiation of anticoagulation to cardioversion was significantly longer than dabigatran (median 67 vs. 35 days; p<0.01). There were no thromboembolic events in either anticoagulation group. There was one bleeding event in the warfarin group manifested by hematuria resulting in hospitalization and discontinuation of warfarin prior to completing four weeks of anticoagulation after cardioversion. There were no bleeding events in the dabigatran group. Three patients (10%) in the warfarin group had their cardioversion rescheduled (p=0.08). Two of these three patients had documented subtherapeutic INRs resulting in rescheduling of the cardioversions.

The warfarin group had more pharmacist visits (median 8 vs. 2; p<0.01) and technician visits (median 3.5 vs. 2; p<0.01). Medication costs were higher for patients receiving dabigatran than warfarin (median $141.90 vs. $4.83; p<0.01). However, the total costs of anticoagulation, which included drug costs, pharmacist and technician time, and lab costs, averaged $183.50 for warfarin and $193.20 for dabigatran (p<0.01); (Table 2). Patients on warfarin had an average of 11 INRs checked from initiation of anticoagulation to the end of the required four week period following cardioversion.

Discussion

The results of this study show that in patients with AF or atrial flutter undergoing DCCV for restoration of sinus rhythm, dabigatran significantly reduces the number of days from initiation of anticoagulation to cardioversion compared to warfarin. Both groups in this study had similar background characteristics such as mean age, male gender, and $CHADS_2$ or HASBLED scores. These results were similar to those of a study from another VA health system which found that dabigatran significantly reduced the median number of days to cardioversion by 33 days and had similar overall costs compared to warfarin.[6] Similar conclusions were also made in a limited number of studies using non-veteran populations.[7,8] One of these studies concluded that dabigatran improves the efficiency of an elective DCCV service by significantly lowering the rates of rescheduling compared with warfarin (9.7% vs. 34.4%) and reduces the time between initial assessment and DCCV by an average of 22 days.[8] In addition to the obvious improvements in efficiency, these findings have a meaningful impact on clinical practice as studies have suggested that success of electrical cardioversion is inversely related to duration in AF.[9]

Reasons observed for rescheduling in the warfarin group included subtherapeutic INRs and patient unavailability. The rescheduling rate in the warfarin group of our study was lower than those found by other studies previously mentioned,[6,8] which may be a result of different scheduling procedures between health care systems. Another reason may be a selection bias since several patients were included in the dabigatran group that had been converted from warfarin due to variable or subtherapeutic INRs. For these patients, measuring rates of rescheduling in this study did not adequately capture the delays in cardioversion related to subtherapeutic INRs.

There were no statistically significant differences in thromboembolism and bleeding events in this study, which has been

Table 2: Cost comparison between warfarin and dabigatran

	Warfarin (N=30, 44.1%) mean (SD) median (min-max)	Dabigatran (N=38, 55.9%) mean (SD) median (min-max)	P-value
Pharmacist visits (per 15min)	9.3 (4.7) 8.0 (4-26)	2.2 (0.4) 2.0 (2-3)	<0.01
Technician visits (per 15min)	3.7 (2.8) 3.5 (0-12)	1.9 (0.4) 2.0 (0-2)	<0.01
INR counts	11.2 (4.4) 11.0 (5-23)	n/a	
Medication costs ($)	5.40 (2.04) 4.83 (2.85-10.97)	158.10 (58.08) 141.9 (113.5-399.90)	<0.01
Total costs ($)	183.50 (95.02) 157.80 (59.65-410.20)	193.20 (59.38) 175.40 (145.60-441.10)	<0.01

demonstrated in previous studies.[10-12] A large post-hoc analysis of the RE-LY study demonstrated that dabigatran appeared no worse than warfarin for thromboembolic and bleeding outcomes in patients undergoing both electrical and pharmacologic cardioversion.[11] Another retrospective analysis confirmed no statistically significant differences in thromboembolic and bleeding events with dabigatran versus warfarin.[12] A meta-analysis comparing all DOACs, including dabigatran, rivaroxaban, apixaban, and edoxaban, to warfarin for cardioversion found no significant differences in thromboembolism, stroke, or major bleeding between groups.[13]

The numbers of technician and pharmacist encounters documented in 15-minute increments were significantly fewer in the dabigatran group due to absence of INR monitoring. The total cost for warfarin therapy was slightly lower than the total cost for dabigatran therapy. However, the cost analysis did not factor in phlebotomist costs or indirect costs such as the patients' time off work and travel costs for INR monitoring. Also, additional pharmacist time was probably required to review technician notes and telephone calls, and this was not measurable through chart review. As a result, the actual total costs of warfarin are likely higher than estimated, and the minor increase in cost of dabigatran found in this study is negligible when considering other factors.

This study is especially meaningful for the VA health care systems which are focused on improving timely access to care. Measures that will achieve clinical goals in a shorter time frame and reduce rescheduling rates are needed. Utilizing dabigatran in place of warfarin in the appropriate patients will achieve the goal of cardioversion in a shorter amount of time, reduce patient visits, travel costs, phlebotomist and pharmacist time, and rescheduling, thereby increasing available appointments in VA hospitals and improving efficiency and access to care.

The major limitation of this study is that it is a retrospective, single-center study with a small sample size. Many patients were excluded because they were already established on anticoagulation for a period of time prior to the decision to perform elective cardioversion, or they received TEE-based cardioversion. A lengthy time period of 61 months was required to obtain sufficient data, and many of the warfarin patients in this sample had cardioversion prior to the availability of dabigatran at the studied facility.

Conclusions

Dabigatran significantly decreases the number of days from initiation of anticoagulation to cardioversion, as compared to warfarin, with a minor increase in total costs. Implementation of dabigatran as the preferred agent in VA and other health care systems may improve timely access to care and make elective cardioversion services more efficient.

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Effects of Atrial Fibrillation Cardioversion after Percutaneous Mitral Balloon Valvuloplasty on Echocardiographic Left and Right Atrial Functions

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Abstract

Amongst patients with mitral stenosis (MS), the most common complication is AF.Our study aimed at evaluating the effect of AF cardioversion after Percutaneous Mitral Balloon Valvuloplasty (PMBV) on echocardiographic atrial functions.

The study included 34 patients with MS and AF, presenting to Ain-shams University hospitals, who underwent successful PMBV then randomized into 2 different groups according to AF management strategy. Group-I patients (n=16) received DC cardioversion after amiodarone infusion (within 24 hours post-PMBV) in addition to anticoagulation. Group-II patients (n= 18) were kept on the rate control strategy for AF and anticoagulation. Atrial functions were evaluated by echocardiography before and 48-72 hours after PMBV.

Both groups were homogenous regarding demographic, clinical and echocardiographic data before PMBV. Both groups showed significant improvement in MVA (Group-I: 0.953 ± 0.144cm2 to 2.26 ± 0.463cm2, p=0.000, Group-II: 0.942 ± 0.171cm2 to 1.95 ± 0.40cm2 , p=0.0000), left atrial emptying fraction (Group-I:16.11 ± 6.93% to 26.16 ± 5.51%, p=0.000 , Group-II: 18.49 ± 5.47% to 26.12 ± 7.68%, p=0.002), left atrial function index (Group-I: 4.48 ± 2.32 to 6.84 ± 3.35, p=0.001 , Group-II: 3.34 ± 1.42 to 7.80 ± 4.17, p=0.006) as well as estimated systolic pulmonary artery pressure (Group-I: 49.06 ± 13.86 to 38.25 ± 7.29, p=0.01 , Group-II: 53.44 ± 14.52 to 39.88 ± 10.67, p=0.003). For group-I patients, reduction in left atrial end-diastolic volume was significant (120.84 ± 32.82 mL to 95.31 ± 19.27mL, p=0.012) and TAPSE showed significant improvement (17.57± 4.96 to 21.08 ± 2.52,p=0.018). When percentage improvement in variables was compared between both groups, none of the indices used to evaluate atrial functions showed any significant difference between both groups.

Atrial functions improve post-PMBV. No additional improvement in atrial functions occurs after cardioversion in patients who have already undergone PMBV, at least within 72-hours.

Introduction

Atrial fibrillation is the most common sustained cardiac arrhythmia and its prevalence is ~1–2% of the general population, but higher with increasing age and in patients with concomitant heart disease especially mitral valve diseases.[1] Amongst patients with MS, the most common complication is AF.[2] Despite declining incidence of rheumatic heart disease worldwide, it remains the most common cause of MS.

Mitral stenosis is a disease of plateaus[4] it takes 1 to 2 decades after the onset of rheumatic fever before signs of MS appear, followed by another period of 1 to 2 decades before mild symptoms occur. During this time, the onset of AF may cause further decompensation, beginning of AF is a fundamental moment in MS which is often caused by atrial inflammation and remodeling. AF occurs in 40–75% of patients who are symptomatic for MS, precipitates such symptoms, greatly increases the risk of systemic embolization, and reduces cardiac output and exercise capacity.[5] Systemic embolization most often occurs in patients with AF and MS.

Protection of the sinus rhythm in patients with MS is very important for reduction the risk of cerebral embolism, conservation of cardiac output and exercise capacity, and reduction of symptoms.[3]

On reviewing the literature, we didn't find any study that evaluated atrial functions by echocardiography in patients cardioverted to sinus rhythm after PMBV. In this study, we aimed at evaluating the effect of AF cardioversion post-PMBV on echocardiographic atrial functions.

Patients and Methods

The study included 34 patients with MS and AF who all underwent a successful PMBV (from November 2011 to December 2013) then randomized into 2 different groups according to the AF management strategy:

1. Group-I patients (n=16) received DC cardioversion after amiodarone infusion (within 24 hours post-PMBV) in addition to anticoagulation.

Key Words:
Mitral Stenosis, Atrial Fibrillation , Cardioversion.

Disclosures:
None.

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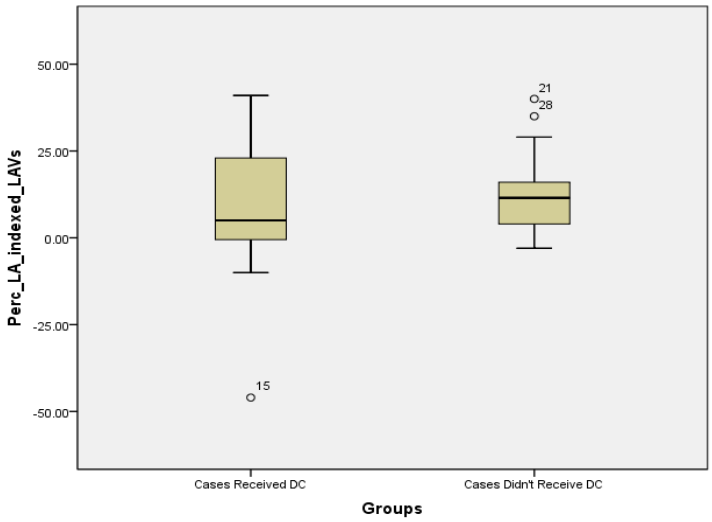

Figure 1: Comparing Percentage Change in LAFI between both groups

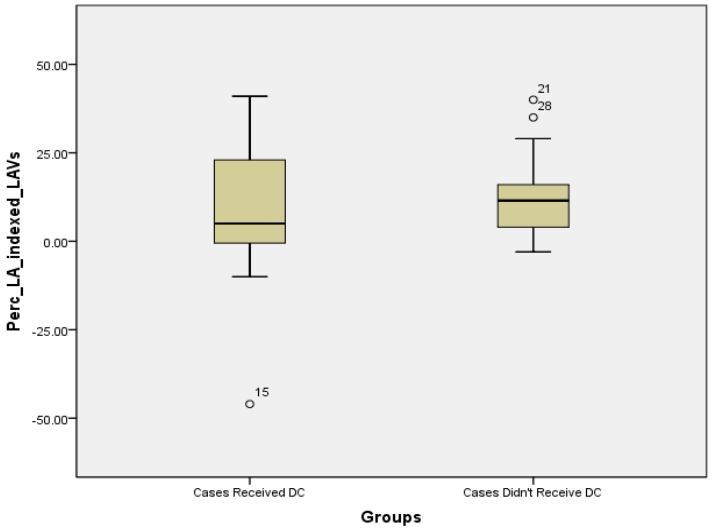

Figure 2: Comparing Percentage Change in indexed LAVs between both groups

2. Group-II patients (n= 18) were kept on the rate control strategy for AF as well as anticoagulation. Atrial functions were evaluated by echocardiography before and 48-72 hours after PMBV.

All Patients Were Subjected To The Following

- Proper history taking, thorough clinical examination.
- Routine laboratory investigations including INR, as well as an ECG.
- Conventional 2D Echocardiography: was performed using GE Vivid S5 machine. It was done before and 48-72 hours after PMBV (and DC for group-I). it included:

Thorough assessment of MVA, mean PG, Wilkin's score, presence and degree of other valvular lesions especially mitral regurgitation, tricuspid regurgitation.[6]

Thorough assessment of left atrial (LA) and right atrial (RA) volumes (end-systolic volume "ESV" and end-diastolic volume "EDV")[7] and emptying fraction (EF). For left atrium, a rhythm-independent index was calculated; the left atrial function index (LAFI) as below:[8]

Statistical Analysis

All data were gathered, statistically analyzed and tabulated. All numerical variables were expressed as mean ± standard deviation (SD), and categorical variables were expressed as percentage (%). Changes in continuous variables were evaluated with the paired t-test or Mann Whitney test. For all analysis a P value of < 0.05 was considered statistically significant.

Results

Both groups were homogenous regarding demographic, clinical and echocardiographic data before PMBV with no significant differences that might have confounded the results post-PMBV.

There were significant changes in some variables some within the same group following PMBV. Both groups showed significant improvement in MVA (Group-I: 0.953 ± 0.144cm2 to 2.26 ± 0.463cm2, p=0.000, Group-II: 0.942 ± 0.171cm2 to 1.95 ± 0.40cm2 , p=0.0000) , left atrial emptying fraction (Group-I: 16.11 ± 6.93% to 26.16 ± 5.51%, p=0.000 , Group-II: 18.49 ± 5.47% to 26.12 ± 7.68%, p=0.002), left atrial function index (Group-I: 4.48 ± 2.32 to 6.84 ± 3.35, p=0.001 , Group-II: 3.34 ± 1.42 to 7.80 ± 4.17, p=0.006) as well as estimated systolic pulmonary artery pressure (Group-I: 49.06 ± 13.86 to 38.25 ± 7.29, p=0.01 , Group-II: 53.44 ± 14.52 to 39.88 ± 10.67, p=0.003).

For group-I patients, reduction in left atrial end-diastolic volume was significant (120.84 ± 32.82 mL to 95.31 ± 19.27mL, p=0.012) and also TAPSE showed significant improvement (17.57± 4.96 to 21.08 ± 2.52, p=0.018).

However, when the percentage improvement in variables was compared between both groups, none of the indices used to evaluate atrial functions showed any significant difference between both groups. This might mean that AF cardioversion after PMBV has no additional effect on atrial function, at least within 72 hours. (table1, figures 1,2)

$$\text{Left atrial function Index (LAFI)} = \frac{\text{LA emptying fraction} \times \text{LVOT VTI (cm)}}{\text{LAESV indexed to BSA (cc/m}^2\text{)}}$$

LAFI units = (cm) x (m^2) /cc (ie units cancel out)
LVOT VTI = velocity time integral of the left ventricular outflow tract (cm)
LAESV = maximal left atrial volume in end systole (cc)
BSA = body surface area

LAEF (LA emptying fraction) = [(LAESV-LAEDV)/LAESV] X 100

Discussions

The main objective of our study was to compare between the percentage improvements in atrial functions in both study groups. We aimed at studying the effect of cardioversion of AF on atrial functions in such very high risk group (i.e having moderate to severe MS as well as AF of long duration and thus expected to have the worst atrial functions). Those high risk patients are the most symptomatic patients and the most vulnerable ones who actually need more treatment options. However, none of the indices used to evaluate atrial functions showed any significant difference between both groups. The exact explanation for such results couldn't be fully addressed.

To the best of our interest, no other studies were designed to evaluate atrial functions by echocardiography after AF cardioversion post-PMBV. Nevertheless, there were studies to evaluate atrial functions following each procedure separately, that is, following AF cardioversion or following PMBV alone.

One study[9] included 41 patients with chronic AF (including 7

patients with moderate to severe MS). In the 28 patients who maintained sinus rhythm after 6 months, significant improvements were found in LA and RA volumes and dimensions. The echocardiographic re-assessment in our study was done much earlier, This point may highlight the issue of both the occurrence of atrial stunning (i.e delay in the onset of organized atrial contraction after a successful cardioversion of AF) post-cardioversion as well as the need for time for the occurrence atrial reverse remodeling and hence, improvement in atrial volumes and functions

Reviewing the available literature revealed more or less agreement on the presence a time-course following cardioversion during which gradual improvement of atrial functions occurs before reaching a plateau. The exact time-course varied from a study to another, but ranged from few weeks to few months post-cardioversion. However, the issue of occurrence of atrial stunning and its duration post-cardioversion is still an area of debate in the literature. Whereas some studies highlighted the importance of the hemodynamic effect of atrial stunning, other studies refuted its hemodynamic significance.

Some studies[10] claimed almost complete recovery of atrial functions within 24-hour after cardioversion. However, that study excluded valvular AF and > 50% had AF for less than 4 weeks. Other studies reported significant improvement in LA function immediately after cardioversion, with subsequent further improvement over time, as the case in the cohort of Thomas et al.[8] which adopted and validated the LAFI as a rhythm-independent index for LA function.

On the other hand, other studies showed dissociation of right and left atrial recovery following AF cardioversion. One study[11] found that the right atrium resumed its mechanical function immediately after cardioversion, whereas the left atrium was stunned beyond day 7.

Last and not least, there are studies that suggested that improvement in atrial functions following cardioversion is related to the AF duration pre-cardioversion. One of these studies[12] found that left atrial mechanical function is greater immediately, after 24 hours and after 1 week in patients with brief AF duration compared with those with prolonged AF.

Limitations

• Lack of further serial follow up especially echocardiographic studies that might have limited our ability to study the real effect of AF cardioversion post-PMBV on atrial function.

• It included a single medical center (Ain Shams University hospitals).

• Small number of patients included in the study (34 patients).

Conclusions

• Improvement in atrial function in patients who have undergone AF cardioversion post-PMBV doesn't occur early, at least within the first 72 hours.

• The PMBV per se lead to significant immediate improvement in LAEF, LAFI and systolic PAP.

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Malignancy Associated Iatrogenic Iliopsoas Abscess -Venous Access Complication From Ablation Procedure

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Abstract

Iliopsoas abscess is a rare condition with a high rate of mortality and morbidity if left untreated. It can occur from hematogenous or lymphatic spread from distant structures or as a result of contiguous spread from adjacent structures. The disease typically occurs in patients with immunocompromised status and the symptoms can be non-specific.[1,2] Generally, infectious complications from venous access during atrial fibrillation (AF) procedure are uncommon, and an iatrogenic iliopsoas abscess from percutaneous cardiac procedures has never been reported. We present the first case of iliopsoas abscess from an ablation procedure.

Case Report

A 64-year-old Caucasian male with history of coronary artery disease, persistent AF, hypertension, and peripheral vascular disease was admitted for AF ablation. Surgical history includes aortobifemoral bypass and multiple hip arthroplasties due to trauma 15 years ago. He does not have a history of intravenous drug use (IVDU), inflammatory bowel disease (IBD), or any other immunocompromising conditions.

During the procedure, routine bilateral femoral and right internal jugular veins were used for intravenous access. After standard aseptic method, a modified seldinger technique was used for all venous access. A duo-decapolar deflectable catheter was advanced to the coronary sinus and the lateral right atrium through an 8-F short sheath in the right internal jugular vein. An 11- French (F) AcuNav "Siemens" catheter was advanced via the left femoral vein to guide the transseptal punctures. On the right femoral vein, a 3.5mm "Thermocool SmartTouch" ablation catheter and 20mm "Lasso" circular mapping catheter were advanced to the left atrium through 8.5-F and 8-F SL-1 sheaths, respectively. At the end, the catheters were removed and the long SL-1 sheath was exchanged for short sheaths. The sheaths were then removed and a manual pressure was performed until adequate hemostasis. During his stay, he did well without any complication or access issue. Standard groin care instructions were given.

One week after the procedure, the patient developed left groin pain radiating to the left knee. The patient denied any fever, weight loss, night sweat, chills or rigors. A conservative management using NSAIDs was opted. The pain continued to worsen prompting an emergency room (ER) visit. On ER presentation, his vital signs were within normal limits. Physical examination was positive for pain on the left hip that was exacerbated by palpation. A 3 x 8 cm area of erythema and tenderness on the left flank was noted. The femoral vein area was thoroughly examined. The area was well healed without any sign of infection. Cardiovascular examination was negative for murmur. Laboratory examination revealed mild leukocytosis (WBC=14.5 K/uL). Other important pertinent laboratory tests include ESR (53 mm/hr), CRP (10.51 mg/dL), Creatinine (1.59 mg/dL), Lactate (1.3 mmol/L) and Creatine Kinase (46 U/L). Urinalysis was unremarkable. CT scan of the abdomen revealed an approximately 6 cm multiloculated fluid collection arising from the iliac involving the left psoas, iliacus, and quadratus lumborum muscles (Figures 1 and 2). In addition, a curvilinear, soft tissue density mass in the central mesentery measuring 2.5 x 6.4 cm was also found. The vascular grafts from prior procedures were widely patent. CT guided abscess aspiration and drain placement were performed. Prior to the culture data, the patient was treated empirically with vancomycin and piperacillin/tazobactam. Microbiology examination revealed Eschericia coli and Prevotella loeschii. The flow cytometry did not reveal any malignancy. The patient was treated according to

Key Words:
Psoas Abscess, Ablation, Femoral Venous Access, Peripheral Vascular Disease.

Disclosures:
None.

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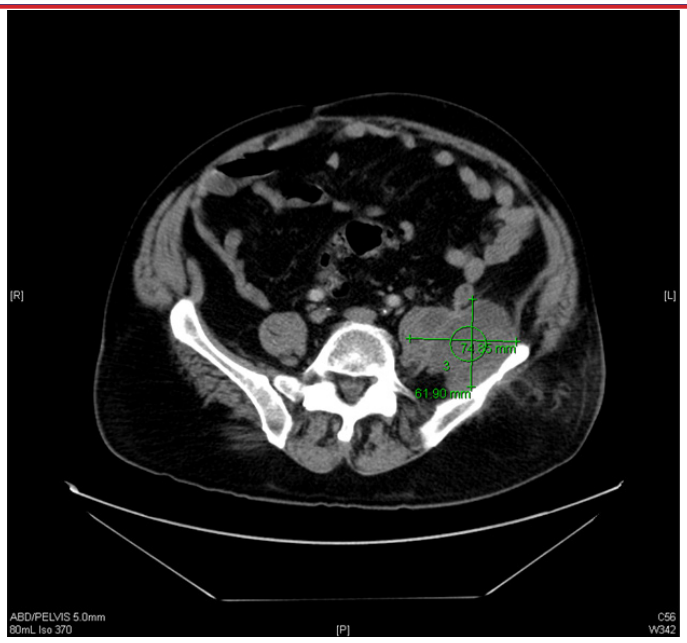

Figure 1: Transverse section of the CT shows multiloculated fluid collection arising from the left iliac fossa measuring ~ 6.2 x 7.5 cm involving the involving the left psoas, iliacus, and quadratus lumborum muscles

the culture and sensitivity data with ertapenem 1 gram daily from the time of drain removal for a total of two weeks. The patient remained stable and was discharged with a close follow-up. The patient was scheduled for biopsy of the suspicious mass in the central mesentery.

Two months after the ablation procedure, the patient was seen in electrophysiology clinic for follow-up. At that time, he had finished the antibiotic course and felt well. From a cardiac standpoint, he remained asymptomatic from his AF after the ablation procedure. Despite lack of symptoms, due to the significant size of the mesenteric mass, the patient underwent exploratory laparotomy and biopsy of the suspicious mass as planned. Pathology examination confirmed grade 1-2 (low grade) follicular lymphoma. The patient subsequently had PET scan for staging purpose. There was no other suspicious lesion identified and the retroperitoneal abscess previously drained a couple months earlier had improved, consistent with a positive response to antibiotics. The patient was referred to an oncologist for further treatment. Due to the indolent nature of this lymphoma, close follow-up with imaging was recommended; however, no treatment was necessary at this stage.

Discussion

Iliopsoas abscess is rare and typically occurs in a high-risk population such as patients with diabetes, malignancy, HIV, IV drug users, and other immunocompromising conditions. It can be classified as primary or secondary. Primary psoas abscess typically involves hematogenous or lymphatic spread from a distant site.[1,2] It is typically monomicrobial with Staphylococcus aureus as the most common organism.[3] The rich blood supply of the iliopsoas muscles predisposes it to the primary infection.[4] Secondary psoas abscess, on the other hand, occurs from contiguous spread from an adjacent infectious area.[5] This is typically polymicrobial infection involving enteric bacteria from gastrointestinal tract, genitourinary tract, and vasculature.[4]

In this case, malignancy is one of the possible risk factors that likely contributed to the immunosuppressive state and predisposed him to develop iliopsoas abscess. As described in some case reports, malignancy can often mimic psoas abscess;[6-8] however, these patients typically did not improve with antibiotics. On the other hand, colorectal malignancy, inflammatory, or any infectious process in the colorectal area, although uncommon, can cause micro-perforation with subsequent gut bacteria leakage causing abscess formation. However, in this case, there was no evidence to support this process as a mechanism; therefore, considering the timing of presentation post ablation procedure, we believe this was caused by vascular access contamination.

There were only two reported cases of iliopsoas abscess as a complication of vascular access. These involve central venous catheter (CVC) and dialysis catheter. Kwok et al. reported psoas abscess from subclavian central venous catheter.[9] Similarly, Hsiao et al. reported iliopsoas abscess from tunneled jugular vein catheterization in a hemodialysis patient.[10] On both of these cases, the catheter was placed >72 hours, whereas in our case, the access catheters were only placed for less than four hours.

Most venous access complications in electrophysiology procedures involve superficial skin and subcutaneous infections, hematoma, pseudoaneurysms, and arterio-venous fistula. Infectious complication from femoral arterial access during the cardiac catheterization procedure is estimated to be less than 0.1%.[11] Femoral access complications are often associated with location of puncture, number of attempts, catheter material, and catheter size. Other possible causes include compromised technique, poor hygiene, prolonged indwelling sheath time, and the femoral access closure device.[12-15]

Possible sources of infection associated with CVC include colonization of the skin, intraluminal contamination, and rarely contamination of the infusion fluid.[16] Biofilm depositions on the internal and external surface of vascular catheters play an important role in the colonization process.[17] Intraluminal contamination typically occurs when the catheter is in place for more than two weeks or in patients with implanted devices.[18] Contamination of infusion fluid generally involves gram-negative bacilli.[16] Our case is unique in several ways: first, the access site was without any sign of infection, and most importantly, the catheter was only placed for a

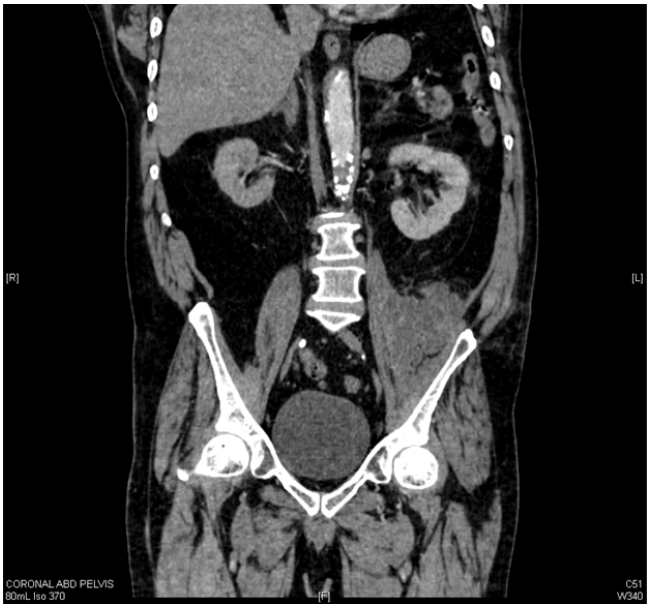

Figure 2: Coronal section of the abscess

short period of time.

It is unclear whether our case represents primary or secondary infection. Although the negative blood culture and the type of microorganism point towards secondary infection as a cause, the presence of infection foci and the subsequent contiguous spread were not evident. Besides malignancy, other possible reasons that could have predisposed this patient to this condition are the presence of a foreign body implantation such as a vascular graft and his history of multiple pelvic surgeries involving bone grafts, although these structures did not appear to be infected from the CT scan. In this case, perhaps his altered pelvic anatomy predisposed him to develop retroperitoneal infection.

Conclusions

This case report highlights the importance of careful vascular access preparation to prevent contamination and raise awareness that fatal vascular access complication can occur. Electrophysiologists should be aware of the risk factors associated with infection and should further evaluate patients, especially when pain develops late after the ablation procedure.

Key Teaching Points

• Psoas abscess is rare and typically occurs in patients who are immunocompromised.

• Infectious complication from vascular access, associated with ablation procedure, is rare but can be fatal if not diagnosed early.

• The symptoms of psoas abscess are non-specific and highly variable; therefore, a high index of suspicion is needed.

• Altered pelvic anatomy and the presence of a foreign body from a medical device implantation may predispose patients to develop psoas abscess.

• Electrophysiologists should re-evaluate and perform detailed examinations in patients who complain of worsening groin or pelvic pain after the ablation procedure.

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Shock Lead Dislodgement Related To Its Small Hair-Pin Curve In A Pocket -A Case Of Ratchet Syndrome

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Abstract

There have been few reports about ratchet syndrome. We report a case of ratchet syndrome caused by small hair-pin curve of lead that triggered the lead retract itself. A 69-year-old man with a past history of inferior wall myocardial infarction, presented with progressive congestive heart failure. He underwent implantation of cardiac resynchronization therapy with an implantable cardiac defibrillator (CRTD) at our hospital. At 33 days after implantation, shock lead dislodgement was revealed. X-ray showed that the lead tip was in left subclavian vein, leaving its screw out, and a large part of the proximal portion of the lead was retracted into the pocket, while the other two leads remained in appropriate positions and the device had not rotated. An X-ray series showed that a hair-pin curve had been expanding gradually from just after implantation. In this case, relatively stiff shock lead was markedly bent and expanded the curve in the pocket, and ratchet-like movement occurred. We here report a new type of ratchet syndrome.

Introduction

Lead dislodgement is an unusual complication and a significant dangerous occurrence. Twiddler syndrome and reel syndrome, consisting of lead dislodgement caused by generator rotation on its long axis and transverse axis, respectively, have been previously reported.[1-3] Ratchet syndrome is another mechanism of lead retraction, caused by ratchet-like movement of the lead through the suture sleeve.[3,4] We here report a case of ratchet syndrome caused by a small hairpin curve of the lead.

Case Report

Patient was a 69-year-old man. He had inferior wall myocardial infarction in 2000 and progressive congestive heart failure despite appropriate medical therapy. He had New York Heart Association class III heart failure, with ejection fraction of 27%. PQ interval was 281 ms (first degree atrioventricular block) and QRS durations was 131 ms. CRT-D (cardiac resynchronization therapy with an implantable cardiac defibrillator, QUADRA ASSURA, St. Jude Medical, St. Paul, MN, USA) was performed in October 2014 at our hospital. In this case, extrathoracic puncture technique was used. The lead insert site and the pocket site were separated, and leads were connected to the device through a subcutaneous tunnel. Passive fixation lead Quaretet model 1458-85, SJM was positioned in the lateral cardiac vein for left ventricular pacing. Active fixation lead Optisense model 1999-52, SJM was positioned in the right atrial appendage. Active fixation shock lead Durata model 7122Q-58, SJM was positioned at right ventricular apex. The threshold of the shock lead was 0.5 V, and amplitude was 11.7 mV after the operation. At 24 days after implantation, the patient heard repeated alarms from his chest and had hiccups lasting two days, which suggested phrenic nerve stimulation. When he attended our hospital for routine follow-up at 33 days after implantation, shock lead dislodgement was found. Right ventricular capture failed at maximum output. No ventricular electrogram was detected. Stored telemetry data showed that shock lead noise was increased from 24 days after implantation, which indicated lead detachment from the endocardium.

Chest X-ray showed that the shock lead tip was positioned in left subclavian vein and the proximal portion of the lead was retracted into the pocket. However, the other two leads remained in appropriate positions and the generator was not rotated in the pocket (Fig. 1). Surgical revision was performed 6 weeks after first implantation. The operative findings showed that, the generator was fixed on the fascia, and the atrial lead and left ventricular lead were covered with tissue behind the pocket (Fig. 2); however, the shock lead showed no adhesion to tissue and could be moved in the pocket. Each sleeve was secured by one suture to the original position. However, the shock lead slipped in the sleeve when it was pulled. There was no damage of

Key Words:
Dislodgement, CRT, Ventricular, Proximal.

Disclosures:
None.

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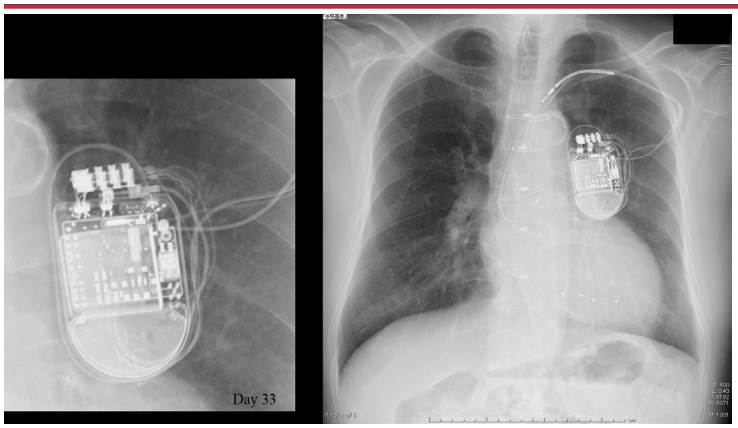

Figure 1: Chest X-ray showed shock lead dislodgment at 33 days after implantation. The shock lead tip was in the left subclavian vein, while the other leads and pulse generator remained in the original positions

the lead, and it was successfully repositioned at the right ventricular apex. After reoperation, there were no subsequent problems. A small hair-pin curve of the shock lead in the pocket was found in the present case. Differences in the length of each lead caused the small hair-pin curve in the pocket. An X-ray series showed that the hair-pin curve had been expanding gradually from just after implantation (Fig. 3).

Discussion

In this case, a large part of the proximal portion of the lead was retracted into the pocket, but the generator was fixed in the pocket and had not rotated. The mechanism in this case is completely different from that of reel syndrome and twiddler syndrome. Ratchet syndrome is due to ratchet-like movement of the lead in the sleeve. When ligation of the suture sleeve is insufficient, the pendula-like movement of the generator due to movement of the arm may cause ratchet syndrome.[4-6] The relatively stiff shock lead was markedly bent and could expand the hair-pin curve in the pocket (Fig. 4). It cannot be denied the possibility that the hair-pin curve became a trigger to pull the lead. Once ratchet-like movement occurred in the suture sleeve due to the hair-pin curve, the lead could slide into the pocket repeatedly. In order to avoid ratchet syndrome, it is important not only to ligate the suture sleeve firmly, but also to avoid such a small hair-pin curve. As the DF4 lead is very stiff around the connecter, it may easily induce pendulum-like movement. As the atrial and left ventricular leads were strongly fixed behind the pocket, ratchet syndrome could not occur in these leads. This in a case of ratchet syndrome, not reel syndrome. We considered the other cause is the material of the lead. In previously reported cases, the material of the dislodged leads was polyurethane or silicon-polyurethane copolymer

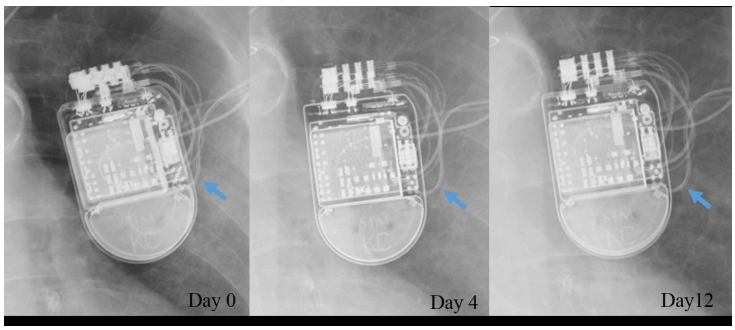

Figure 3: X-ray series showed that a hair-pin curve of the shock lead had been expanding gradually from just after implantation

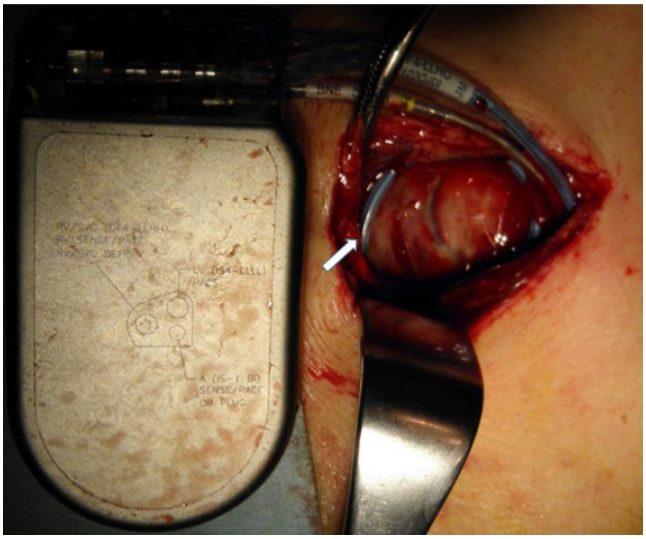

Figure 2: At operation, the generator was fixed on the fascia, and the atrial lead and left ventricular lead were covered with tissue behind the pocket; however, the shock lead showed no adhesion to tissue and could be moved in the pocket (white arrow)

.[4,7,8] Our present case also had a polyurethane lead. Polyurethane has a surface lubricity and a low coefficient of friction compared to silicon. The less friction between the lead and the sleeve, the more slippery inside the sleeve.

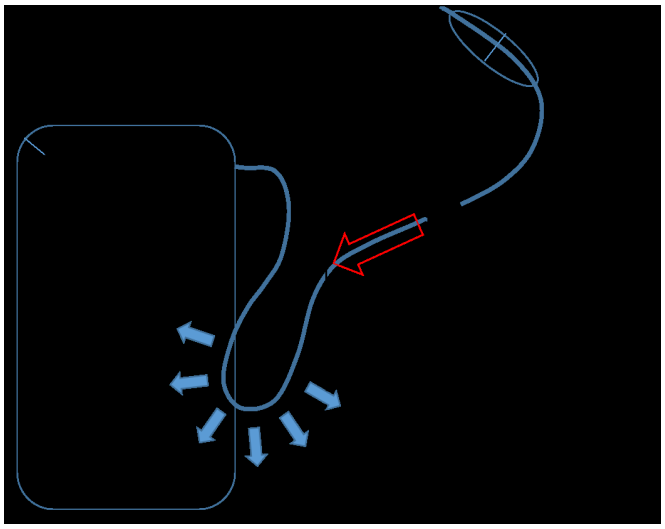

Figure 4: The relatively stiff shock lead was markedly bent and expanded the curve in the pocket, and consequently pulled the lead into the pocket, which caused ratchet-like movement in the suture sleeve, and the lead could slide into the pocket repeatedly

Conclusion

A small hair-pin curve may be one of the causes of ratchet syndrome.

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Persistent Atrial Fibrillation And Atrial Flutter Complicated By Tachycardiomyopathy Because Of Intermittent Conduction Through Accessory Pathway

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Abstract

The term tachycardiomyopathy refers to a specific form of tachycardia-related cardiomyopathy caused by supraventricular or ventricular tachyarrhytmias that are both associated with ventricular rates higher than 120 bpm. The arrhythmias which are most frequently associated with these forms of heart disease are atrial fibrillation and atrial flutter, particularly found in the elderly population. The most frequent clinical manifestation is heart failure. In this case we are reporting a clinical case of a patient that came to our attention because of an episode of heart failure associated with atrial fibrillation and atrial flutter. The patient had also prolonged and repetitive strips of rapid conduction with wide QRS morphology. We don't know if the cause is pre excitation or ectopia. We showed that those strips of tachycardia with wide QRS, particularly when they were associated with atrial flutter, were so fast and consistent to determine the left ventricular contractile dysfunction; we showed also that those strips of wide complex tachycardia were caused by pre-excitation through an accessory right posteroseptal pathway and supported by the reentry circuit of common atrial flutter. The block of conduction through the accessory pathway and the elimination of atrial arrhythmia allowed the regression of left ventricular contractile dysfunction. We believe that this case is interesting because it shows that there is a strict continuity between sophisticated electrophysiological mechanisms and clinical manifestation.

Introduction

The term tachycardiomyopathy refers to a specific form of tachycardia-related cardiomyopathy caused by supraventricular or ventricular tachyarrhytmias that are both associated with ventricular rates higher than 120 bpm. The arrhythmias which are most frequently associated with these forms of heart disease are atrial fibrillation and atrial flutter, particularly found in the elderly population. The most frequent clinical manifestation is heart failure.[1] Previous experiments with animals showed that the electrophysiological stimulation by atrial pacing leads to hemo- dynamic alterations, which appear early in the beginning of the 24 hours. These hemodynamic alterations are: the reduction of cardiac output and of ejection fraction, the increase of end diastolic intracavitary pressure and of peripheral vascular resistance. Furthemore these hemodynamic alterations appear to be linked to two factors: the duration/chronicity of the tachycardia and the mean ventricular frequency.[2] The diagnosis of these forms of heart disease can be not immediate. In fact, especially in the elderly population, the opposite is more frequent: heart failure, with the electromechanical feedback and the neurohumoral activation is responsible of atrial fibrillation.[3] Here we report the clinical case of a patient that came to our attention because of episode of heart failure associated with prolonged and repetitive strips of rapid conduction through an accessory pathway during atrial fibrillation and atrial flutter.

Key Words:
Accesory Pathway, Tachycardiomyopathy, Atrial Fibrillation.

Disclosures:
None.

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Case Report

G.C. is a 72 years old male. In 1991 he underwent a left pneumonectomy because of lung adenoma; seven years later a bilateral inguinal lymphadenectomy. In 2008, he had the first episode of atrial fibrillation, which was treated with electrical cardioversion; in 2011 he had his second arrhythmia treated with electrical cardioversion and antiarrhythmic prophylaxis therapy with dronedarone until another relapse in 2012. At this time neither clinical or echocardiographic signs of left ventricular dysfunction were present. A baseline 24 hours ECG recording showed some short stretches of wide-QRS tachycardia interpreted as non-sustained ventricular tachycardia. In 2012 the patient underwent a radio frequency pulmonary veins ablation with sinus rhythm restoration. He was assigned to antiarrhythmic therapy with amiodarone, digoxin and bisoprolol. In 2013 the baseline 24 hours ECG recording proved the persistence of

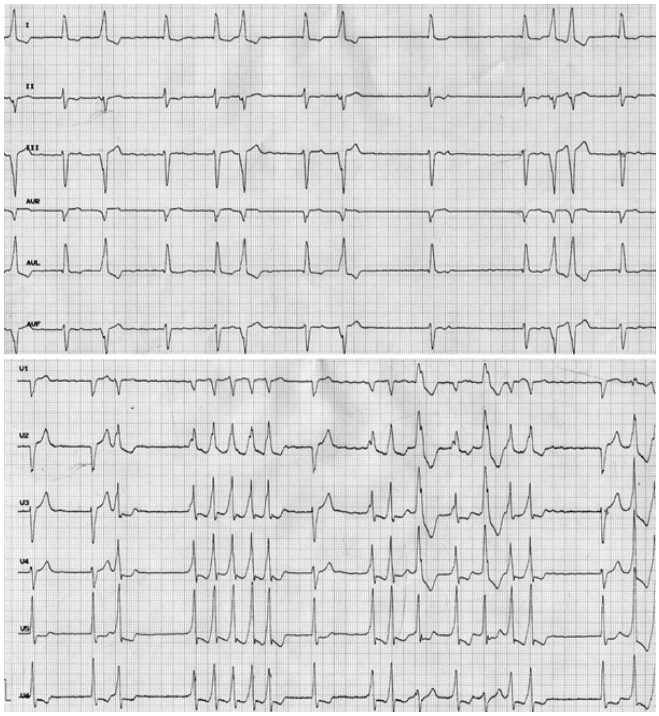

Figure 1: Atrial fibrillation with heart rate < 100 bpm alternating with strips of tachycardia with a wide QRS morphology, iterative, 3–10 sec in duration, with variable heart rate (ranging from 90 to 160 bpm), not showing critical coupling and Ashman Phenomenon

sinus rhythm and the disappearance of the strips of non-sustained ventricular tachycardia. In february 2015 he experienced another atrial fibrillation that was treated effectively with electrical cardioversion. A few weeks later the patient arrived in the Emergency Department because of dyspnoea and palpitations. The clinical examination showed the presence of rales > 50 % of the two lung fields and high jugular venous pressure. The brachial blood pressure was 120/80 mmHg, the body temperature was 36.7 C, the hourly diuresis was 20 cc/h, the heart rate was 98 bpm; the peripheral pulse oximetry was 88 %. The chest X ray showed alveolar oedema. The main laboratory parameters were: creatinine 1.9 mg/dl; hemoglobin: 12 mg/dL, Na: 134 mEq/L, K: 4.5 mEq/L, pH: 7:42, pO2: 86%, pCO2: 38, bicarbonates: 24, lactates: 0.9. The ECG examination showed the presence of atrial fibrillation with heart rate < 100 bpm. This arrhythmia was alternating with strips of tachycardia with a wide QRS morphology having suspected delta wave with negative polarity in limb leads and positive polarity in leads I, aVL, and V3 to V6. The strips were: iterative, appeared after the cycle lengthening, lasted 3-5 sec with variable heart rate ranging 90 - 160 bpm and without critical coupling (fig. 1). The echocardiogram showed a not dilated left ventricular with severe contractile dysfunction (EF 30 %), septal-to-posterior wall motion delay as a measure for LV dyssynchrony and moderate functional mitral regurgitation. The patient was initially treated with furosemide and oxygen with good clinical response and resolution of fluids overload. A few days later we planned to perform a coronary angiography that excluded the presence of coronary artery disease. Then we restored the sinus rhythm through the electrical cardioversion and we planned to perform the electrophysiological study for detailed diagnosis and treatment of the arrhythmia. The question was: is this arrhythmia a ventricular tachycardia or a pre-excited supra ventricular tachycardia ? However, the next day there

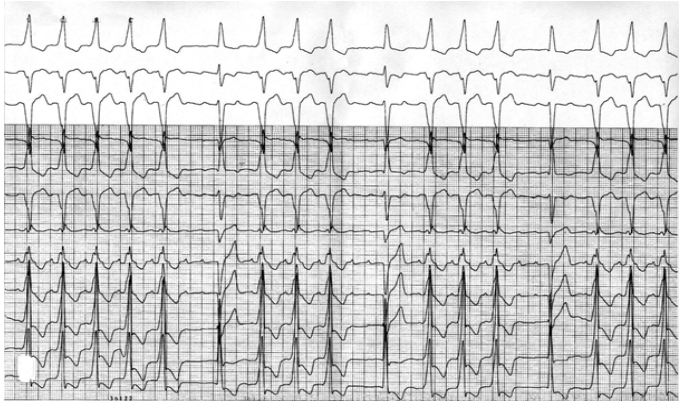

Figure 2: Atrial flutter steadily conducted to the ventricles with a 2.1 ratio and wide QRS totally pre excited, showing delta wave with negative polarity in limb leads and positive polarity in leads I, aVL and V3 -V6 suspected for conduction through a posteroseptal pathway

was a recurrence of typical atrial flutter that are conducted to the ventricles with a 2.1 ratio and wide QRS totally pre excited, identical in morphology to those present during atrial fibrillation and suspected of conduction through a posteroseptal pathway (fig. 2). With typical atrial flutter, the wide QRS conduction was costant, ranging 110 - 130 bpm in rate. This longtime high rate was responsible of cardiomyopathy. The patient was symptomatic for palpitations and mild exertional dyspnoea. The electrophysiological study, performed during atrial flutter and wide QRS showed a short HV interval in confirmation of the initial activation of the ventricle by an accessory pathway (fig. 3). We wanted to perform the ablation of the accessory pathway or of the atrial flutter but this was not possible because it was very difficult to access the left subclavian and femoral veins: in fact, in the past, the patient underwent a left pneumonectomy and bilateral inguinal lymphadenectomy. Therefore we performed the electrical cardioversion and we assigned anti arrhythmic therapy with amiodarone. The patient was discharged from hospital with sinus rhythm. One month later he was asymptomatic; sinus rhythm persisted and echocardiographic data had significantly improved with decrease of septal to posterior wall motion delay, decrease of mitral regurgitation and improvement in systolic function.[4]

Discussions

This case captured our interest for three reasons in particular. The first concerns the diagnosis of tachicardiomiopathy that was very difficult to make because of two factors. The most important: the phases of fast ventricular conduction with wide QRS were not constant during atrial fibrillation, which was the first arrhythmia detected at the time of admission in the hospital, but the strips with fast and wide QRS were developed in the patient during atrial flutter, a few days later, after the restoration of sinus rhythm. At first it seemed unlikely that fast and wide QRS runs, when they were in the context of atrial fibrillation, iterative, mostly conducted with narrow QRS and intermediate ventricular rate, could sustain a ventricular contractile dysfunction. But when the patient developed atrial flutter he had totally wide, fast and constant QRS strips. At this point, the correlation with the left ventricular contractile dysfunction appeared to be more plausible.[5] The second factor that initially discouraged the diagnosis of tachycardiomyopathy was the knowledge that, most frequently in the elderly population, the atrial fibrillation and the atrial flutter are a result of heart failure and not the cause.[3]

The second aspect that captured our interest was the diagnosis of

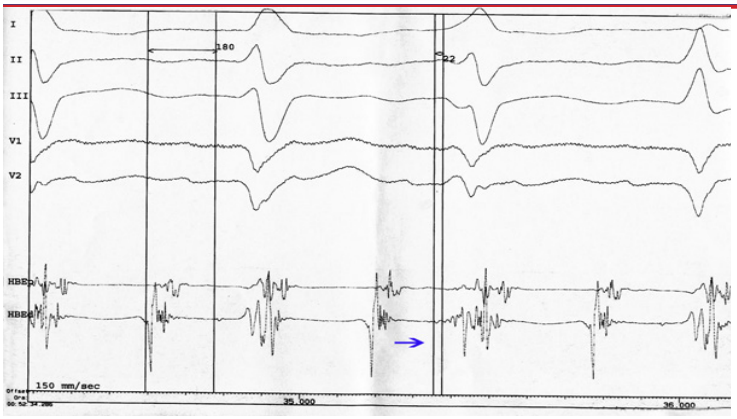

Figure 3: The electrophysiological study, performed during atrial flutter and wide QRS pre excited showing a short HV interval in confirmation of the initial activation of the ventricle by accessory pathway

runs of wide complex tachycardia. Indeed this clinical case shows us the hard dilemma of wide QRS during atrial fibrillation: ventricular ectopy, preexcitation or aberrant ventricular conduction?[6] We immediately ruled out the third ipothesis: the QRS morphology was not aberrant and there was no Ashman phenomenon. However, on the basis of the ECG only, it was much more difficult to distinguish between ventricular ectopy and pre-excitation even if the morphology of the QRS and the absence of fixed coupling, clearly suggested a ventricular pre-excitation through a posteroseptal right accessory pathway.[7] Objections to the diagnosis of pre-excitation came from the presence of certain elements in favor of ventricular ectopy such as the tendency to grouping, the iterative nature and the compensatory pauses. Furthermore, the patient had never presented ventricular preexcitation unless an error occurs in the interpretation of non sustained ventricular tachycardia that was observed in 2012 during 24 hours ECG recording. Therefore, on the basis of all these arguments it seemed highly probable that the runs of wide QRS were caused by ventricular pre-excitation trough a posteroseptal right accessory pathway which was manifest only when the atrial activation was non originated in the sinus node but in the circuit of atrial fibrillation and, particularly, of atrial flutter. This pathway was easily depressed by various antiarrhythmic drugs such as amiodarone.

The third aspect that captured our interest was the most intriguing: to explain why pre-excitation was constant during atrial flutter. Probably this depends on the reentry circuit of the common flutter in which the wave front rotates around this counterclockwise. In this way, as the activation of coronary sinus and ostium precede the activation of AV node and bundle His, the wave front can activate the posteroseptal pathway in advance and make the preexcitation manifest.

The electrophysiological study, although limited by the inability to perform the ablation, has demonstrated, during typical atrial flutter conducted with wide complexes, a virtual HV interval. The study therefore confirmed the diagnostic hypothesis that, during atrial flutter, the conduction to the ventricles occurs mainly through the accessory pathway.

Conclusions

This case report shows that more sophisticated mechanism than those initially evident can be hidden behind an episode of a heart failure. The conduction to the ventricles through an accessory pathway can be supported by the presence of atrial arrhythmia and therefore not be evident during sinus rhythm. If the pre excited complexes are rapid and prolonged they can be responsible of tachycardiomyopathy and heart failure. As other cases of tachycardiomyopathy demonstrate , the signs of left ventricular contractile dysfunction may regress with the control of the heart rate. In this specific case, this meant the blocking of the conduction through the accessory pathway and the elimination of atrial arrhythmia. The latter supports the conduction through the accessory pathway. It remains to prove the long-term effectiveness of the applied treatment, that is the pharmacological therapy with amiodarone plus atrial electrical cardioversion. We are aware of the limitation of not having been able to subject the patient to ablative treatment because of lack of vascular access.

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"Two for the Price of One": A Single-Lead Implantable Cardioverter-Defibrillator System with A Floating Atrial Dipole

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Abstract

In patients known to be a high risk for sudden cardiac arrest, implantable cardioverter defibrillators (ICD) are a proven therapy to reduce risk of death. However, in patients without conventional indications for pacing, the optimal strategy for type of device, dual- versus single-chamber, remains debatable. The benefit of prophylactic pacing in this category of patients has never been documented. Although available atrial electrograms in a dual chamber system improve interpretation of stored arrhythmia events, allow monitoring of atrial fibrillation and may potentially reduce the risk of inappropriate shocks by enhancing automated arrhythmia discrimination, the use of dual-chamber ICDs has a number of disadvantages. The addition of an atrial lead adds complexity to implantation and extraction procedures, increases procedural cost and is associated with a higher risk of periprocedural complications. The single lead pacing system with ability to sense atrial signals via floating atrial electrodes (VDD) clinically became available in early 1980's but did not gain much popularity due to inconsistent atrial sensing and concerns about the potential need for an atrial lead if sinus node fails. Most ICD patients do not have indications for pacing at implantation and subsequent risk of symptomatic bradycardia seems to be low. The concept of atrial sensing via floating electrodes has recently been revitalized in the Biotronik DX ICD system (Biotronik, SE & Co., Berlin, Germany) aiming to provide all of the potential advantages of available atrial electrograms without the risks and incremental cost of an additional atrial lead. Compared to a traditional VDD pacing system, the DX ICD system uses an optimized (15 mm) atrial dipole spacing and improved atrial signal processing to offer more reliable atrial sensing. The initial experience with the DX system indicates that the clinically useful atrial signal amplitude in sinus rhythm remains stable over time. Future studies are needed to determine reliability of atrial sensing during tachyarrhythmias, particularly atrial fibrillation as well as clinical utility and cost-effectiveness of this technology in different populations of patients.

Introduction

An implantable cardioverter defibrillator (ICD) is a proven life-saving therapy for patients at high risk of sudden death. However, device selection strategy, a single - versus dual-chamber system, in patients without conventional indications for pacing remains debatable. The majority of patients enrolled in the landmark clinical trials that evaluated the utility of ICDs for prevention of sudden death received single-chamber devices.[1] The concept of prophylactic pacing in ICD patients without pacing indications has been tested in a number of large randomized clinical trials. In the DAVID (Dual Chamber and VVI Implantable Defibrillator) trail, dual chamber pacing was associated with worse outcomes than VVI back up (40 beats/min) pacing, most likely due to ventricular desynchronization caused by right ventricular (RV) pacing.[2] In subsequent trials, dual-chamber programming that minimizes unnecessary RV pacing by using special pacing algorithms (AV Search Hysteresis, Boston Scientific or Managed Ventricular Pacing, Medtronic) or atrial based (AAI 60 beats/min) pacing have yielded no improved outcomes compared to VVI back up pacing.[3-5] Yet, about two thirds of patients meeting criteria for a primary prevention ICD are implanted with dual chamber devices in the US; the majority of them have no conventional indications for pacing.[6] An ICD system using a single lead with floating atrial dipole, which can provide diagnostic capability of a dual-chamber system without placing an additional atrial lead, has recently become available. In this article we discuss a rationale for its use in ICD candidates who do not require pacing and review initial clinical experience with this system.

Key Words:
Implantable Cardioverter-Defibrillator, Floating Atrial Electrodes, VDD Pacing, DX ICD System.

Disclosures:
Alexander Mazur, - lecture honorarium from Biotronik
Nicole E. Worden - travel grant from Biotronik
Musab Alqasrawi, - travel grant from Biotronik
Siva M. Krothapalli - none.

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Potential Advantages of an Atrial Lead in ICD Patients

Although there is no proven benefit of pacing in ICD patients without traditional pacing indications, recording of atrial electrograms has a number of potential diagnostic and therapeutic advantages. First, the distinction between supraventricular and ventricular arrhythmias using ventricular or far-field electrograms is limited and availability of atrial electrograms improves correct interpretation of

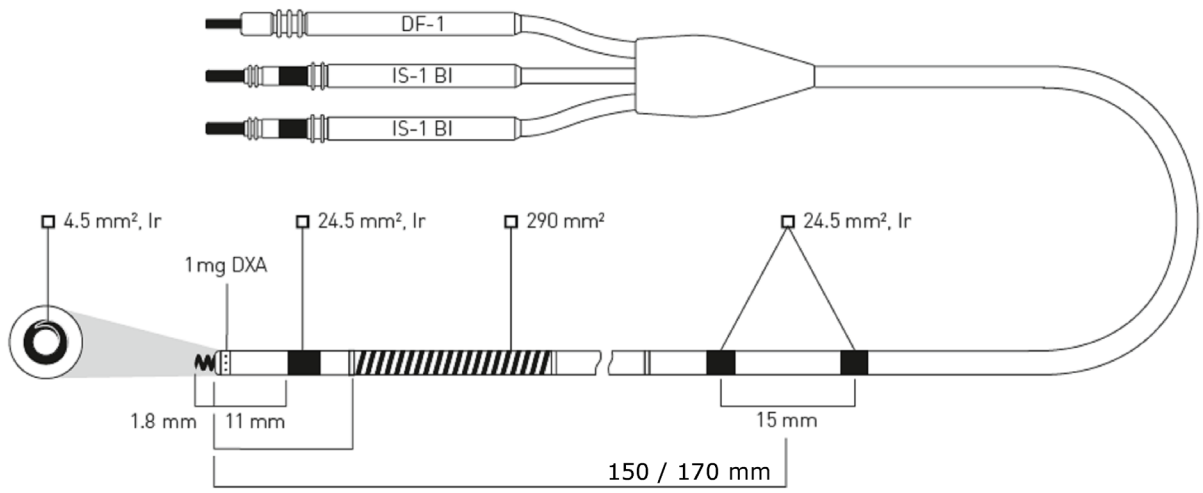

Figure 1: The Biotronik Linox Smart DX active fixation lead. The atrial dipole is mounted 15 -17 cm from the tip of the lead. Courtesy of Biotronik

stored arrhythmia events triggering ICD therapy.[7] Correct diagnosis of arrhythmia treated by ICD is critical for guiding an appropriate therapeutic approach.

Secondly, although published data are mixed, the presence of an atrial lead can potentially reduce the risk of inappropriate ICD therapies by enhancing automated arrhythmia discrimination.[8-11] While appropriate device programming with a relatively high detection cut off rate may significantly reduce the risk of inappropriate ICD shocks for supraventricular arrhythmias regardless of device selection (single versus dual), this strategy is not practical in patients with a relatively slow ventricular tachycardia (VT).[10] Inappropriate shocks predominantly for supraventricular arrhythmias have been reported in 11.5% - 17.4% of patients enrolled in major ICD clinical trials.[12, 13] Poorly tolerated high voltage ICD shocks can cause significant psychological stress and adversely affect patient's acceptance of the live-saving ICD therapy. Although the causality remains unclear, inappropriate ICD shocks have been associated with increased morbidity and mortality in heart failure patients.[12-15]

Finally, the presence of an atrial lead allows monitoring of atrial fibrillation (AF). This aspect of an ICD patient's management has become increasingly important with advent of remote monitoring with automatic wireless data transmission capability that allows early detection of clinically significant events such as AF, ventricular arrhythmias or device malfunction.[16] It is well recognized that AF is associated with adverse outcomes in heart failure patients and the most common trigger of inappropriate ICD shocks.[13-15] Asymptomatic AF is commonly found in ICD recipients.[10, 17] Although there is no consensus on the optimal anticoagulation strategy in patients with brief asymptomatic episodes of AF detected by implantable devices, there seem to be no argument that heart failure patients with sustained forms of AF should be managed with anticoagulation to reduce the risk of thromboembolic complications. In addition, early detection and prompt management of sustained AF by restoration of sinus rhythm or adequate control of ventricular rate can potentially prevent decompensation of heart failure and avoid inappropriate ICD shocks.

Disadvantages of the Addition of an Atrial Lead in ICD Patients

The addition of an atrial lead in ICD patients has a number of disadvantages. This adds complexity to implantation and extraction procedures, prolongs procedure and fluoroscopy time, increases procedural cost and is associated with higher rate of adverse outcomes.[1, 6, 10, 18] An outcome analysis of 104, 049 ICD implantation procedures using the National Cardiovascular Data ICD Registry found that selection of a dual- versus a single-chamber device was associated with increased risk of periprocedural complications and in-hospital mortality[6] More recent analysis of data from the same registry by Peterson et al. revealed that the use of a dual-chamber ICD compared with a single chamber ICD was associated with almost two-fold higher risk of tamponade and mechanical complications requiring surgical correction while 1-year hospitalization and mortality rates were similar.[1]

A Single-Lead ICD System with Floating Atrial Electrodes

The single lead pacing system that affords atrio-ventricular (AV) synchrony through floating atrial electrodes (VDD) was introduced

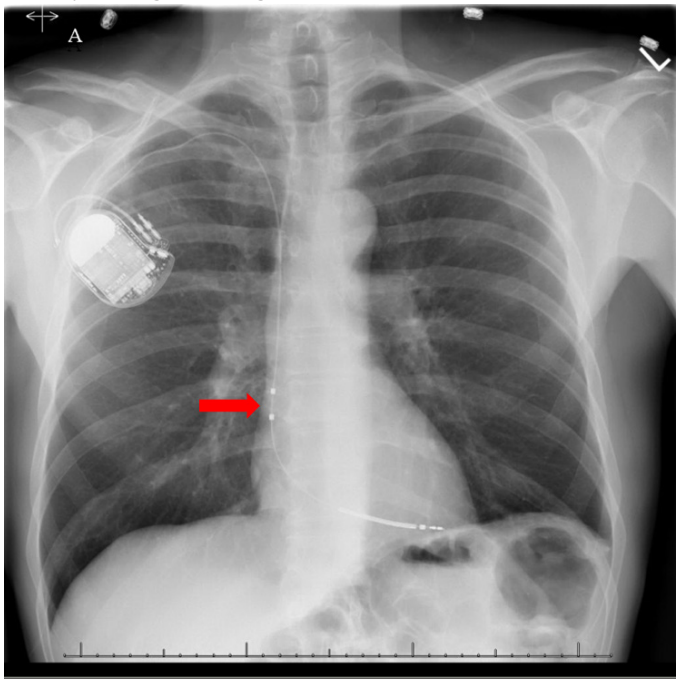

Figure 2A: A chest X-ray images showing placement of the Biotronik Linox Smart DX active fixation lead in the apex

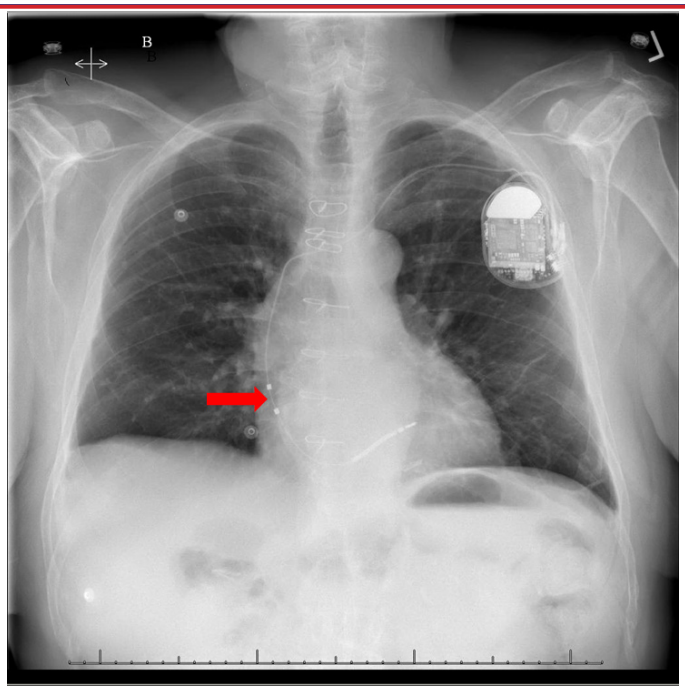

Figure 2B: A chest X-ray image showing placement of the Biotronik Linox Smart DX active fixation lead in the septum

into clinical practice in early 1980's as a simplified alternative to a dual chamber pacemaker for patients with complete AV block and preserved sinus note function.[19] While conceptually appealing, VDD pacing systems are implanted infrequently (< 1% of pacemaker implants in the US) primarily because of inconsistent atrial sensing causing intermittent loss of AV synchrony and a concern about the potential need for upgrade to a dual-chamber device if sinus node fails.[20] However, most ICD patients do not have indications for pacing at implantation and subsequent risk of symptomatic bradycardia seems to be low. In the Managed Ventricular Pacing Versus VVI 40 Pacing Trial, 5.5% of the 1030 enrolled ICD patients developed an indication for pacing over 2.5 years - some of them due to AV block.[5]

The concept of atrial sensing via floating electrodes was implemented in Biotronik ICDs (Biotronik, SE & Co., Berlin, Germany) in early 2000's in hopes to provide all of the potential advantages of available atrial electrograms without the risks and incremental cost of an additional atrial lead. The system has since undergone a series of device and lead modifications to optimize atrial signal recording and processing (optimization of atrial dipole spacing and distance from the RV tip, improvement of atrial signal processing and filtering, implementation of automatic atrial sensitivity control, adjustment of blanking periods, among others) prior to its commercial release (Biotronik, personal communication). The current generation of the system (DX system) consists of a VR-T DX device and a Linox Smart DX active fixation lead. The Linox Smart DX lead is a 7.8 French single coil true bipolar lead, which contains 15 mm spaced pair of atrial ring electrodes mounted 15 -17 cm from the lead tip (Figure 1). Atrial electrodes are floating and usually not in direct contact with myocardium. The DX ICD system has no atrial pacing capability but allows optional AV synchronous VDD pacing. Compared to a traditional VDD pacing system, the DX ICD system has a number of unique features that offer more reliable atrial sensing. The optimized atrial dipole spacing covers a relatively large area of atrial surface of 49 mm2. This provides better flexibility with its positioning within the atrium and improves stability of the atrial signal (Figure 2). To minimize atrial undersensing, the DX devices use a pre-amplifier, which progressively increases atrial gain up to four times. High gained atrial signals are then band-pass filtered to exclude signal frequencies outside the atrial component range (30-70 Hz) (Figure 3). While VDD pacemakers use a static sensitivity setting, the adaptive sensing feature implemented in DX ICDs helps to prevent oversensing of far-field noise. The DX ICD system received regulatory approval in Europe in 2011 and in the US in 2013.

DX ICDs are equipped with the SMART tachycardia discrimination algorithm, which is based on analysis of the tachycardia onset, average heart rate, heart rate stability and beat-to beat relation between atrial and ventricular signals (Figure 4). The algorithm has been described in details elsewhere.[21,22] Previous clinical studies have shown that the SMART algorithm allows discrimination between supraventricular and ventricular tachycardias with sensitivity of 100% and specificity of 64-89%.[21,23] In a simulation study, the algorithm showed 95% specificity for correct detection of supraventricular tachyarrhythmias.[24]

Recent studies evaluating the Biotronik DX ICD system have demonstrated stability of atrial signal within the clinically acceptable range over time.[22,25] In a study of 116 patients implanted with a DX ICD system, mean P wave amplitude varied from 5.0 to 6.1 mV during 6-month follow up in different body positions. None of the patients had P-wave amplitude lower then 0.4 mV. Appropriate atrial sensing was observed in 93.8% of sensing tests with sensitivity setting of 0.4 mV.[25] Iori et al. evaluated P-wave amplitude stability in 13 patients implanted with a DX ICD. The authors analyzed daily P-wave measurements using the Biotronik Home Monitoring™ system over a 200-day follow up. Mean P-wave amplitude was 4.2 ± 1.9 mV, whereas 95% of all daily measurements varied less than 50% of the mean P-wave value.[22]

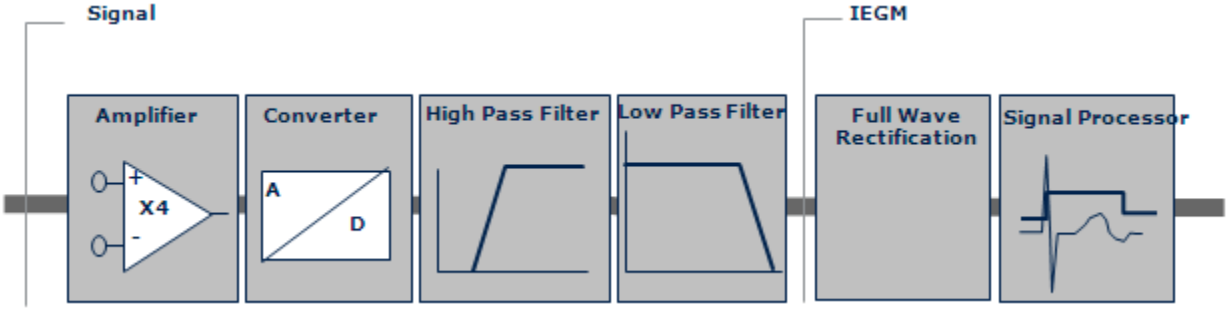

Figure 3: The schematic shows atrial signal processing in the Biotronik DX ICD system, which includes a dedicated atrial input stage with up to 4-fold signal amplification and noise filtering. Courtesy of Biotronik

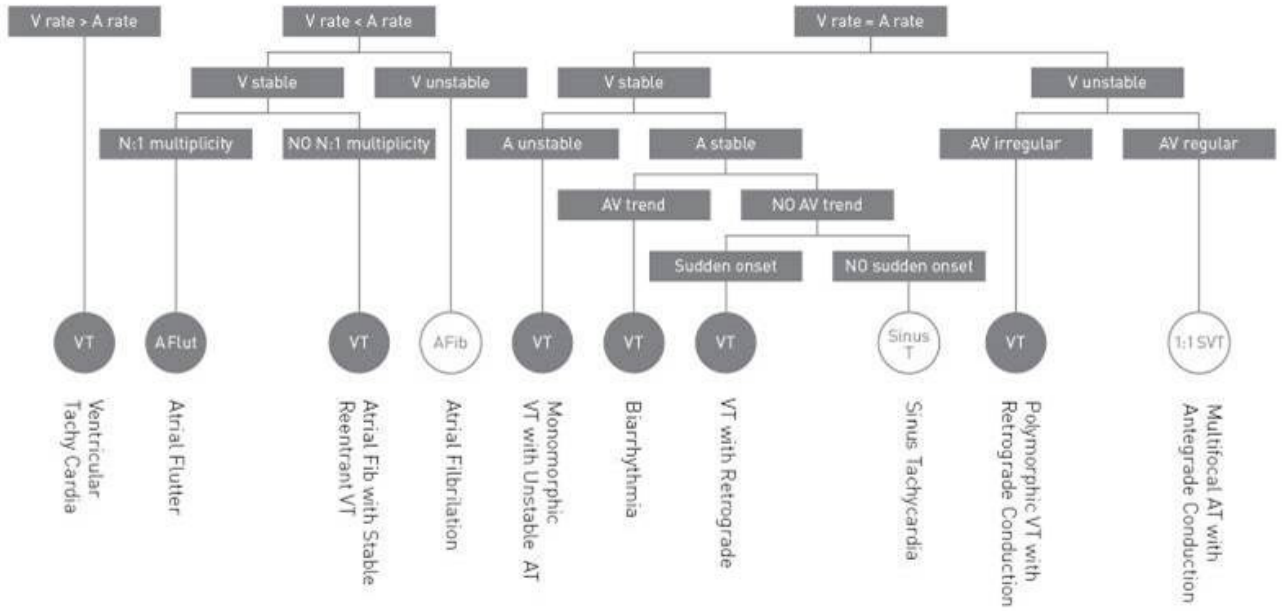

Figure 4: **Rhythm discrimination criteria employed in the SMART Detection algorithm. A and V denote atrial and ventricular, respectively. Courtesy of Biotronik**

The ADRIA (Belos A+ versus DR Clinical Investigation of Arrhythmia Discrimination) multicenter study randomized 249 patients without indications for pacing to either a single lead atrial sensing (A+) system (an early generation of the Biotronik single lead with floating electrode system which is now called DX ICD) or to a conventional dual chamber ICD.[23] The A+ system was found to be equivalent to a dual chamber ICD in terms of arrhythmia discrimination (specificity of supraventricular tachycardia discrimination: 61.8% and 66.2% for the A+ group and dual chamber group, respectively) while required significantly shorter implantation time. The vast majority of the misclassified supraventricular tachyarrhythmias were relatively slow sinus tachycardia. Low specificity of the SMART discrimination algorithm found in this study was attributed to a combination of low programmed VT detection cut off rate (≤ 130 bpm per study protocol), a relatively high incidence of abnormal atrial sensing (over- or under sensing) during supraventricular events, and definition of the Onset criterion to be triggered by a single ventricular premature beat (once the Onset criteria is met, the algorithm classifies the rhythm as VT regardless of other SMART criteria). The Onset criterion has been refined in later generation of devices (Biotronik, personal communication). Analysis of 492 misclassified sinus tachycardia episodes revealed that the percentage of patients with atrial over-or undersensing was significantly higher in the A+ arm compared to the dual chamber arm (36% versus 11% of patients, respectively).[23] As discussed earlier, the system has since undergone a series of modifications to optimize atrial sensing prior to its commercial release. Published clinical experience with current generation of devices (DX) is limited. In the Linox DX Study, 23 patients had total 88 spontaneous tachyarrhythmia events. All 15 ventricular events were appropriately diagnosed and treated by the device. In 54 out of 73 (74%) non-ventricular events, ICD therapies were appropriately withheld. Inappropriately treated events were due to supraventricular tachycardia (7 events), sinus tachycardia (4 events), T-wave oversensing (7 events), or electrocautery noise (1 event).[25] In the study by Iori et al., twenty spontaneous tachyarrhythmia events (3 ventricular and 17 supraventricular) were recorded in the VT zone. All events were correctly diagnosed by the device.[22]

In our center, we followed 35 patients who were implanted with the DX ICD system. We found that the atrial signal amplitude remained in the clinically useful range (mean 5.4 - 8.7 mV) over a mean follow up of 432 ± 197 days. There was no difference in atrial signal amplitude between apical and septal lead positions. All stored arrhythmia events showed readily interpretable atrial electrograms (Figure 5). The majority of the supraventricular events (82%) were correctly classified by the device and ICD therapies were appropriately avoided.[26]

Conclusions

A single lead ICD system with floating atrial dipole, which can provide the benefit of available atrial electrograms without the risks and incremental costs of an additional atrial lead, is a promising alternative to a dual chamber ICD in patients without conventional pacing indications. The initial experience with the Biotronik DX system indicates that the clinically useful atrial signal amplitude remains stable over time. However, since this is a relatively new technology many questions remain. Future studies are needed to determine: (1) long-term lead durability, (2) impact of floating electrodes on complexity of lead extraction comparing to a conventional single coil

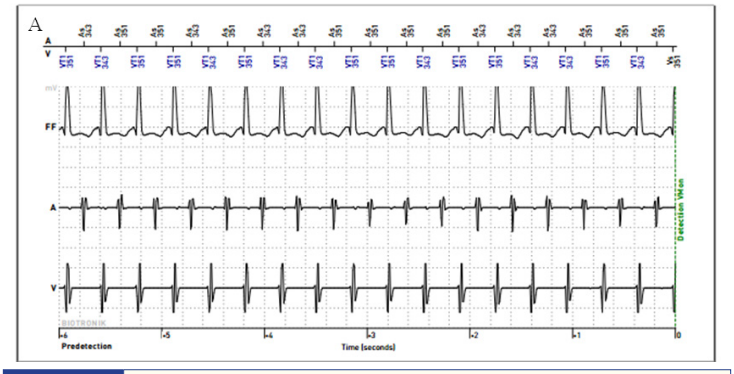

Figure 5A: **An examples of stored arrhythmia events during supraventricular tachycardia**

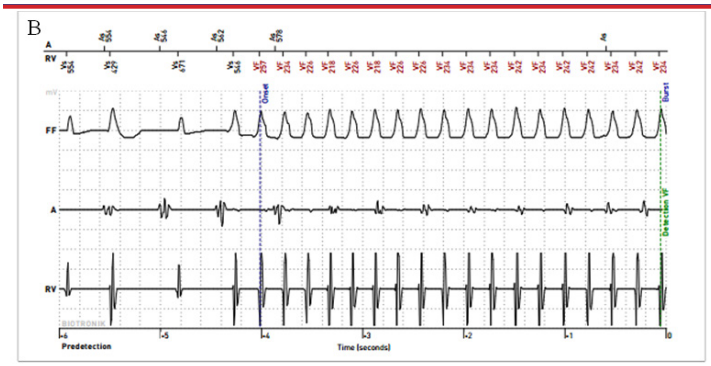

Figure 5B: An examples of stored arrhythmia events during ventricular tachycardia

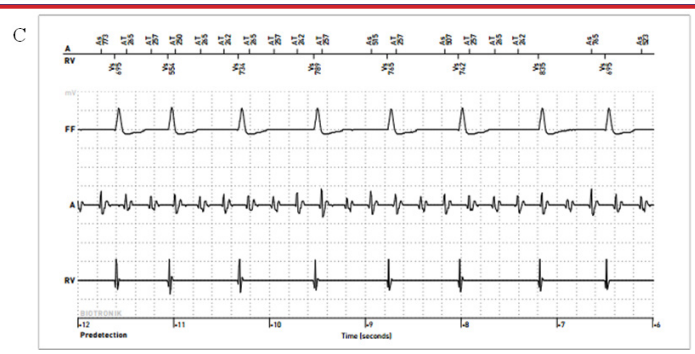

Figure 5C: An examples of stored arrhythmia events during atrial flutter

ICD lead, (3) reliability of atrial sensing during tachyarrhythmias, particularly atrial fibrillation, (4) subsequent need for atrial pacing and device upgrades in patients implanted with this system, and (5) clinical utility and cost effectiveness of this technology in different patient populations (primary versus secondary prevention indication, primary arrhythmogenic syndromes such as Long QT or Brugada, etc.).

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Safety And Efficacy Of Uninterrupted Periprocedural Apixaban In Patients Undergoing Atrial Fibrillation Catheter Ablation: A Metaanalysis Of 1,057 Patients

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Abstract

Apixaban (factor Xa inhibitor) is a novel anticoagulant and may be beneficial during atrial fibrillation (AF) ablation for prevention of thromboembolic events. However, the adverse effects of periprocedural apixaban therapy have not been thoroughly evaluated. A meta-analysis was performed to evaluate the safety of apixaban for anticoagulation in AF ablation. We searched the online databases till October 2015 for studies comparing Apixaban with Vitamin K antagonists in atrial fibrillation patients undergoing catheter ablation. Primary outcome of our study was composite of thromboembolic event and bleeding (includes major and minor bleeding). A total of 1,057 atrial fibrillation patients in 3 studies undergoing catheter ablation were included in this analysis. Zero thromboembolic events were reported in the apixaban group and 1 in the VKA group with no statistical difference (OR 0.75; 95% CI 0.03-18.49). No major differences were observed for the primary outcome (OR 0.92; 95% CI 0.54-1.55), risk of overall bleeding (OR 0.94, 95% CI 0.55- 1.58), major bleeding (OR1.37; 95% CI 0.33-5.67), minor bleeding (OR 0.89; 95% CI 0.50-1.55), pericardial effusion (OR 0.50; 95% CI 0.18-1.38) and groin hematoma (OR 1.36; 95% CI 0.70-2.65). Uninterrupted apixaban administration in patients undergoing AF catheter ablation was non-inferior to VKA without increasing the risk of major and minor bleeding.

Introduction

Atrial fibrillation (AF) catheter ablation has been given a Class I recommendation (2012 AHA/ACC guidelines), for patients with symptomatic paroxysmal atrial fibrillation who are intolerant or refractory to at least one antiarrhythmic agent.[1] Traditionally, patients undergoing catheter ablation for AF had anticoagulation (Vitamin K antagonist [VKA] e.g. warfarin) discontinued 3 to 5 days prior to the procedure and were bridged with heparin or a low molecular weight heparin after the procedure until the patients were therapeutically anticoagulated with warfarin. However, there has been an increasing trend of the uninterrupted anticoagulation with VKA in patients undergoing AF ablation. In a recent meta-analysis, Nairooz et al [2] evaluated the role of uninterrupted VKA versus interrupted VKA with heparin bridging in AF ablation. They included 13 studies (1 randomized and 12 observational) with 17, 434 patients undergoing AF ablation, of which 7877 patients managed with uninterrupted approach and 9557 with interrupted approach. There was a significantly lower incidence of major bleeding (OR 0.72, 95% CI 0.54-0.95; p=0.02), minor bleeding (OR 0.33, 95% CI 0.21-0.52; p<0.0001), combined stroke and transient ischemic attack (OR 0.25, 95% CI 0.10-0.62; p=0.003) with uninterrupted VKA as opposed to an interrupted VKA and bridging heparin/enoxaparin strategy. Similarly, with advent of newer oral anticoagulant (NOAC's) (especially dabigatran, rivaroxaban and apixaban, numerous studies have demonstrated thromboembolic safety profile in patients not only with non-valvular AF but also undergoing AF ablation with lower bleeding rates. In light of these findings, 3 studies have been conducted so far (1 retrospective and 2 prospective) assessing the safety and efficacy of uninterrupted apixaban in patients undergoing AF ablation as compared to VKA.[3-5] In view of these studies, we aim to perform a meta-analysis to assess for safety uninterrupted

Key Words:
Apixaban, Atrial Fibrillation Ablation, Anticoagulation, Complications.

Disclosures:
None.

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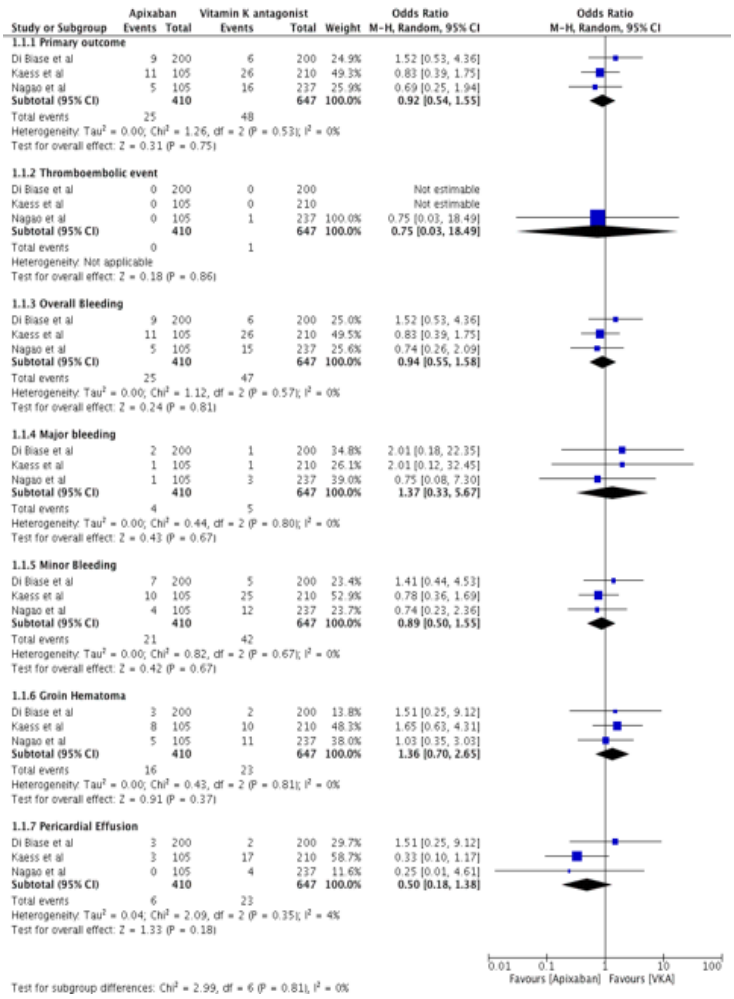

Figure 1: **Forest plot of primary outcome, thromboembolic events, overall bleeding events, groin hematoma, pericardial effusion in patients undergoing ablation of atrial fibrillation with uninterrupted apixaban compared to uninterrupted vitamin K antagonist**

periprocedural apixaban in patients undergoing AF ablation.

We searched PubMed, The Cochrane Library, EMBASE, EBSCO, Web of Science and CINAHL databases from the inception through October 15, 2015 comparing uninterrupted apixaban with uninterrupted VKA peri AF ablation. All endpoints were reported through the longest follow up available. The primary safety outcome in our study was a composite of thromboembolic event and overall bleeding. Individual outcomes assessed in our study were thromboembolic event, overall bleeding, major and minor bleeding, groin hematomas and pericardial effusion. Random effects model was followed to estimate the odds ratios (OR) and respective 95% confidence intervals (CI) using Cochrane Collaborative software, RevMan 5.3. Measure of heterogeneity between the studies was assessed using the chi square test and was considered significant if p values < 0.10 or I2 > 50%.

Three trials (2 prospective, 1 retrospective) with a total of 1,057 patients were included in the analysis, of those 410 on uninterrupted apixaban versus 647 uninterrupted VKA. Characteristics of included studies and periprocedural anticoagulation strategy are described in table 1. Zero thromboembolic events were reported in the apixaban group versus 1 in the VKA group with no statistical difference (OR 0.75; 95% CI 0.03-18.49). No statistical significant difference in the primary outcome (OR 0.92; 95% CI 0.54-1.55) was observed in our study. Consistently, no difference was observed in risk of overall bleeding (OR 0.94, 95% CI 0.55- 1.58), major bleeding (OR1.37; 95% CI 0.33-5.67), minor bleeding (OR 0.89; 95% CI 0.50-1.55), pericardial effusion (OR 0.50; 95% CI 0.18-1.38) and groin hematoma (OR 1.36; 95% CI 0.70-2.65) in the apixaban group as compared to VKA group (figure 1).

This is the first meta-analysis of the currently available literature comparing uninterrupted apixaban to uninterrupted VKA in patients undergoing AF ablation. Among 1,047 patients who underwent AF ablation, we demonstrated that there was no difference in the primary outcome (i.e. composite of thromboembolic events and bleeding) in either group. Although non significant there were no thromboembolic events in the apixaban group as compared one event in the VKA group. Interestingly there was also no significant difference observed in the secondary endpoints of major bleeding, minor bleeding, pericardial effusion or groin hematoma in either strategy. Interestingly, the periprocedural activated clotting time in VKA group was significantly higher in all 3 studies: 258±26 versus 288±34, p<0.001;[5] 342.1±23.1 versus 363.1±26.5, p<0.001;[4] 275±54 versus 313±47, p<0.001,[3] apixaban and VKA groups respectively. However no difference in the bleeding events were observed in the both groups.

Based on our study, apixaban was the non-inferior to uninterrupted VKA in patients undergoing AF ablation. In a recent meta-analyses by Lu et al assessing the safety and efficacy of apixaban in patients undergoing atrial fibrillation ablation, apixaban was as effective as VKA (that corroborates with our study), but our study is essentially different from this meta-analyses as we only included trials in which apixaban was used in uninterrupted fashion, and excluded all trials where apixaban was either stopped a night before or started on post-procedure day 1 (as included in Lu et al meta-analysis).[6]

Also other NOAC agents that have been compared to VKA include dabigatran and rivaroxaban. There has been conflicting data with Steinberg et al [7] and Sardar et al [8] demonstrating an increase in neurologic complications with dabigatran compared to VKA. This is contrary to the meta-analysis conducted by Honhloser et al [9] and Providencia et al [10] who demonstrated no significant differences in the composite of neurologic and bleeding complications between the dabigatran and uninterrupted VKA groups. Rivaroxaban has even lesser data and no meta-analysis to compare the uninterrupted Rivaroxaban against uninterrupted VKA.

Given the lack of literature, a randomized controlled trial AFAXA (Apixaban During Atrial Fibrillation Catheter Ablation: Comparison to Vitamin K Antagonist Therapy; NCT02227550) will provide valuable information as the study compares fixed dose apixaban (5 mg two times a day) with uninterrupted VKA (goal INR 2.0-3.0) in AF ablation.[11] The primary outcome of the study is composite of all-cause mortality, stroke (ischemic stroke, subarachnoid hemorrhage and hemorrhagic stroke), and major bleeding events with follow-up period of up to 4 months.

One of the major limitations of the current meta-analysis includes reliance on retrospective and prospective and lack on any randomized controlled trials. In the trial by Kaess et al,[5] irrespective of the patient's home apixaban dose or renal function, a fixed dose of 2.5 mg was administered to apixaban group, which could potentially result in decreased bleeding events. Despite, heterogeneity in trials design,

Table 1: Descriptive characteristics of included studies

Name, year	Type of study	n, Study /Control	Anticoagulation protocol	Follow-up period	Thromboembolic complications, n (%)			Bleeding events, n(%)		
					AG	VG	p	AG	VG	p
Di Biase et al, 2015	Prospective multicenter registry	400; 200/200	Apixaban 2.5 mg or 5 mg two times a day according to creatinine clearance for up to 3 weeks pre-procedurally. Patients were instructed to take their apixaban dose the morning of the procedure without any discontinuation and to take next dose the same night of the procedure.	30 days post-procedure	0	0	>0.99	9 (4.5%)	6 (3%)	0.43
Nagao et al, 2014	Retrospective case control study	342; 105/237	Anticoagulation was started 4 weeks before; apixaban was dosed into 2.5 mg or 5 mg two times a day based on creatinine clearance, age (2.5 mg BID for ≥ 80 yrs) and weight (2.5 mg for ≤ 60 kg). On the procedural day, the dose of apixaban was administered in the morning and in the night as usual days in the Apixaban group.	3 months post-procedure	0	1 (0.4%)	0.51	5(5%)	15 (6%)	0.57
Kaess et al, 2014	Prospective case control study	325; 105/210	Anticoagulation atleast 4 weeks before the procedure; All patients received apixaban 2.5 mg in the morning of procedure followed by their usual dosage in the evening; 95% of patients in apixaban were on 5 mg BID and 5% on 2.5 BID	Till the time of discharge (2 days for majority of patients)	0	0	>0.99	11 (10.5%)	26 (12.3%)	0.71

AG: Apixaban Group; VG = Vitamin K Antagonist Group

study protocols, and baseline characteristics of study population, the test of heterogeneity was non significant.

Conclusion

In this meta-analysis of patients undergoing AF ablation, apixaban was safe and non-inferior to uninterrupted VKA without any increase the risk of thromboembolic event, major and minor bleeding. Although the results from randomized controlled trials are pending, our study demonstrates that safety and efficacy of apixaban in comparison to uninterrupted VKA, and hence supports its use in AF ablation.

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The Wearable Cardioverter/Defibrillator – Toy Or Tool?

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Abstract

After the success story of implantable cardioverter/defibrillator systems, prevention of sudden cardiac death (SCD) remains one of the main duties in cardiology. For patients with unkown or transient risk profile for SCD, a wearable cardioverter/defibrillator (WCD) has been established for temporary and effective prevention of sudden arrhythmic death. Several studies have shown safety and efficacy of the WCD, even though randomized studies proving a mortality benefit are still lacking. This review provides an overview of actual WCD data and usage, special indications and possible risks and complications. WCD use is effective and adequate for temporary prevention of SCD in chosen populations. In particular, it provides secured time for sophisticated risk stratification to identify patients at persistent risk for SCD. Nevertheless, prospective randomized trials seem mandatory to prove a prognostic relevance and the economic value of this device.

Introduction

Sudden cardiac arrest (SCA) due to tachyarrhythmias remains a major cause of death in western countries.[1,2] The implantable cardioverter/defibrillator (ICD) has been used for more than 30 years and is considered one cornerstone for primary and secondary prevention of sudden cardiac death (SCD) in high-risk patients.[3] Decades have passed since the milestone trials in ICD therapy. The MADIT, MADIT-II and SCD-HeFT trial enrolled patients between 1990 and 2001.[4-6] Since then, interventional and drug therapies for these patients have evolved tremendously and concomitantly may have affected risks for SCD. Additionally, ICD therapy may be accompanied by several device-related problems, especially lead failure.[7] Recently, van der Heijden et al. described an overall-incidence for device related adverse events of 20% inappropriate shocks, device infections of 6% and 18% lead failures within 12 years of follow-up.[8] ICD therapy has been shown to be cost-effective.[9,10] However, a relevant proportion of patients getting implanted do not meet evidence-based criteria for implantation.[11] Therefore, careful but however secured risk assessment before ICD implantation may be even more cost-effective.

Key Words:
Sudden Cardiac Death, Ventricular Arrhythmia, Wearable Cardioverter/Defibrillator.

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Risk Stratification

A large number of possible risk markers like microvolt T-wave alternans, tests for autonomic dysfunction or signal averaged ECG have been proposed. Though, they did not find their way into clinical routine and are actually not supported by the guidelines.[12] The only evidence-based risk stratifying marker today remains left ventricular ejection fraction, thereby reading "left ventricular ejection fraction (LVEF)".[12]

Having said this, in a recent study, Sjöblom et al. investigated evolution of LVEF in 91 patients after myocardial infarction (MI).[13] 45% of the patients met the ICD criteria of LVEF ≤35% 40 days after MI. However, the authors found further significant improvement in LVEF in 6 more patients at 3 months follow-up (p=0.01), meaning that these patients no longer met the criteria for ICD implantation. These findings show that there is further improvement in LVEF beyond the initial 40 days post MI. Furthermore, 10% of the patients presented with life-threatening ventricular arrhythmias within the first 9 weeks post MI, emphasizing the arrhythmic risk and the need for antiarrhythmic prophylaxis in this early phase. Accordingly, in patients with recent onset non-ischemic cardiomyopathy, the IMAC study showed no benefit from early ICD implantation.[14]

Wearable Cardioverter/Defibrillator

For patients with unkown or transient risk profile for SCD, a wearable cardioverter/defibrillator (WCD) (LifeVest®, ZOLL, Pittsburgh, PA, USA) has been established for temporary but however effective prevention of sudden arrhythmic death (Figure 1). The WCD continuously analyzes the heart rhythm using 4 non-adhesive electrodes incorporated in a light garment. The ECG is registered via 2 non-standard leads (front-back and side-side). When a life-threatening arrhythmia is detected, the WCD runs an alarm cascade

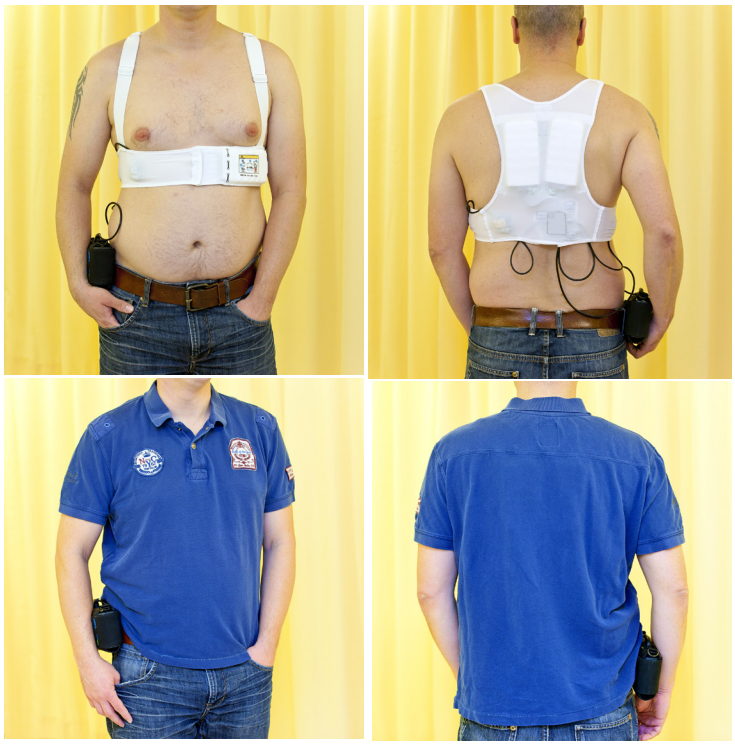

Figure 1: Wearable Cardioverter Defibrillator (WCD)

including audible, visual and tactile alarms. If the patient is conscious, he can withhold any therapy by pressing two response buttons on the monitor. In case of unconsciousness and consequently release of the response button, the WCD will deliver a biphasic shock after having deployed contact gel through the contact electrodes. Programming of detection rates can include a ventricular tachycardia (VT) and a ventricular fibrillation (VF) zone, programmable from 120 to 250 beats per minute. The shock energy can be chosen from 75 to 150 J. All ECG with detected arrhythmias are stored in the device and regularly transferred to a webserver where the attending physician can review all episodes as well as the patient's compliance. Since the arrhythmia detection of the WCD is performed via surface non-adhesive electrodes, there is a considerable risk for motion-related noise artifacts.

The WCD is used in patients at undefined or temporary risk for SCD as well as in patients at known persistent high risk but with transient contraindications for implantation of an ICD. Common indications for WCD wearing are shown in table 1.

WCD often gets misclassified as an alternative to permanent ICD or a "bridge to ICD". This does not give sufficient consideration to the capabilities and the concept of WCD usage. This review provides an overview of actual WCD data and usage, special indications and possible risks and complications.

Clinical Data

In 1998, Auricchio et al. reported the first 10 patients with successful termination of ventricular arrhythmia by the WCD.[15] Subsequently, WCD was shown to be safe and effective in detection and termination of VF.[16-18]

Table 2 summarizes available data on WCD. Despite the manifest gaps in evidence, based on these registries and case reports, the actual ESC guidelines on prevention for SCD give a Class IIb level of evidence C indication for the WCD "for adult patients with poor LV

Table 1: Common indications for wearable cardioverter/defibrillators[49]

Acute myocardial infarction with/without PCI and a LVEF ≤35%
Coronary revascularization (PCI or CABG) and a LVEF ≤35%
Non-ischemic cardiomyopathy, (acute) myocarditis, stress (Takotsubo) cardiomyopathy, peripartum cardiomyopathy, LVEF ≤35%
Waiting for heart transplantation
ICD explantation until re-implantation
Post VT ablation in patients with only moderately reduced LVEF.

systolic function who are at risk for sudden arrhythmic death for a limited period, but are not candidates for an implantable defibrillator (e.g. bridge to transplant, bridge to transvenous implant, peripartum cardiomyopathy, active myocarditis and arrhythmias in the early post-myocardial infarction phase)".[12]

Epstein et al. analyzed 8453 patients wearing the WCD early post MI[19] and found 133 patients (1.6%) receiving 309 appropriate shocks. Beyond that, 114 inappropriate shocks occurred in 99 patients. Mean time from MI to WCD prescription was 9±9 days and mean time from prescription to first shock delivery was 22±32 days. This shows that commonly accepted waiting time between MI and ICD implantation of 40 days and 3 months respectively nevertheless may remain a period at risk for life-threatening arrhythmias. These findings are consistent with those of the VALIANT study which found the highest mortality in the first 30 days after MI.[20] The DINAMIT[21] and IRIS[22] study suggested no survival benefit from ICD implantation early post MI, even though in both studies, the rate of SCD was halved in the ICD group. Unfortunately, this reduction of SCD was negated by an increased number of non-sudden cardiovascular deaths.[23] The reason for this difference has not been clarified sufficiently. Furthermore, relevant differences are obvious comparing the populations of these two studies with a population of a recent heart failure trial, e.g. in terms of optimized heart failure medication. Given the great improvement in heart failure therapy and interventional development for the treatment of acute MI in the last years, the amount of non-sudden cardiac deaths may therefore be relevantly reduced, leaving the amount of preventable arrhythmic death at the disposal of antiarrhythmic devices.

Despite the great amount of descriptive or cohort studies on WCD and the presumed self-evident benefit of the WCD, most of these studies lack a control group, not to mention a randomization. Therefore, the net benefit of the WCD still remains to be proven. The only randomized controlled trial on patients after MI is the multicenter VEST trial with a total of 1900 randomized patients (www.clinicaltrials.gov, NCT01446965), which is about to complete enrollment. The primary endpoint is sudden death mortality.

The recently published WEARIT-II prospective registry[24] enrolled 2000 patients receiving WCD for a median of 90 days. 40% of the patients had ischemic cardiomyopathy, 46% had non-ischemic cardiomyopathy and 14% had congenital heart disease. Authors reported 120 ventricular tachyarrhythmias in 41 patients (2%) and only 10 patients (0.5%) receiving an inappropriate shock. Even though the WEARIT-II registry represents the greatest prospective database on WCD published to date, it still does not answer the relevant unsettled questions on hard endpoints in WCD use.

Special Indications

Especially for possibly transient circumstances which may temporarily elevate the risk for life-threatening arrhythmias,

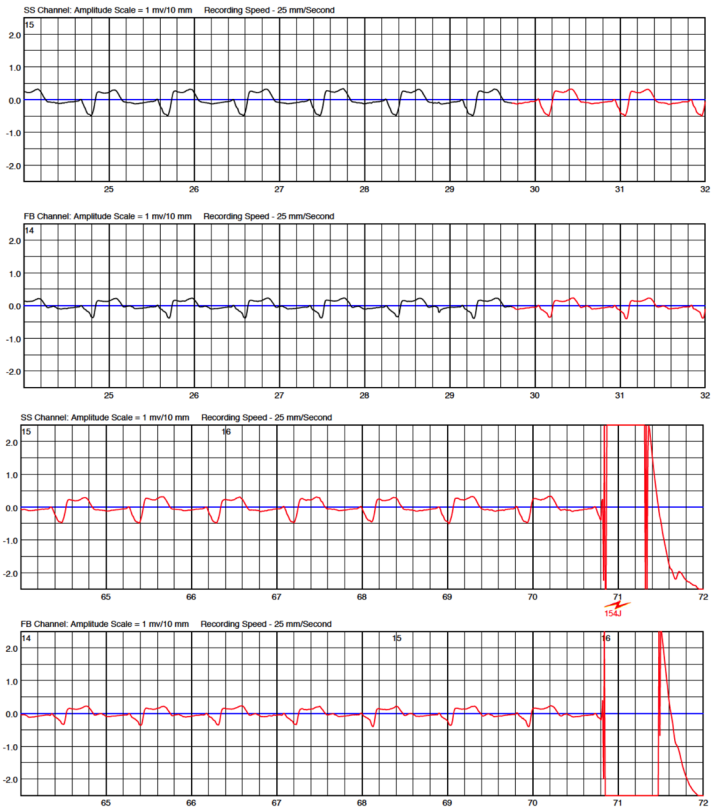

Figure 2: ECG shows normal sinus rhythm with T wave oversensing. The patient did not press the response buttons and therefore received an inappropriate therapy. Fortunately, the shock was triggered to the true R-wave

the WCD offers protected time for any further diagnostics, risk stratification, re-evaluation or simply letting any sort of therapy work without letting the patient at risk during this period.

Rare Cardiomyopathies

Successful use of the WCD has been described in acute or suspected myocarditis,[25, 26] stress cardiomyopathy, [27, 28] noncompaction cardiomyopathy,[29] alcohol toxic cardiomyopathy,[30] congenital heart disease[24, 31, 32] as well as in children.[33] Candidates for cardiac transplantation can likewise be provided a WCD until transplantation.[34] However, since these days waiting for a donor organ may take several years, implanting an ICD has to be seriously considered.

ICD therapy in inherited arrhythmia syndromes like long QT syndrome, Brugada syndrome or arrhythmogenic right ventricular dysplasia is challenging due to the rather young patient age, limited available data and elevated complication rate.[35] WCD can facilitate and cover time to diagnosis and risk stratification in these patients. In the study by Rao et al., among 119 patients with inherited arrhythmias receiving a WCD, the predominant indication was pending genetic testing.[32] Again, the WCD should not be considered as a bridge to ICD in these patients, but rather as a tool for serving protected time to exclude a diagnosis or to stratify the patient as low-risk and thus omitting ICD implantation.

Peripartum Cardiomyopathy

The concept of temporary prophylaxis for SCD of the WCD is particularly attractive for transient pathologies leading to a temporarily elevated risk for SCD. Peripartum cardiomyopathy (PPCM) represents a rare idiopathic cardiomyopathy leading to heart failure LV dysfunction towards the end of pregnancy or in the months following delivery.[36] Even if initial LVEF often is severely affected at the time of diagnosis, there is a high potential for LVEF recovery after starting an optimal heart failure medication regimen.[37] In a large cohort of 107 patients with PPCM wearing a WCD, Saltzberg et al. did not report any arrhythmic event (though 3 patients died after WCD use).[38] This may eventually be due to the retrospective character of their analysis. On the contrary, we recently reported 12 consecutively admitted patients with first diagnosis of PPCM.[39] 7 patients presented with a LVEF of ≤35% and received a WCD for 3 to 6 months. Among these 7 patients, we observed 4 events of VF in 3 of the patients. Patients significantly recovered in LVEF during follow-up. Our data strongly suggest an elevated risk for life-threatening arrhythmias in these young mothers early after diagnosis of PPCM and warrant an uninterrupted use of the WCD in all patients in the early phase of PPCM during recovery.

ICD Explantation Due To Infection

Due to increasing numbers of ICD implantations and subsequent generator exchanges, numbers of device infections with need of system explantation are increasing, too. Especially for patients with secondary prophylactic indications for an ICD, continuous monitoring after explantation seems mandatory. Besides inpatient monitoring for the period of antibiotic therapy, outpatient management using a WCD for this period seems reasonable. Tannawuttiwat et al. presented a retrospective analysis of 97 patients wearing a WCD after ICD removal.[40] 2 patients received 4 shocks, 1 patient received 2 unnecessary shocks. 8 patients (8.2%) died (5 patients in hospital, 3 patients at home), no one was wearing the WCD at the time of death. In a cost-effectiveness model, the WCD was shown to be cost-effective in comparison to inpatient strategy until re-implantation.[41]

Malignancies

WCD can successfully be used in cancer patients who often present a contraindication for ICD implantation.[42] Special considerations can be raised on patients with planned radiotherapy adjacent to an implanted ICD. Depending on the local findings and the planned radiation protocol, an explantation of the ICD with temporary use of a WCD for the radiation period and and subsequent re-implantation may be a favorable strategy, as reported by Bowers et al.[43]

Renal Disease

Patients who are in end-stage renal disease are known to have a high risk for ventricular arrhythmias, but are as well known to show reduced benefit from primary prophylactic ICD therapy due to competing risks.[44] Nevertheless, Wan et al. reported 84 SCA episodes in 75 patients on hemodialysis showing the important arrhythmic burden in these patients.[45] Not all of these episodes were tachyarrhythmias, but 18 episodes were described as asystoles not treated by the WCD.

The actually enrolling WED-HED study (www.clinicaltrials.gov, NCT02481206) is a multi-center, prospective, randomized controlled clinical trial with 1:1 assignment of treatment and control. It will evaluate the impact of WCD use on sudden cardiac death in incident hemodialysis patients.

Risks and Complications of WCD Wearing

The WEARIT/BIROAD registry reported two patients with unsuccessful defibrillation due to incorrectly placed therapy

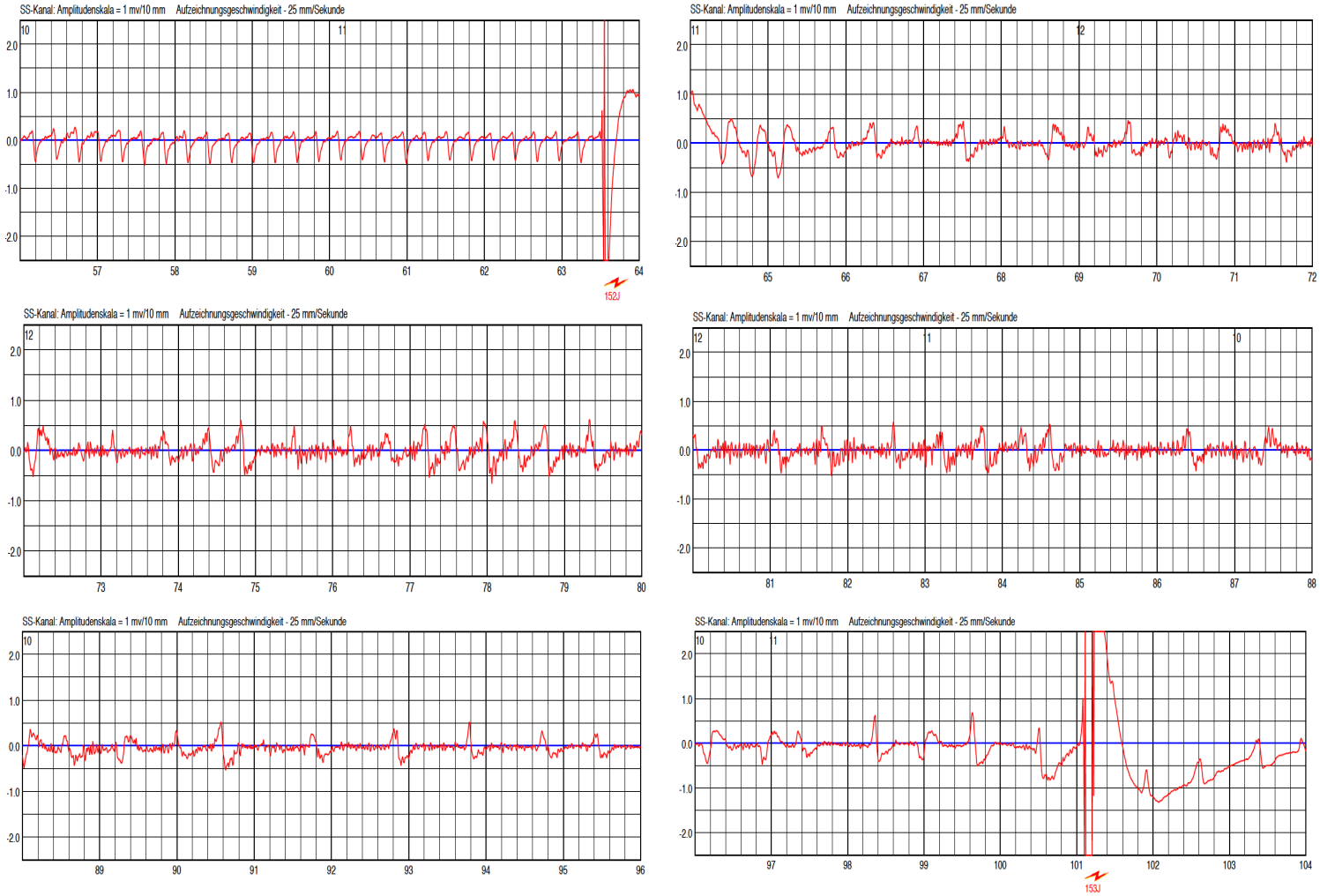

Figure 3: **Episode of a patient with dilative cardiomyopathy. Patient fell on the floor and remained unconscious. ECG shows ventricular tachycardia that was adequately detected and WCD shock was delivered. After WCD shock, the patient remained unconscious and developed irregular ventricular rhythm going along with some noising leading to oversensing and delivery of another – inappropriate – WCD shock**

electrodes.[18] Accurate and thorough training and instruction of the patients therefore seems mandatory. The effectiveness and reliability of the WCD mainly depends on the patient's compliance.
In the WEARIT/BIROAD registry 65 out of 289 patients discontinued WCD use before prematurely, 30% did so due to comfort or lifestyle issues.[18]

LaPage et al. reported one case of missensing a fatal ventricular arrhythmia in a patient with unipolar pacemaker stimulation.[46] Unipolar stimulation should be avoided in patients wearing the WCD.

Sudden cardiac arrest may be due to asystole in some patients. Chung et al. reported 23 patients showing asystole events, 17 of which died.[47] Asystole is a relevant cause of SCD in patients with reduced LV function[48] and to date, there are no data about the relevance of backup pacing on mortality benefit in ICD patients.

Since the WCD is not able to provide pacing for bradyarrhythmia, asystole may lead to SCD even though the patient is wearing the WCD. Nevertheless, an asystole event will trigger the alarm cascade and may call possible bystander's attention to the patient.

Inappropriate therapies are another concern during WCD use. They are reported occurring in 0.5-3% of the patients.[24, 32] Like in implanted devices, there is the possibility of T wave oversensing. If the patient fails to press the response buttons, inadequate shock will be delivered (Figure 2). Since the WCD is programmed to deliver a "synchronized" shock in case of regular VT, a "synchronized" shock triggered by an oversensed T wave may happen with a high risk of induction of VF. This underlines again the need for a dedicated training of the patient in handling the WCD.

One of our patients presented a hemodynamic instable VT and fell unconscious. VT was detected and shocked by the WCD. Immediately after WCD shock, the patient developed irregular ventricular rhythm. This rhythm was inappropriately classified as a ventricular tachyarrhythmia by the WCD. Since the patient was still not fully conscious, he failed to press the response buttons and therefore received a second shock, which was inappropriate (Figure 3). Besides the psychic and painful consequences, inadequate therapies bear the risk for proarrhythmogenity by triggering malignant arrhythmias. The concept of pressing the response buttons gives relevant safety, but however there are possible scenarios in which the patient may not be capable to withhold therapies, as shown in our case.

Undersensing due to low amplitudes during VF is a major concern in ICD. Low amplitudes in VF may even more occur in surface ECG. In one patient, we noticed VF undersensing due to very low amplitudes during VF (Figure 4).

Workflow

The LifeVest Network® (Zoll, Pittsburgh, PA, USA) permits

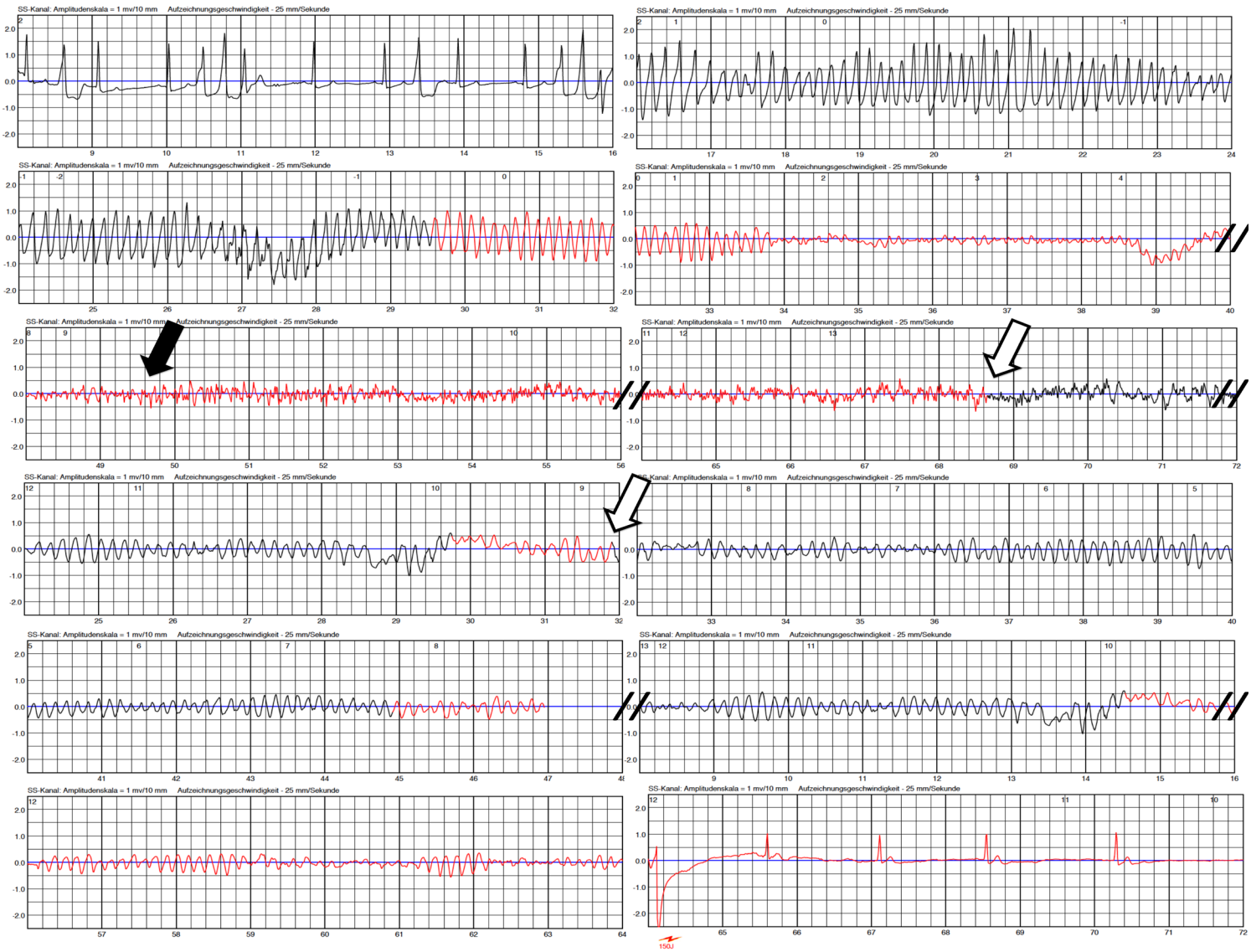

Figure 4: **Spontaneous ventricular fibrillation (VF) occurred in this patient with peripartum cardiomyopathy. Amplitude of VF rapidly decreased followed by myopotentials (black arrow) which were possibly linked to hypoxia-related seizures. Due to this high-frequency low-amplitude signals, VF criteria were no longer satisfied and detection was cancelled (white arrows). VF was redetected several more times. Probably due to some increase in VF amplitude, VF was finally redetected and the life-saving shock was successfully applied 80 seconds after onset of the tachycardia**

surveillance of WCD patients via remote monitoring. As a result of increasing patient numbers being considered for WCD wearing, the process of screening, prescription, training and remote monitoring of the patients becomes more and more time consuming. Increasing patient numbers require structured and optimized patient management strategies to assure both, reliable logistics and adequate handling of critical events. In our department, we have established a workflow determining responsibilities and sequences in the course of a WCD wearing (Figure 5). Screening possible patients for WCD wearing is performed by a trained nurse using a screening protocol considering the indications listed in table 1. The decision for WCD wearing is then taken by a physician taking into account device-related issues (efficacy and safety), patient-related factors (compliance, aptitude, acceptance), and disease-related aspects (indications and survival benefit). Cautious instruction of the patient (and, if feasible, family members) is performed by the manufacturer when supplying the device. WCD data (arrhythmia events, compliance, etc.) is available through the telemonitoring system. Any event reported in LifeVest-Network® is verified by the responsible nurse and submitted for further review to the physician, if classified as "critical event". "Critical events" were defined as: (1) any therapy delivery, (2) any sustained or non-sustained tachycardia, (3) any abnormality in the ECG not convincingly attributed to noise. In order to identify patients at nontransient, enduring risk for SCD, a careful follow-up for re-evaluation of LVEF is scheduled after 3 months. We use this standardized workflow to facilitate and optimize patient management in clinical routine.

Perspective

The WCD also offers new diagnostic options that may be used in future versions. The exceptional chance of this device consists in a continuous ECG monitor for 3 to 6 months. It already detects asystole events (without giving any therapeutic options), but it could just as well detect other arrhythmias. By detecting asymptomatic atrial fibrillation, the WCD could enable stroke prevention at an

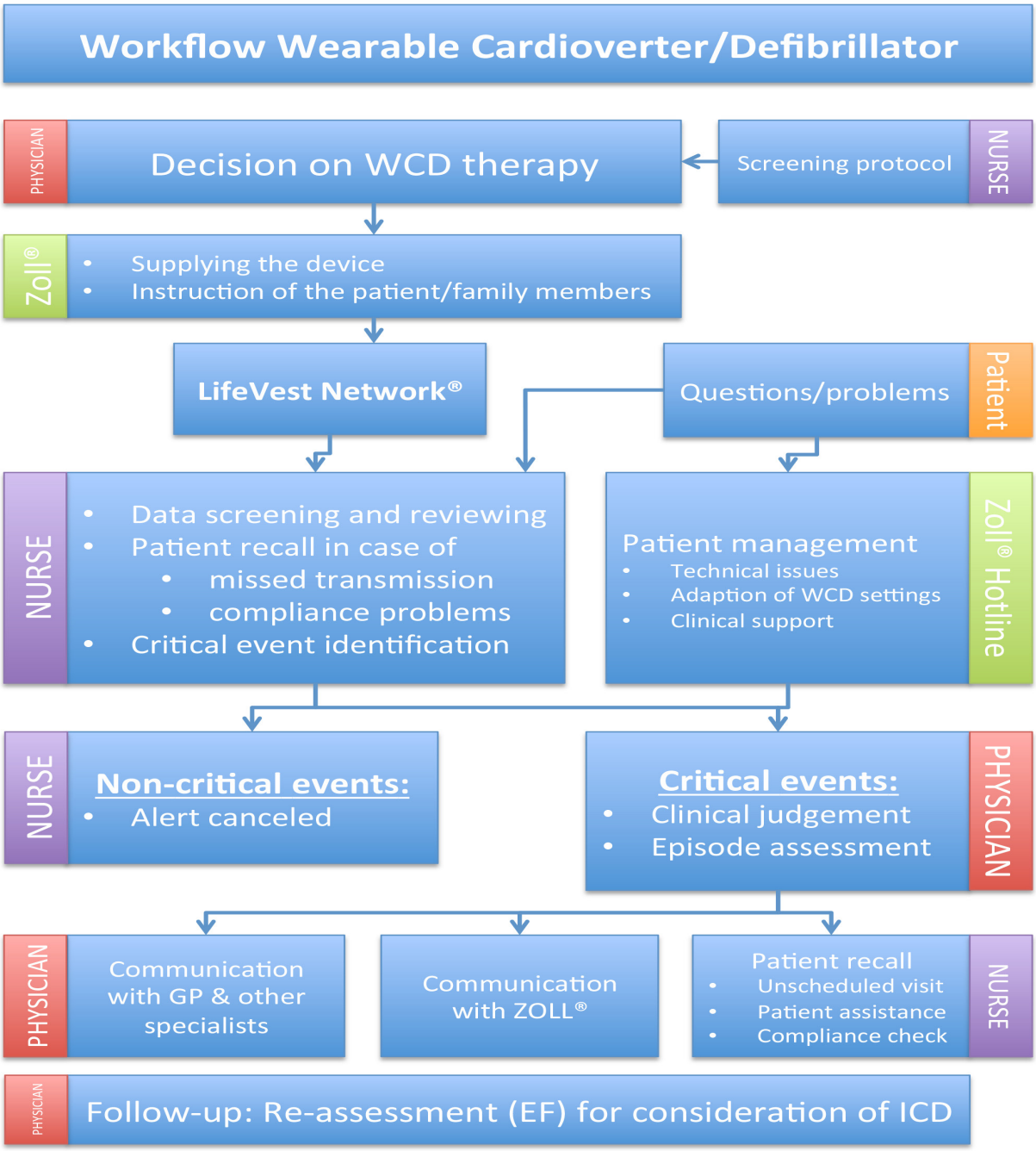

Figure 5: **Workflow of the Wearable Cardioverter/Defibrillator (WCD) program at Hannover Medical School (GP: general practitioner, EF: left ventricular ejection fraction)**

early stage. Continuous analysis of the ECG during this long period in high-risk or assumingly high-risk patients has never been done before. Additionally, the device can offer supplemental parameters, such as heart failure indices or tests, which may be relevant in some patients. Technicians and developer of the manufacturer should yield this hoard to discover new unprecedented insights in rhythmic and arrhythmic evolution in these patients. This tool offers completely new options for future ECG risk stratification.

Conclusions

WCD use is effective and adequate for temporary prevention of sudden arrhythmic death in chosen populations. In particular, it provides secured time for sophisticated risk stratification to identify patients at persistent risk for SCD. Nevertheless, prospective randomized trials seem mandatory to prove a prognostic effect/relevance and the economic value of this device.

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Table 2: Registries on WCD (MI: myocardial infarction, PPCM: Peripartum cardiomyopathy, NICM: non-ischemic cardiomyopathy, CHD: congenital heart disease, IA: inherited arrhythmias)

Publication	Year	Patients (n)	Etiology	Prospective/ retrospective	Appropriate shocks	Compliance (h/d)	Cumulative wearing time	Unnecessary shocks
WEARIT/ BIROAD[18]	2004	289	Miscellaneous	Prospective	6	n/a	Mean 3.1 months	6 (2%)
Klein[50]	2009	354	Miscellaneous	Retrospective	27 (27.6%)	Mean 21.3	Mean 106 days	0
Saltzberg[38]	2009	258	PPCM/ NICM	Retrospective	0/2	18.3/17.0	Mean 75±81/56±54 days	0/0
Dillon[17]	2010	2105	Miscellaneous	Retrospective	54	Median 21.3	Median 36 days (3-365)	34
Chung[47]	2010	3569	Miscellaneous	Retrospective	76 (2.1%)	Mean 19.9±4.7	Mean 52.6±69.9 days	67 (1.9%)
Rao[32]	2011	162	CHD, IA	Retrospective	0/2%	Mean 19	Mean 27/29 days	0/3%
Epstein[19]	2013	8453	Post MI	Retrospective	146 shocks in 133 (1.6%) patients	Median 21.8	Mean 69±61 (median 57) days	114 in 99 patients
Zishiri[51]	2013	4958	Miscellaneous	Retrospective observational cohort study	18 shocks in 11 patients	n/a	n/a	n/a
Tanawuttiwat[40]	2014	97	Explantation of ICD	Retrospective	4	Median 20	Median 21 days	2
Sasaki[52]	2014	9		Retrospective	1	Mean 23.7	Mean 21 days	0
Duncker[39]	2014	9	PPCM	Prospective	4	Mean 22.0±2.4	Mean 133±103 days	0
Opreanu[34]	2015	122	Candidates for cardiac transplant	Retrospective	7	Mean 17±7 (median 20)	Mean 127±392 (median 39) days	2
WEARIT-II[24]	2015	2000	ICM, NICM, CHD,	Prospective	120 in 41 patients	Median 22.5	Median 90 days	10 patients

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Anemia: An Independent Predictor Of Adverse Outcomes In Older Patients With Atrial Fibrillation

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Abstract

Both anemia and atrial fibrillation are common in older people and their prevalence is age dependent which increases as population ages. Anemia, especially acute onset, predisposes to new onset atrial fibrillation which is likely to be mediated through inducing heart failure first and this predisposition seems to be potentiated by the presence of renal impairment. Anemia adds to the comorbidity burden of patients with atrial fibrillation and independently increases the risks of adverse outcomes such as increased hospitalization, mortality, bleeding and thromboembolic events. Early detection and correction of anemia in patients with atrial fibrillation may have a positive impact on reducing these adverse events.

Introduction

Anemia, defined as a reduced hemoglobin concentration or hematocrit value, is one of the most common disorders globally affecting about 24.8% of the overall world population.[1] The prevalence of anemia is higher in older people and seems to increase with aging and with increased comorbidity burden. For example, the prevalence of anemia is about 11% in men and 10.2% in women aged 65 years and about 25% in men and 20% in women above the age of 85 years.[2] In the frail older population living in care homes the anemia prevalence is even much higher reaching around 48% to 63% of the total residents reflecting their multiple comorbidities and advanced age.[3] Similarly, atrial fibrillation (AF), the most common sustained cardiac arrhythmia, is age dependent and its prevalence doubles with each decade of life from 0.55% at the age of 50 to 60 years reaching about 12% in those above the age of 75 years with an annual incidence of around 2%.[4] Therefore, AF appears to affect mainly older people with about 80% of the total AF population are 65 years of age or older and by the year 2050, this percentage will increase to around 88%.[5] Patients with AF have twice the mortality risk compared to those in sinus rhythm likely due to the associated comorbidities, including anemia, in AF patients.[6] Anemia commonly coexists with chronic conditions such as heart failure and diabetes mellitus and appears to be an independent predictor of adverse outcomes associated with these conditions.[7,8] AF, as a chronic condition, is not an exemption and this review explores the relationship between anemia and AF and its role as an independent predictor of adverse outcomes in patients with AF.

Key Words:
Anemia, Atrial Fibrillation, Adverse Outcomes.

Disclosures:
None.

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Methods

We have performed a search of Medline and Embase from January 1969 to November 2015 using keywords relating to anemia, atrial fibrillation and adverse outcomes. Only English language articles were selected. Articles were reviewed for relevance by abstract. A manual review of citations in retrieved articles was performed in addition to the electronic literature search. The final list of cited references was chosen on the basis of scientific quality and relevance to the topic of review.

Does Anemia Precipitate New Onset AF?

The answer to this question is still not clear. It appears that the relationship between anemia and new onset AF is complex especially in the presence of comorbid chronic kidney disease (CKD) or heart failure. Recently, it has been shown that anemia, defined as a hemoglobin of <13 g/dL, was 1.5 times more likely to be associated with new onset AF in a Japanese 15-year prospective cohort study of 132,250 subjects aged 40 to 79 {hazard ratio (HR) 1.50, 95% confidence interval (CI) 1.24 to 1.83, p<0.0001} compared to normal hemoglobin level. CKD, defined as an estimated glomerular filtration rate (eGFR) of <60 mL/min/1.73m^2, was 2.56 times more likely to be associated with new onset AF (2.56, 2.09 to 3.13, p<0.0001) compared to normal kidney function. The combination of CKD and

Box 1: Characteristics of patients with combined anemia and AF.* [13,14]

- Older
- More prevalence of:
  - Heart failure
  - Coronary artery disease
  - Acute coronary syndrome
  - Peripheral arterial disease
  - Chronic kidney disease
  - Diabetes mellitus
  - Stroke
- Higher scores in bleeding risk scales
- Higher history of major bleeding events especially gastrointestinal bleeding.
- Higher scores on thromboembolic risk scales
- Higher thromboembolic events
- Receive less oral anticoagulation therapy
- Higher rate of oral anticoagulation therapy discontinuation
- Higher mortality rate
- Higher hospitalization rate

*Compared to those with AF alone.

anemia conferred a synergistic threefold higher risk for new onset AF (3.22, 2.43 to 4.19, P<0.0003) which is higher than would have been expected from the individual effects of CKD or anemia alone. Borderline hemoglobin level increased the risk for new onset AF only in patients with CKD but not in patients with normal kidney function confirming the synergistic action between anemia and CKD in precipitating new onset AF. This may be due to the fact that the pathogenesis of both AF and CKD is associated with common risk factors such as advancing age, hypertension and diabetes mellitus in addition to the hemodynamic changes associated with anemia itself such as reduced oxygen carrying capacity which may contribute to the susceptibility of new onset AF development.[9] In another retrospective cohort study of Medicare patients without pre-existing AF or end stage renal disease who were followed up from 2006 to 2008, advanced CKD and anemia were independently associated with incident AF (HR 1.13, 95% CI 1.09 to 1.18, p<0.0001 and 1.05, 1.03 to 1.07, p<0.0001 respectively). No synergistic effect between renal function and anemia was investigated in this study.[10] The onset of anemia may be another determinant factor for the new onset AF precipitation. Chronic anemia alone was not directly associated with incident or prevalent AF in one study.[11] In a single center community based retrospective study of 3,867 patients over the age of 65 years, new onset AF was found in 7.5 % of the anemic patients and 5.5% of the non-anemic patients however, after the adjustment for comorbid conditions, chronic anemia was not associated with new onset AF (p=0.922). Chronic anemia seems to require other comorbid factors like heart failure to precipitate AF as suggested in this study cohort.[11] The cardiac effects of the acute onset may be different from the chronic onset anemia. Baseline cardiac status, severity and rapidity of the onset of anemia may affect cardiac hemodynamics. For example, in acute anemia hemodynamic stress occurs due to the acute drop in hemoglobin concentration leading to tachycardia, as a compensatory physiologic response, that may leave less time for the heart to adapt. On the other hand, the gradual decrease in hemoglobin levels in chronic anemia could allow the heart to adapt before heart failure or AF develops making chronic anemia better tolerated. Other factors specific to old age such as reduced muscle mass, reduced exercise capacity and reduced sympathetic responses may lead to reduced

Table 1: Studies on anemia as a predictor of mortality or hospitalization in patients with AF

Study	Population	Aim To	Main findings
Puurunen, 2014 [14]	861 patients with AF undergoing PCI	Analyse impact of anemia on outcome of patients with AF undergoing PCI	Anaemia predicted all cause mortality (HR 1.62, 95% CI 1.05 to 2.51, p=0.029)
Sharma, 2009 [15]	13,067 Medicare beneficiaries hospitalized with AF	Investigate the association of anemia with mortality and hospitalizations in patients with AF	Anemia predicted mortality (HR 1.66, 95% CI 1.28 to 2.17) and hospitalization (1.28, 1.15 to 1.43)
Lee, 2015 [16]	166 patients with AF	Investigate role of anemia in predicting CV outcome.	Anemia predicted mortality and hospitalization (HR 0.83, 95% CI 0.71 to 0.96, P=0.015).
Christiansen, 2013 [17]	729,088 patients with AF associated hospitalization	Examine the excess risk of hospitalization in patients with AF	Anemia increased risk of hospitalization (RR 3.8, 95% CI 3.7 to 3.8)
Suzuki, 2012 [18]	1942 patients with AF	Identify predictors of heart failure events in patients with AF	Anemia increased risk of mortality or hospitalization (HR 3.01, 95% CI 1.78 to 5.10, p<0.001)
Vidal-Perez, 2013 [19]	798 patients with AF in primary care.	Describe predictors of mortality or hospitalization.	Anemia predicted end points (HR 1.37, 95% CI 1.08 to 1.75, p=0.010)
Westenbrink, 2015 [20]	18,113 patients with AF in RE-LY study	Determine if anemia predicts CV events	Anemia predicted all cause mortality or myocardial infarction (HR 1.50, 95% CI 1.32 to 1.71)
Westenbrink, 2014 [21]	18,201 patients with AF in ARISTOTLE study	Test whether anemia predicts CV outcomes	Anemia predicted all cause mortality (HR 1.68, 95% CI 1.46 to 1.93, p<0.0001)
Takabayashi, 2014 [22]	3,821 patients with AF in Fushimi study	Test relationship between anemia and heart failure in patients with AF	Anemia predicted heart failure hospitalization (OR 1.6, 95% CI 1.00 to 2.36, p=0.049)

PCI= Percutaneous coronary intervention, CV=Cardiovascular, HR=Hazard ratio, CI=Confidence interval, RR=Relative risk, OR=Odds ratio.

Table 2: Studies on anemia as a predictor of bleeding or thromboembolic events in patients with AF

Study	Population	Aim To	Main findings
Puurunen, 2014 [14]	861 patients with AF undergoing PCI	Analyse impact of anemia on outcome of patients with AF undergoing PCI	Anemic patients had more thromboembolic events (29.1% vs 19.4%, p=0.002), stent thrombosis (3.9% vs 0.7%, p=0.002), minor (7.0% vs 3.3%, p=0.028) and total bleeding (25.2% vs 21.7%, p=0.059) events
Westenbrink, 2015 [20]	18,113 patients with AF in RE-LY study	Determine if anemia predicts thromboembolic or bleeding events	Anemia predicted stroke or systemic embolism (HR 1.41, 95% CI 1.12 to 1.78) and major bleeding (2.14, 1.87 to 2.46)
Westenbrink, 2014 [21]	18,201 patients with AF in ARISTOTLE study	Test whether anemia predicts major bleeding	Anemia predicted major bleeding (HR 1.92, 95% CI 1.62 to 2.28, p<0.0001)
Shireman, 2006 [23]	26,345 patients with AF on warfarin	Develop a bleeding risk model	Anemia predicted major bleeding (HR 2.36, 95% CI 1.76 to 3.17)
Katoh H, 2014 [25]	184 patients with AF on dabigatran	Determine risks of bleeding	Anemia was a predictor of major bleeding (β=0.457, p=0.02)
Goodman 2014 [26]	14,264 patients with AF on warfarin or rivaroxaban	Identify predictors of bleeding	Anemia predicted major bleeding (HR 1.88, 95% CI 1.59 to 2.22, p<0.0001)
Friberg, 2012 [27]	90,490 patients with AF	Investigate risks for bleeding	Anemia predicted major bleeding (HR 1.40, 95% CI 1.28 to 1.53)
Beyth, 1998 [28]	264 patients with AF on warfarin	Evaluate outpatient bleeding risk index	Anemia or other morbidity increased annual probabilty of bleeding from 11% to 44%
Gage, 2006 [29]	3791 patients with AF	Find a bleeding risk scheme	Anemia was validated as a part of the bleeding risk scheme
Fang, 2011 [30]	9,186 patients with AF	Develop a bleeding risk stratification score	anemia was validated as part of the bleeding risk scheme (HR 3.27)

PCI= Percutaneous coronary intervention, HR=Hazard ratio.

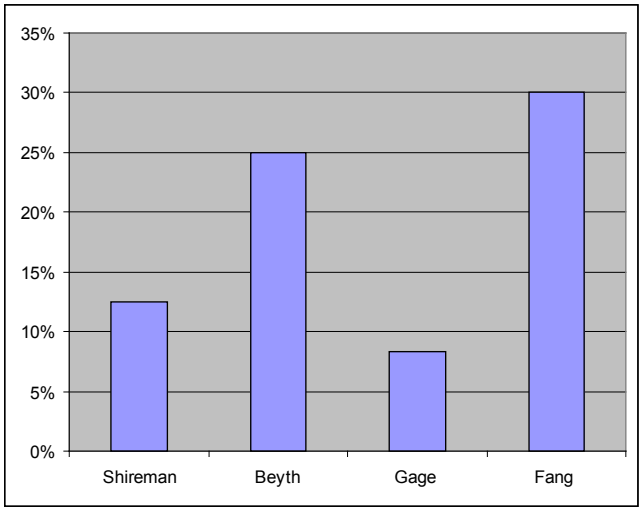

Figure 1: Weighting of anemia versus other risk factors for bleeding in 4 commonly used bleeding risk scores[23, 28-30]

oxygen demands and assist in the adaptation to the gradual decrease in hemoglobin levels in chronic anemia. It is possible that chronic anemia, if left untreated, may reach a threshold to precipitate heart failure first as an intermediate stage and subsequently precipitates AF. Therefore, patients with combined heart failure and anemia are likely to be at a higher risk for incident AF compared to those with anemia alone. In summary, anemia especially with acute onset appears to precipitate new onset AF mediated by inducing heart failure first and potentiated by the presence of renal impairment.

Anemia Increases The Comorbidity Burden Of Patients With AF

Patients with AF often have other cardiovascular comorbidities such as chronic heart failure, stroke, valvular heart disease, hypertension and diabetes mellitus.[12] The co-existence of anemia and AF further increases this comorbidity burden. For example, in the Fushimi-Japan AF Registry, patients with anemia and AF had higher prevalence of comorbidities compared to those with AF alone. They were older, mean (SD) age 79.6 (10.3) vs. 73.4 (10.5) years, p<0.001, had more prevalence of heart failure (43.1% vs. 25.8%, p<0.001), coronary artery disease (19.5% vs. 14.8%, p=0.006), peripheral arterial disease (6.2% vs. 4.2%, p=0.04), chronic kidney disease (52.5% vs. 22.3%, p<0.001) and history of major bleeding (4.2% vs. 1.5%, p<0.001). They tended to have a higher thromboembolic risk with greater mean (SD) CHA2DS2-VASc scores, 4.22 (1.64) vs. 3.35 (1.68), p<0.001, a higher prevalence of previous stroke (25.8% vs. 18.6% p<0.001) and received less oral anticoagulation therapy (44.4% vs. 52.4%, p<0.001).[13] In the prospective multicenter Atrial Fibrillation undergoing Coronary Artery Stenting (AFCAS) study, anemic patients with AF were older, more often had diabetes, CHA2DS2-VASc score >4, HAS-BLED score ≥3, prior history of heart failure, chronic renal impairment and acute coronary syndrome (p<0.05 for all) compared to those with AF alone.[14] Characteristics of patients with combined AF and anemia compared to those with AF alone are summarised in Box 1.

Anemia And Adverse Outcomes

Anemia is associated with chronic conditions and appears to increase the comorbidity burden of these conditions leading to adverse outcomes including increased mortality.[7, 8] AF, as a chronic condition, is not an exemption and patients with comorbid anemia and AF appear to have a worse outcomes compared to those with AF alone.

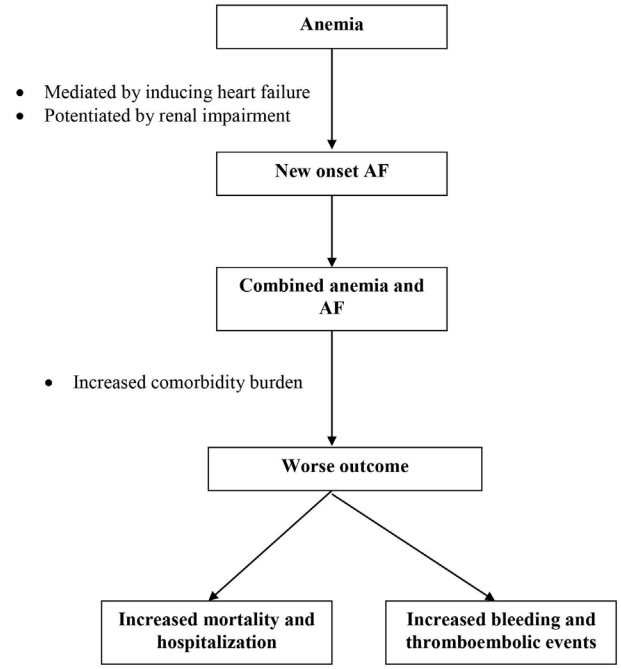

Figure 2: Relationship between anemia and AF: Anemia predisposes to new onset AF through inducing heart failure and potentiated by the presence of renal impairment. The coexistence of anemia and AF increases the comorbidity burden and worsens the overall outcome

Hospitalization And Mortality Risks

Anemia is an independent predictor of mortality and hospitalizations in older people with AF independent of the demographic factors, comorbid conditions or the use of cardiovascular medications. In a retrospective study of 13,067 Medicare beneficiaries in the US, mean age 79.8 years, hospitalized with AF, Hematocrit (Hct) was significantly (P <0.0001) associated with increased risk of death and re-hospitalisation. Patients in the lowest Hct category (<25%) had the worst survival, whereas patients with Hct's of 40% to 44.9% or 45% to 49.9% had the most favorable survival. The trend was of an increasing risk of mortality with a decreasing Hct value. In comparison to Hct of 40% to 44.9%, the adjusted HRs for all cause mortality were 1.66 for Hct <25%, 1.50 for 25% to 29.9%, 1.28 for 30% to 34.9% and 1.07 for 35% to 39.9%. The risk of re-hospitalization was 1.28 fold higher in the Hct category 25% to 29.9% (adjusted HR 1.28, 95% CI 1.15 to 1.43) compared to the category 40% to 44.9% after one year of follow up.[15] In another prospective study of 166 patients, mean (SD) age 71.0 (10.0) years, with persistent AF referred for echocardiographic examination in Taiwan, low hemoglobin concentration was also a predictor of cardiovascular events (mortality and hospitalization). Fifty four patients had anemia, mean (SD) hemoglobin 11.0 (1.4) g/dl compared to 112 non anemic subjects, mean (SD) hemoglobin 14.6 (1.2) g/dl, p=0.001. In the multivariate analysis hemoglobin was independently associated with increased cardiac events (HR 0.83, 95% CI 0.71 to 0.96, P = 0.015) after an average of 20 months follow up. The addition of hemoglobin to the clinical and echocardiographic data significantly improved the prediction of adverse cardiac events (P = 0.010).[16] In a Danish nationwide retrospective study, patients with AF were more likely to be admitted to hospital compared to those in sinus rhythm. When adjusted for age, sex and time period, patients with AF had a relative risk of 8.6 (95%CI 8.5 to 8.6) for cardiovascular related

admissions and 4.0 (95% CI 4.0 to 4.0) for non-cardiovascular related admissions. Anemia was identified as an independent predictor of hospital admissions increasing hospitalization by almost 4 folds in patients with compared to those without AF {Relative risk (RR) 3.8, 95% CI 3.7 to 3.8} and was also associated with a longer mean length of hospital stay (6.3 vs 5.6days).[17] Heart failure events defined as an increased mortality or hospitalization were independently increased by the presence of anemia in a prospective Japanese study of 1942 patients (HR 3.01, 95% CI 1.78 to 5.10, p<0.001). Anemia diagnosis formed a part of a risk score to identify patients with AF who are at risk for the incidence of new hospitalization or death with a diagnosis of heart failure (the H2ARDD score: 2 points for heart diseases, 1 point for anemia, 1 point for renal dysfunction, 1 point for diabetes and 1 point for diuretic use).[18] In the primary care, anemia was also identified as a risk factor for hospitalisation or mortality (HR 1.37, 95% CI 1.08 to 1.75, p=0.01) in a cohort of 798 patients with AF followed up for a mean (SD) of 2.8 (0.7) years.[19] The presence of anemia was associated with the composite endpoint of all-cause mortality or myocardial infarction (adjusted HR 1.50, 95% CI 1.32 to 1.71) in a retrospective analysis of the RE-LY study, all-cause mortality (adjusted HR 1.68, 95% CI 1.46 to 1.93, p<0.0001) in the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial and of all-cause mortality at 12-month follow-up (HR 1.62, 95% CI 1.05 to 2.51, p=0.029) in the AFCAS study.[20, 21, 14] Anemia likely to increase hospitalization through increasing adverse events. For example, after one year of follow up of the Fushimi-Japan AF Registry, patients with anemia had more heart failure related (7.4% vs 3.7%, p<0.01) and more major bleeding related hospitalisation (3.2% vs 1.3%, 0.01) and in a national registry study of 26,345 patients with AF, anemia was an independent risk factor for major bleeding that led to hospitalisation (HR 2.36, 95% CI 1.76 to 3.17).[22, 23] (Table 1)

Bleeding And Thromboembolic Risks

Anemia has been shown to be associated with an increased risk of thromboembolic and bleeding events in anticoagulated patients with AF. A retrospective analysis of 17,796 patients with available hemoglobin results in the RE-LY study showed that anemia was present in 12% of the population at baseline and the presence of anemia was associated with stroke or systemic embolism (adjusted HR 1.41, 95% CI 1.12 to 1.78). Anemia was also associated with a higher risk of major bleeding complications (adjusted HR 2.14, 95% CI 1.87 to 2.46) and discontinuation of the anticoagulant therapy (adjusted HR 1.40, 95% CI 1.28 to1.79). The association between anemia or hemoglobin and the different cardiovascular endpoints did not differ according to gender, major comorbidities, treatment allocation, eGFR, aspirin use or prior use of warfarin. The incidence of events was lower in patients with transient anemia than in patients with chronic anemia (adjusted HR 0.66, 95% CI 0.49 to 0.91). Anemia remained a predictor of bleeding complications, even after adjustment for the HAS-BLED score. During the course of the study, patients with anemia spent more time below the therapeutic range than those without anemia (26% vs. 22%, P < 0.0001), whereas the times above the therapeutic range were comparable.[20] In the AFCAS study of 861 patients, anemia was common affecting 30% of AF patients and was associated with major adverse cardiac and cerebrovascular thrombotic events (29.1% vs 19.4%, p=0.002) and minor bleeding events (7.0% vs 3.3%, p=0.028) compared to those without anemia. The incidence of stent thrombosis was also significantly higher in anemic versus non-anaemic patients (3.9% vs 0.7%, p=0.002).[14] The thromboembolic events associated with anemia seem to also affect the functional outcome. In the Acute STroke Registry and Analysis of Lausanne (ASTRAL) study, AF was more common in patients with compared to those without anemia (33.5% vs 25.2%, p<0.001) and the presence of anemia was a predictor of worse stroke functional outcomes as well as short and long term mortality.[24] In the ARISTOTLE trial anemia predicted major bleeding (adjusted HR 1.92, 95% CI 1.62 to 2.28, p<0.0001). Patients with anemia were older (median 73 vs. 69 years), had higher mean CHADS2 score (2.4 vs. 2.1), and were more likely to have experienced previous bleeding events (mean 20.1% vs. 16.2%) compared to those without anemia.[21] Pre-existing anemia was associated with major bleeding (β=0.457, p=0.02) in a retrospective Japanese study of 184 patients with AF on dabigatran treatment after a mean (SD) follow up of 383 (190) days. The baseline hemoglobin concentration also correlated negatively (r=-0.160, p=0.03) with the development of major bleeding.[25] In the Rivaroxaban Once-daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial (ROCKET) in Atrial Fibrillation, anemia at baseline was independently associated with major bleeding risk in both rivaroxaban and warfarin arms (HR 1.88, 95% CI 1.59 to 2.22, p<0.0001).[26] In 90,490 patients of the Swedish AF cohort study without anticoagulant treatment, anaemia a significant predictor of major bleeding (HR 1.40, 95% CI 1.28 to 1.53).[27] Anemia is also highly scored as an independent risk factor for bleeding in several commonly used risk stratification schemes validated to assess the risk of bleeding in patients with AF before initiating oral anticoagulation therapy.[23, 28-30] (Figure 1) Anemia appears to be an independent risk for bleeding regardless of the duration of oral anticoagulation. In a prospective cohort study to investigate the significance of anemia as a risk factor for bleeding in patients with AF newly started compared to those on long term oral anticoagulation, anemia remained a significant risk factor (HR 2.21, 95% CI 1.53 to 3.18, p<0.001) irrespective of the timing of initiation of anticoagulation therapy.[31] (Table 2)

Discussion

The coexistence of anemia and chronic conditions not only further adds to the comorbidity burden but it appears to be a detrimental factor in worsening the outcomes.[7, 8] AF is not an exemption to this observation. In AF population anemia clearly predicts adverse outcomes including increased mortality, bleeding, thromboembolic events and hospitalization. (Figure 2)

Mechanism Of Adverse Outcomes

Anemia may increase mortality through increasing the risk of coronary ischemic events. This may be due to the fact that anemia may predispose to left ventricular hypertrophy and subsequently to heart failure. Anemia is associated with cardiovascular compensatory changes including high cardiac output, low systemic vascular resistance and sodium and water retention increasing the cardiac workload.[32] In patients with established atherosclerosis, anemia appears to be a direct risk factor for myocardial ischemia and increased mortality.[33] In a meta-analysis of 27 studies, anemia was associated with increased mortality risk in patients with acute coronary syndrome.[34] The increased risk of bleeding induced by anemia may be explained by the fact that in the normal conditions, with normal red blood cell count, the flow and number of erythrocytes force the platelets centrifugally towards the endothelial lining. This facilitates the contact of

the platelets to the vessel wall. Therefore, platelet adhesion and aggregation occurs to reduce any bleeding when the vascular integrity is disrupted by injury. In patients with anemia and reduced red blood cell count this relationship is compromised with more luminally rather than marginally placed platelets impairing the process of platelet aggregation and adhesion increasing the risk of bleeding.[35] Anemia also decreases the amount of adenosine diphosphate that is available to contribute to collagen induced platelet aggregation at the site of injury.[36] The thromboembolic events precipitated by anemia may be due to the fact that anemia may aggravate myocardial ischaemia and unveil significant coronary obstruction in patients with established atherosclerosis. The hemodynamic changes associated with anemia such as increased heart rate and cardiac output lead to myocardial hypertrophy increasing myocardial oxygen demands and exaggerating the imbalance between myocardial oxygen demand and supply.[37] The duality of anemia to predict both bleeding and thromboembolic events is not unusual as it is shared by the other risk factors for ischemic stroke such as age or hypertension. Increased hospitalization risk is likely to be due to the increased adverse outcomes induced by anemia as stated above.

Implications For Clinical Practice

The relationship of anemia with adverse outcomes could be due to the possibility that anemia acts as a mediator of adverse outcomes and therefore correction of anemia may improve outcomes. The other possibility is that anemia may merely act as a marker for persons with worse prognosis related to their underlying complex condition and comorbidity burden. However, in the Randomized Etanercept North American Strategy to Study Antagonism of Cytokines (RENAISSANCE) trial, correction of anemia improved the outcome. For each one g/dL increase in the hemoglobin concentration there was an improvement in the left ventricular hypertrophy with a 4.1 g/m2 decrease in left ventricular muscle mass and a 15.8% reduction in mortality risk after 24 weeks of follow up.[38] Anemia appears to identify patients with AF who are at increased risk for thromboembolic events who could benefit most from oral anticoagulation therapy and who are also at risk for bleeding complications. These findings suggest that close monitoring of oral anticoagulation is important in patients with combined AF and anemia. Anemia enhances the performance of the bleeding risk scales and is already included as an independent predictor in four of them. However, anemia may not enhance the performance of the thromboembolic risk scales such as CHA2DS2-VASc as older people (≥75 years) are likely to benefit from oral anticoagulation therapy regardless of their risk stratification.[39]

Physicians may under estimate the magnitude of the bleeding risk of anemia in patients with AF. In a study to describe physicians' assessment of patient's risk of bleeding using data from national clinical registry of AF, anemia was the most significantly associated with physician-assigned bleeding risk being lower than empirically calculated bleeding risk (adjusted estimate, 1.36, 95% CI, 1.30 to 1.42).[40] The bleeding risk predicted by anemia, especially gastrointestinal bleeding, could be limited by the inability to account for the effects of antiplatelets or nonsteroidal anti-inflammatory drugs used over the counter. Another factor is whether the use of oral anticoagulation may have a confounding effect on calculating the bleeding risk. However, in the Loire valley AF project, anemia was an independent risk factor for bleeding in 7156 patients with AF whether on vitamin K antagonist or not (HR 2.49, 95% CI 1.27 to 4.88).[41] Anemia therefore appears to be a modifiable risk factor, which suggests that prevention or treatment of anemia could improve the prognosis in patients with AF.

Conclusions

Anemia is common in patients with AF, increasing their comorbidity burden and independently associated with increased risks of adverse outcomes. The early detection and treatment of anemia may have a positive effect in improving the outcomes however future research is needed to confirm that anemia is a modifiable risk factor in patients with AF.

Key points

- The prevalence of anemia and atrial fibrillation is age dependent.
- Anemia predisposes to new onset atrial fibrillation especially when renal impairment is present.
- The coexistence of anemia and atrial fibrillation increases the comorbidity burden and is associated with increased risk of adverse events.
- Early detection and treatment of anemia may improve the clinical outcomes in patients with atrial fibrillation.

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Atrial Fibrillation And Sleep Apnea: Considerations For A Dual Epidemic

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Abstract

Atrial fibrillation (AF) is the most common cardiac arrhythmia and shares many of the same risk factors as another common clinical condition, sleep apnea. The estimated prevalence of sleep apnea has increased over the past decade, and reflects a parallel increase in the most prominent risk factors of obesity and overweight. Both obstructive and central sleep apnea have been associated with AF in multiple studies, with the risk of AF increasing 2-4-fold compared to those without sleep breathing disorder. Continuous positive airway pressure (CPAP) has been shown to reduce the rate of AF recurrence following catheter ablation in patients with sleep apnea. However, the mechanisms by which sleep apnea precipitates AF or vice versa, remain unclear. In this Review, we examine the current date linking AF and sleep apnea, discuss the existing data supporting a mechanistic link between the two conditions, present the existing evidence for the effectiveness of CPAP in this growing population, and suggest approaches to screen AF patients for sleep breathing disorders.

Introduction

Atrial fibrillation (AF) is the most commonly encountered arrhythmia in clinical practice. There are an estimated 33 million individuals with AF worldwide, with approximately 5 million new cases annually. The incidence and prevalence of AF increases with age, with a 2-3-fold increase between ages 60 and 80.[1,2] Sleep disordered breathing (SDB), characterized by respiratory pauses of at least 10 seconds during sleep that result in oxyhemoglobin desaturation, is estimated to affect 17% of men and 9% of women aged 50-70.[3] These estimates are significantly increased compared to two decades ago, and reflect a parallel increase in the most prominent risk factors for SBD, overweight and obesity.[3] SDB encompasses a broad clinical spectrum ranging from mild airway resistance to prolonged apnea.

Obstructive sleep apnea (OSA), characterized by recurrent partial or complete collapse of the upper airway during sleep and associated with excessive daytime sleepiness, is estimated to affect 14% of men and 5% of adult women.[3] In the developed world, the majority of OSA cases are secondary, occurring as a result of overweight and obesity.[3] In secondary OSA, local fat deposition in the neck has been implicated as the cause of upper airway collapse and impaired neuromuscular control of the airway. In a small proportion of patients with clinical evidence of OSA, no abnormality of the upper airway can be identified on routine clinical examination. These individuals are considered to have idiopathic OSA. Previous work utilizing acoustic ultrasound and x-ray demonstrated that these individuals often have relatively small mandibles and posterior displacement of the mandibular symphysis, both of which affect the support to the anterior pharyngeal wall.[4]

Central sleep apnea (CSA) is characterized by diminished or absent respiratory effort during sleep, also associated with oxygen desaturation and daytime somnolence. In some cases of CSA, very shallow breathing can alternate with very deep breathing, as is the case with Cheyne-Stokes respiration. The estimated prevalence of CSA varies, but has been thought to account for up to one-fifth of all cases of SDB.[5] Similar to OSA, CSA occurs most often secondary to an underlying condition such as heart failure, neuromuscular dysfunction or narcotic use. Primary or idiopathic CSA is quite rare, and results from decreased input to respiratory motor neurons. The causes of idiopathic CSA are not known.

Association Between AF And Sleep Apnea

Obstructive Sleep Apnea And AF

OSA has been shown to contribute to increased AF burden.[1,6] Epidemiologic studies have identified a strong association of OSA and AF, with an increased risk for AF that is 2 to 4 times that of those without SDB.[7,8] In a large, prospective, community-based

Key Words:
Sleep Apnea, Atrial Fibrillation, CPAP, Outcomes, Arrhythmia Control.

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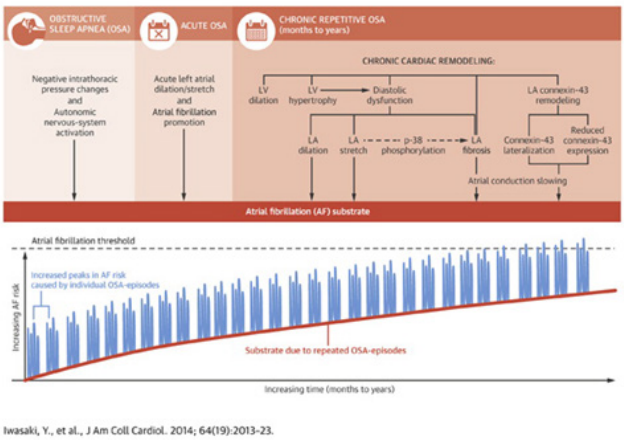
cohort, Mehra and colleagues found that individuals with SDB had 4 times the odds of AF as those without SDB (OR 4.02, 95% CI 1.03-15.74) after adjustment for age, sex, BMI and prevalent coronary heart disease. A secondary analysis of the same cohort found no dose-response relationship between risk for AF and severe to very severe SDB.[7] In contrast, Tanigawa et al observed that the risk of AF was linearly associated with severity of SDB in a community-based study of Japanese men; the odds of AF increased more than 2-fold for those with 5-15 apneic or hypopneic events per hour (2.47, 95% CI 0.91-6.69) and more than 5-fold for those with >15 apneic or hypopneic events per hour (5.66, 95% CI 1.75-18.34).[9] Gami et al prospectively assessed the risk of OSA, as determined by the Berlin questionnaire among 524 patients with AF or atrial flutter referred to a tertiary care center for cardioversion. After adjustment for risk factors, AF was significantly associated with OSA, with AF conferring twice the odds of OSA (OR 2.19, 95% CI 1.40-3.42) compared to a general cardiology population without AF.[10] Not all studies, however, have shown an association between OSA and AF. In a case-control study of patients with lone AF that excluded diabetics, Porthan and colleagues observed that the prevalence of sleep apnea in AF patients did not differ from those without AF (32% versus 29%, p=0.67).[11] However, the number of subjects in this study was small and the power to detect an association was therefore limited.

Central Sleep Apnea And AF

In clinical practice, OSA and CSA often coexist. Generally, patients are considered to have CSA when more than 50% of their apneic and hypopneic episodes are associated with reduced or absent respiratory drive.[5] As discussed above, this condition is prevalent among particular populations such as those with heart failure and primary neuromuscular disorders, and has also been associated with AF. Sin et al found AF to be associated with CSA in a retrospective analysis of 450 individuals with CHF referred to a tertiary care sleep center.[12] In this analysis, AF conferred a 4-fold increase in the risk of CSA (4.13, 95% CI 1.53-11.4), but no increased risk for OSA. An association between CSA and AF has also been observed in community-based cohorts without overt heart failure or underlying cardiac dysfunction. In an analysis of the Sleep Heart Health Study, we demonstrated that CSA conferred double the risk for incident AF (OR 2.06, 95% CI 1.23-3.44, p=0.0057) in an unselected population without clinical signs of SDB.[13] This association was also confirmed prospectively by Leung et al in a population with presumed idiopathic CSA, free of heart failure, coronary artery disease or stroke. The risk of AF was higher in those with CSA (3.3% versus 1.7%, p<0.001) than in those without SDB.[14]



Iwasaki, Y., et al., J Am Coll Cardiol. 2014; 64(19):2013-23.

Figure 1: Mechanisms by Which OSA Leads to AF

Potential Mechanisms

Although the majority of evidence supports a strong association between sleep apnea and AF, it remains unclear whether SDB is causal in the development of AF, as the two conditions share many of the same risk factors. Furthermore, the mechanism by which this may occur remains unclear. For example, obesity is a common risk factor for SDB and AF. But whether the link underlying the association is obesity itself or resulting effects on left atrial pressure and size, inflammatory and pro-fibrotic molecules, insulin resistance, or increased mean arterial blood pressure and atrial fibrosis is unknown. It has been suggested that the physiologic changes of SDB including intermittent hypoxia, hypercarbia, and intrathoracic pressure fluctuations predispose to arrhythmia through electrical and structural remodeling.[15]

The proposed mechanism by which hypoxia promotes AF is via autonomic nervous system dysfunction and electrical remodeling. In a dog model of intermittent hypoxia, Lu and colleagues found that hypoxia initially resulted in parallel changes in heart rate variability (HRV) indices associated with sympathetic and parasympathetic activity such that the atrial effective refractory period (AERP) and AF vulnerability were not affected.[16] However, with repeated hypoxic episodes, the parasympathetic indices of HRV were increased to a greater extent relative to sympathetic indices, and the AERP and AF vulnerability were also increased. This suggests that autonomic system imbalance may precipitate electrical changes in the atria that predispose to AF. Autonomic nervous system dysfunction is further supported in the development of AF based on studies of CSA patients in whom increased concentrations of plasma and urinary norepinephrine and epinephrine have been documented, independent of left ventricular dysfunction.[17]

Hypercarbia has also been implicated in electrical remodeling. In a sheep model, Stevenson et al found an inverse linear association between the effective refractory periods of the right and left atria and end-tidal CO2 levels in hypercarbic sheep that was not present in the hypoxic or control sheep.[18] In addition, atrial conduction times during pacing at a constant cycle length and during extrastimulus testing were significantly prolonged during and after resolution of hypercapnia. In contrast, no corresponding changes in conduction times were observed in the hypoxic or control sheep during or after resolution of hypoxia. Interestingly, AF vulnerability was eliminated during hypercapnia but was significantly increased following resolution of hypercapnia and normalization of ERP. This suggests that hypercapnia may not promote AF acutely, but rather may promote electrical substrate remodeling over time after repeated exposure.

There is also data suggesting that hypercapnia can result in cardiac structural changes. In studies of ventricular myocytes isolated from rat hearts, White et al observed that exposure to medium with high levels of CO_2 resulted in decreased cell to cell conduction.[19] Vorperian and colleagues exposed anesthesized dogs to an elevated mixture of inhaled CO_2 with resultant decrease in serum pH. They found that hypercarbia resulted in slowed propagation of impulses in the transverse direction, perhaps due to connexin dysfunction.[20] However, it is unclear why these changes would occur selectively in

the transverse rather than longitudinal direction and whether these structural changes occur in the atrium as well.

Fluctuations in intrathoracic pressure have also been implicated in electrical remodeling.[21] Sympathetic stimulation during acute episodes of tracheal obstruction can produce increased intracellular calcium load, leading to shortening of action potential duration and initiation of AF.[22-24] In a porcine model, Linz and colleagues simulated tracheal occlusion with and without the application of negative intrathoracic pressure (NTP).[25] They found a significant decrease (161 versus 96 ms, p<0.0001) in the atrial effective refractory period (AERP) after two minutes of tracheal occlusion with -100mbar. In contrast, tracheal occlusion without NTP had no effect on AERP. The change in AERP was associated with increased inducibility of AF (0% normal breathing or tracheal occlusion without NTP versus 91% with NTP). Linz also investigated the effect of autonomic changes; atropine prevented AERP shortening in NTP, did not affect the AERP during normal breathing and decreased AF inducibility with NTP from 91% to 17%. These data suggest that negative intrathoracic pressure can precipitate electrophysiologic changes that increase the inducibility of AF, and that these changes may be mediated by an autonomic effect.

There is also evidence of structural remodeling resulting from repeated episodes of OSA with fluctuating intrathoracic pressure. Iwasaki and colleagues created a rat model of OSA, in which the airway of intubated rats was occluded at end expiration for 40s followed by an 80s recovery period 20 times per day, 5 days per week for 4 weeks. After OSA cycles, rats were ventilated with room air and then extubated.[26] This group was compared to rats subjected to the same ventilator-arrest cycles but without airway closure, and to rats ventilated with room air throughout the procedure. OSA produced a statistically significant increase in left atrial dilation that was not seen in the sham or control groups. No significant differences in atrial ERP or sinus node recovery time was found between the groups. However, conduction velocity was decreased, and AF inducibility and mean AF duration were increased significantly (p<0.05) in OSA rats compared with sham rats. The investigators also observed structural differences between the groups; there was increased fibrosis, decreased expression of connexin-43, and a lateralized distribution of this protein in OSA rats compared to sham and control rats. These structural changes may explain the changes in conduction velocity and inducibility of AF in the absence of changes in atrial refractoriness.

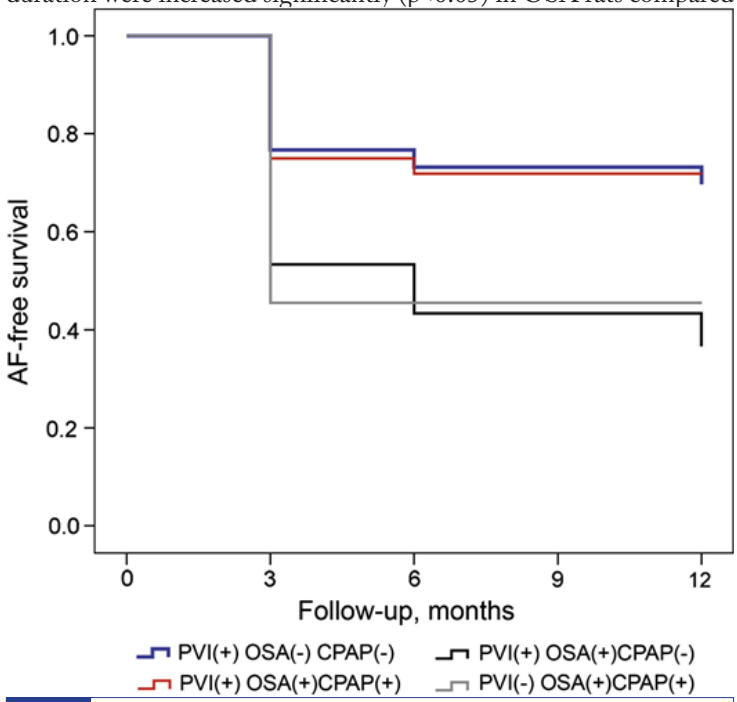


Figure 2: Kaplan-Meier Survival Curves According to Treatment Group

Ramos et al also created a rat model of OSA and similarly demonstrated increased atrial fibrosis (11.9 versus 8.32, p<0.01) in OSA rats compared to sham rats.[27] Amounts of angiotensin-converting enzyme were significantly increased, and matrix metalloproteinase-2 significantly decreased, in OSA rats compared to sham rats.[27] Thus, OSA may also predispose to AF through a mechanism of left atrial fibrosis. Taken together, there is a growing body of evidence that suggests that the physiologic effects of chronic SDB predispose to AF via electrical and structural remodeling that occurs over time (Figure 1)

There is data from humans supporting electrical and structural remodeling secondary to OSA. Dimitri et al compared electrophysiologic parameters among 20 patients with OSA and 20 without OSA undergoing ablation for paroxysmal AF.[15] Electroanatomic maps of the right and left atria were obtained in all patients to compare the voltage, conduction velocity and distribution of complex atrial electrograms. There was no difference in the right or left atrial refractory periods between those with OSA and those without (p=0.9). However, patients with OSA had prolonged conduction times along the coronary sinus and RA (p=0.02), a longer corrected sinus node recovery time (p=0.02), and a greater number (p=0.003) and duration (p=0.03) of complex electrograms along the crista terminalis. OSA patients also had a longer p wave duration (p=0.01), lower atrial voltage (RA p<0.01, LA p=0.02), slower atrial conduction velocity (RA p=0.001, LA p=0.02) and more complex electrograms in both atria (RA p=0.02, LA p=0.01) compared to those without OSA.[15] In prior studies, p wave duration and dispersion, measures of prolonged and heterogeneous atrial conduction have been found to correlate with severity of OSA.[28,29] These data suggest a possible difference in underlying atrial substrate between AF patients with and without sleep apnea.

Clinical Outcomes And Effect Of CPAP Treatment

In humans, OSA confers increased risk of recurrent AF that is mitigated by CPAP therapy. In a population of patients with AF and atrial flutter referred for electrical cardioversion, Kanagala and colleagues found that untreated OSA was associated with increased AF recurrence.[30] Of the 39 patients with OSA, 27 were not receiving CPAP therapy (n=25) or were using it inappropriately (n=2). Among those with OSA, patients receiving CPAP had a lower rate of recurrence of AF at one year than those not receiving CPAP (42% versus 82%, p=0.013). Importantly, the recurrence rate among CPAP-treated patients was similar to control patients without OSA. Additionally, in the 25 patients with untreated OSA, the nocturnal oxygen desaturation was greater among those with recurrent AF (n=20) compared to those without AF recurrence (n=5, p=0.034).

The effect of OSA and CPAP has also been examined among patients undergoing catheter ablation of AF. Patel et al evaluated 3,000 consecutive patients undergoing pulmonary vein isolation between January 2004 and December 2007, of which 640 (21.3%) were identified as having OSA. Overall, patients with OSA had a statistically significant increase in procedural failures (p=0.024) compared to patients without OSA. Among those with paroxysmal

AF, OSA patients had more non-pulmonary vein triggers and posterior wall firing than patients without OSA (20% versus 8%, p<0.001). This was also true in non-paroxysmal AF patients; patients with OSA had more non-pulmonary vein triggers than those without OSA (31% versus 19%, p = 0.001). Importantly, treatment with CPAP reduced the rate of AF recurrence (79% versus 68%, p=0.003). The presence of non-pulmonary vein triggers and absence of CPAP use strongly predicted ablation failure (HR 8.81, p<0.001).

We found a similar pattern of outcomes when we examined 426 consecutive patients undergoing PVI between 2007 and 2010 at our institution. Sixty-two patients had a diagnosis of OSA confirmed by polysomnography, of which 32 were identified as receiving CPAP therapy. At one year following first PVI, 71.8% of OSA patients using CPAP were free of AF recurrence as compared to 36.7% of OSA patients not using CPAP (p=0.01). Survival analysis demonstrated that the rate of recurrence among CPAP-treated individuals was similar to that of patients without OSA at 1 year (67% versus 71.8%, p=0.94). In addition, AF-free survival off antiarrhythmic medications was higher among CPAP users compared to non-users (65.6% versus 33.3%, p=0.02; Figure 2).

In another recent study, the results of polysomnography were compared between patients with and without SDB who have undergone catheter ablation for AF. Naruse et al obtained overnight polysomnograms in 153 patients who had undergone pulmonary vein isolation one week earlier.[31] One hundred sixteen of the 153 patients (76%) were diagnosed with OSA. Over a mean follow-up period of 18 months, AF recurrence in OSA patients not receiving CPAP was higher than in those without OSA as well as those with OSA on CPAP therapy (53% versus 22% versus 33%, respectively; p<0.01). After controlling for LA volume, plasma NT-pro-BNP and LVEF on multivariate analysis, CPAP use was found to decrease the risk of AF recurrence. In Cox model analysis, there were higher rates of AF recurrence following ablation in those with OSA, (HR 2.61, p=<0.05) and improved rates of arrhythmia control among those treated with CPAP (HR 0.41, p<0.01).[31]

A meta-analysis of the effect of OSA on outcomes following catheter ablation of AF by Ng and colleagues found a 25% increased risk of AF recurrence after ablation in OSA patients compared to those without OSA (RR 1.25, 95% CI 1.08 to 1.45, p = 0.003). In secondary analyses, this increase in risk appeared to be present among those diagnosed with OSA according to overnight PSG (RR 1.40, 95% CI 1.16 to 1.68, p = 0.0004), but not among those diagnosed with OSA by the Berlin Questionnaire (RR 1.07, 95% CI 0.91 to 1.27, p = 0.39).[32] A more recent metaanalysis examined 7 studies with a total population of 1,087 individuals.[33] They found that the relative risk reduction of CPAP on AF recurrence ranged from 30% to 56%, with an overall risk reduction of 42% for CPAP (RR 0.58, 95% CI 0.51-0.67, p<0.001). Interestingly, the same magnitude of risk reduction of CPAP on AF recurrence was observed in those who underwent PVI as well as those who did not undergo ablation. Table 1 summarizes the studies that have evaluated the effect of OSA on AF recurrence following catheter ablation.

Finally, the effect of CPAP on AF progression was recently examined in the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF).[34] In this analysis of 10,132 patients with AF enrolled in a nationwide registry, Holmqvist and colleagues documented an 18% prevalence of OSA. Those with OSA were more symptomatic, had greater rates of interventions for AF and higher rate of hospitalization, but a comparable risk of death, stroke, and myocardial infarction. The rate of AF progression was similar between the OSA and no OSA group (HR 1.06, 95% CI 0.89-1.28, p=0.51). Similarly, no difference in the risk of death, stroke, and myocardial infarction was observed between those on CPAP compared to those not receiving CPAP therapy. However, the rate of AF progression for those receiving CPAP therapy was lower than those with OSA not on CPAP, as well as those without OSA (HR 0.66, 95% CI 0.46-0.94, p=0.02).

CPAP therapy may reduce AF recurrence by preventing or reversing the structural changes of SDB. In a prospective, single center study of patients undergoing cardiac MRI prior to PVI, patients with sleep apnea on shorter duration of CPAP therapy were more likely to have persistent than paroxysmal AF, as well as increased LV mass, larger LA dimensions and lower right ventricular ejection fraction.[35] Bayir and colleagues obtained echocardiograms of 30 patients with moderate to severe OSA and free of cardiovascular disease, at baseline and after 6 months of CPAP therapy. They found significant reductions in inter-atrial (39.2 versus 28.7ms, P<0.0001, left atrial (20.5 versus 15.6ms, p=0.002) and right atrial (20.7 versus 13.1ms, p<0.0001) conduction times. Measures of diastolic dysfunction (E/A ratio 0.9 versus 1.1, p<0.0001) were also improved after CPAP.(36) Effects of CPAP have been shown to decrease LA volume as well as LV systolic and diastolic dysfunction.[37-39] One study of 37 patients with chronic heart failure found that CPAP did not affect blood pressure, heart rate or cardiac output significantly.[40] Thus, CPAP may produce physiologic changes that result in decreased LA size and filling, and which reduce the rate of AF recurrence by decreasing filling pressures and preventing substrate changes. However, this study was designed to demonstrate that CPAP in patients with severe heart failure does not lead to hemodynamic compromise, and thus was limited in its ability to shed light on underlying mechanism of CPAP effect.

Table 1: Summary of Studies Examining the Effect of OSA on AF Recurrence

Study	Number Patients	Mean Age	OSA Diagnosis	Mean Follow-Up	% PAF	Ablation Strategy	Method of AF Detection
Patel et al(31)	3,000	55.7	PSG	32 mo	53.4	PVI + LA linear ablation	Event monitor + 48h Holter
Matiello et al(47)	174	52.5	PSG	12 mo	56.3	PVI + LA linear ablation	Holter
Chilukuri et al(48)	109	60	Berlin	11 mo	68	PVI	ECG + telephone, Event monitor for symptoms
Tang et al(49)	178	57.2	Berlin	344 days	100	PVI	ECG + 24h Holter
Chilukuri et al(50)	210	58	Berlin	25 mo	57	PVI	ECG + telephone, Event monitor for symptoms
Jongnarangsin et al(51)	324	57	PSG	7 mo	72	PVI + CFAE	ECG + 30d autotrigger monitor
Naruse et al(33)	249	60	PSG	18.8 mo	54	PVI + LA linear ablation	ECG
Fein et al(32)	426	56.8	PSG	12 mo	57	PVI + LA linear ablation	ECG and Event monitor

Alternatively, CPAP may reduce AF recurrence by mitigating AF triggers. A temporal association between SDB and arrhythmic events has been shown,[41] in which the risk for AF is significantly increased in the immediate post-apneic period, suggesting that SDB may also constitute a trigger for AF. This again suggests that CPAP may modulate the triggers, rather than the substrate for AF. These findings have direct clinical relevance as AF ablation in patients with OSA may require an ablation strategy that emphasizes non-pulmonary vein triggers.

Screening For SDB

The American Academy of Sleep Medicine considers those with AF to be high risk for SDB and recommends evaluation for sleep apnea in these individuals.[42] However, this has not yet become standard practice primarily because sleep apnea remains under-suspected and under-diagnosed by electrophysiology physicians treating patients with AF. In addition, overnight sleep studies are cumbersome and a mechanism for coordinating sleep apnea screening and treatment referral has not been established in electrophysiology clinics. Given the clear evidence for improved arrhythmia control with CPAP therapy following cardioversion and catheter ablation of AF, it remains to be seen whether ablation and antiarrhythmic therapy offer benefit to patients with SDB in the absence of CPAP treatment. In the future, a multidisciplinary approach that involves screening all patients with AF for OSA, and referral to a sleep specialist may become the standard of care.

The gold standard for the diagnosis of sleep apnea is overnight polysomnography, typically conducted in a sleep laboratory, which can be costly and cumbersome for patients. However, these are cumbersome and are less and less covered by insurance companies. Home sleep studies have recently obtained FDA approval for diagnosis of sleep apnea and offer patients and treated physicians the opportunity to assess the presence of SDB in a natural sleeping environment, and often time in timely fashion. All currently available home sleep study devices are able to diagnose OSA, though not all have been validated for use in patients with AF. Some home sleep testing devices also have thoracic impedance bands to allow diagnosis of CSA. Comparisons of portable sleep devices and polysomnopgraphy for the diagnosis of OSA demonstrated good sensitivity and specificity (95.3% and 75%, respectively)[43] and correlation and accuracy (AUC difference=0.04)[44] between major clinical indices such as apnea hypopnea index and respiratory disturbance index.

Conclusions

Atrial fibrillation is the most common cardiac arrhythmia and shares many of the same risk factors as another common clinical condition, sleep apnea. There is a clear association between both obstructive and central sleep apnea and risk for AF. Several studies have shown a link between some of the physiologic changes of SDB and AF, and CPAP has in some cases been shown to reduce the rate of AF incidence and recurrence following catheter ablation in patients with SDB. However, further study is needed to establish a clear mechanistic link between the two conditions.

Future Directions

There are an estimated 5 million new cases of AF per year, which represents a significant proportion of health care costs and morbidity.[1] Gaining insight into the mechanistic role of SDB in the development of AF is key to successful AF prevention and treatment strategies. Additional studies are needed to better understand the mechanism underlying the associations between SDB and AF. In particular, prospective studies examining the feasibility and impact of universal screening for diagnosis and treatment of SDB in patients with AF on arrhythmia outcomes and patient well being are needed.

Clinical Perspective

Atrial fibrillation (AF) and sleep apnea have been associated in multiple studies, with a risk for AF that are 2 to 4 times that of those without sleep disordered breathing. There is emerging evidence from animal and human studies that the physiologic changes of sleep apnea including hypoxia, hypercapnia and intrathoracic pressure fluctuations precipitate electrical and structural changes. Some of these changes occur acutely after an apneic episode, while others occur with repeated exposure over time. There is also evidence that continuous positive airway pressure (CPAP) may reverse some of these changes, thereby reducing the risk for AF recurrence after cardioversion and ablation. However, a detailed understanding of the mechanisms by which sleep apnea precipitates electrical and structural remodeling remains unknown. Further studies are needed to evaluate the feasibility of universal screening for SDB, and the effect of therapy on both the development and progression of AF.

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Idiopathic VPC: Distribution Of FOCI And Tips Of Ablation

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Abstract

Idiopathic Ventricular Premature Contraction (VPC) is currently more routinely referred for electrophysiology evaluation. Usually it carries a good prognosis but, when symptomatic or suspected to produce ventricular dysfunction, will require treatment. Nowadays, RF ablation has great advantages over antiarrhythmic drugs. Classically the outflow tract (right or left), with the typical inferior axis with left (eventually right) bundle brunch block like ECG morphology, is considered the most frequent site of origin for idiopathic VPC, but with the widespread of EP procedures and advancement of technology making possible to map and ablate difficult locations, it is possible to see a growing and changing population referred for idiopathic VPC ablation, displaying that, almost any region of the heart may be source of this kind of arrhythmia that can be successfully treated. A well-planned procedure, with the presumed region of origin settled and employing the current technology and knowledge (tips), will have a high chance of cure.

Introduction

Ventricular premature contraction (VPC) in a apparently healthy young adult with no previous history is not so uncommon, and may cause emotional stress until the accurate diagnosis is done. Described as "idiopathic ventricular arrhythmia", it is defined as the arrhythmia not related with any detectable structural cardiac disease. It accounts for about 20% of all patients referred for evaluation of ventricular arrhythmias. Most patients are symptomatic and will need treatment; other are asymptomatic but have a high burden of the arrhythmia and may be at risk of developing a reversible form of left ventricular dysfunction (tachycardia-induced dilated cardiomyopathy)[1] and will need treatment as well.[2] Pharmacologic treatment of these arrhythmias, usually with beta-blockers, calcium channel blockers and even amiodarone, has only modest efficacy (around 25 to 50%). Most young patients do not desire long-term medical therapy or are not drug tolerant. Some patients can even feel a worsening of symptoms after medications due to drug induced bradycardia or to an increase in VPC burden. Considering that usually the source of the arrhythmia is unifocal, ablation has undoubtedly some advantages over medical treatment, since it has a high chance of cure.[3] Therefore, broadly speaking, the key decision is if the patient needs or not treatment, if so, the best option is usually the RF ablation.

Key Words:
Idiopathic,Ventricular Premature Contraction,Ablation,Outflow tract.

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Distribution of FOCI

Ventricular premature contraction in structural normal heart may arise from any region but the outflow tract VPC / VT is the most common form, known almost as synonymous of idiopathic ventricular arrhythmia; one concern, is to differentiate from initial form of arrhythmogenic right ventricular cardiomyopathy/dysplasia. The reason these arrhythmias come most frequently from outflow is still not clear. The typical electrocardiogram features is the inferior axis and left branch block morphology. For a long time it has been taught that the right ventricular outflow tract (RVOT) accounts for the majority (about 80%) of idiopathic VPCs, however, taken into account the great growing of referred population, the foci location has changed significantly in the last decade. Maybe due to the ability of mapping complex or difficult structures and the widespread of ablation procedures, the kind of patient that is referred for electrophysiology evaluation nowadays has been show a shift to other regions, outside of RVOT. Recently Penela et al. [4] studied 117 patients with outflow tract arrhythmias and found almost the same distribution of foci from left and right side (left: 51%; Right: 49%). A newly and big study from Latchamsetty et al.[5]give a compelling evidence for distribution of foci in current VPC ablations based on 8 international centers, comprising 1,185 patients between 2004 and 2013. They found and described the origin as follow: RVOT: 45%; Aortic Cusps: 15%; Papillary Muscles: 5%; Epicardium: 11%; Other (not specified) origin: 24%. Therefore any area of the heart may be source of idiopathic ectopy.

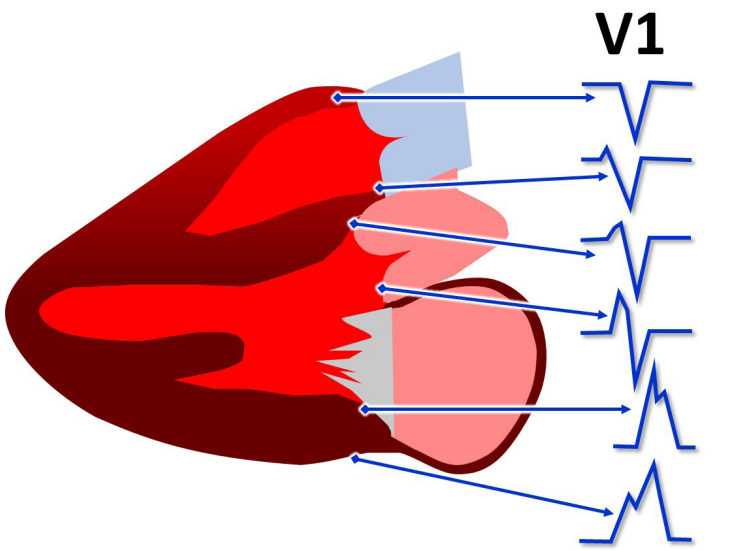

Figure 1: Scheme of the main ECG morphologies of the basal PVCs. There is a progressive modification of the QRS from negative to positive in lead V1 according the origin of the PVC from the anterior RVOT to the epicardium of the posterior left ventricle.

Outflow Tract is still the most common site and is classified as one group apart. This area include the following structures: right ventricular outflow tract (RVOT), left ventricular outflow tract (LVOT), the aortic sinuses of Valsalva, the area of aortomitral continuity, the superior basal septum near the His bundle, the pulmonary artery, and the epicardial surface of the outflow tracts. Although some clinical differences[4] may exist, these arrhythmias have similar characteristics and share the same behavior. Actually the right and left ventricular outflow tracts are in close relationship and this explains the difficult of differentiating them by ECG criterion and the phenomenon of shifting, when 2 discrete morphologies are seeing changing during the catheter ablation.

Tricuspid Annulus was the source of origin of 8% of idiopathic VPC/VT as described by Tada et al.;[6] they show that the majority (74%) of them originated from the septum portion. Yamada et al[7] presented a case report where they did ablation of tricuspid annulus VPC using a halo-type catheter to help mapping.

Mitral annulus ventricular arrhythmias have been described as 5% of idiopathic arrhythmias in a large series;[8] the authors showed that in all patients an S-wave was present in lead V6.

Pappilary Muscles has a rich network of Purkinje fibers,[9] these structures are accountable for 4,2% of idiopathic VT/PVC in one series;[10] they may arise in normal hearts but, when compared with fascicular and mitral annular PVC, it seems that these arrhythmias occur in older patients and are often related with the presence of coronary artery disease and left ventricular dysfunction;[11] they also showed that papillary ectopy has a wider QRS duration than fascicular arrhythmias.

The Fascicles of the left bundle branch are classically knowing as source of a typical idiopathic VT, but it may arise ectopy as well; it is ready identified by a narrow QRS and the characteristic ECG morphology of the fascicle of origin: left posterior fascicle with a right bundle branch block and left axis deviation; left anterior fascicle with morphology of right bundle branch block and right axis deviation; high septal fascicle with relatively narrow QRS complex and normal axis.

Epicardial and/or Peri-Vascular are other source of idiopathic ectopy. [12] Scanavacca et al suggest that these arrhythmias may be accessed by the venous system or by subxiphoid epicardial mapping, but do not recommend an epicardial approach on the first procedure for outflow tract arrhythmias;[13] one concern is the presence of the coronary arteries and phrenic nerves. A delay in the initial time of the QRS complex indicated a epicardial origin as suggest by the Maximum Deflection Index (MDI). [14]

One important aspect in counseling patients with idiopathic arrhythmias, essentially outflow tract, is the challenge of predicting the site of origin, therefore discussion about treatments options and intervention planning. There are several ECG criteria that try to locate the focus (Figure 1), some of them are based on complex process analysis or formulas. The inspection of QRS morphology of the VPC compared with the normal sinus rhythm ("the V2 transition ratio")[15] is practical and helpful, Figure 2.

Beyond morphologic criteria, others ECG characteristics and clinical aspects may be valuable in arrhythmia discrimination. Recently Bradfield et al.[16] demonstrated that arrhythmias that arise from sinus of Valsalva and great cardiac vein have a highly variable coupling interval with the preceding normal QRS, probably due to a lack of electronic coupling with the surrounding myocardial. PVC originated from RV or LV myocardial have a relative fixe coupling interval compare with PVC from sinus of Valsalva and great cardiac vein; a pronounced variability in couple interval (Delta > 60ms) helps discriminate the origin of PVC. Another interesting study from Penela et al.[4] evaluated clinical characteristics in patients with outflow tract arrhythmias; they showed that the presence of hypertension, male gender and age > 50 years were independent predictive of LV outflow tract origin and a score with these three variables was proposed.

Tips of Ablation

Different from reentry ventricular tachycardias, which can be usually reproduced with programmed ventricular stimulation techniques, ventricular premature beats has the disadvantage of being less easily

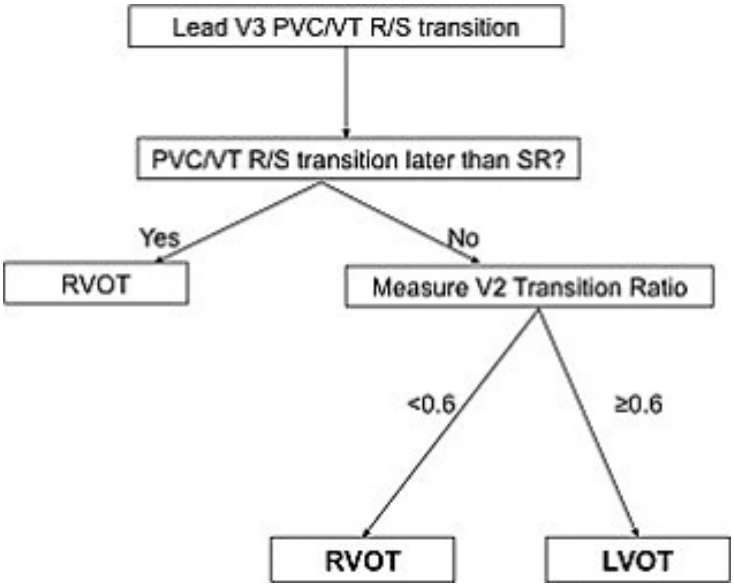

Figure 2: Algorithm developed by Betensky BP et al.[15] for OTA ECG localization. If the PVC transition to an R>S occurs later than the SR transition then the PVC origin is the RVOT (100% specificity). If the PVC transition occurs at or earlier than the SR transition (i.e., SR transition lead V3 or later), then the V2 transition ratio is measured. If the transition ratio is <0.6, then RVOT origin is likely. If the transition ratio is ≥0.6, then LVOT origin is likely (sensitivity 95%, specificity 100%).

reproduced. All antiarrhythmic medications should be discontinued for at least five half-lives before the ablation. Not uncommonly, even in patients with very frequent clinical arrhythmia, it may be necessary to perform the procedure in the absence of ectopic beats. It is helpful to see in the Holter if the arrhythmia is more frequent during the sleep or vigil. In the last case a deep sedation must be avoided.

One of the key point of ablation of idiopathic VPC is to have the arrhythmia (spontaneously) in the moment of the procedure or to identify a protocol that induce the arrhythmia; It is really important for mapping and for having an end point during the procedure. There is no unique maneuver or protocol that works satisfactorily for ever case.

Despite being unpredictable, it is usually possible to trigger the ectopies appearance, so we always try to perform the procedure on the day that the patient was scheduled, but many researchers suspend the procedure if there is no spontaneous arrhythmia.

At the beginning, in the case there are no arrhythmias, with the patient fully monitored and awaked, some ventilation maneuvers (depth breath or Valsalva) may provoke VPC allowing to get recordings (that must be saved) for pace mapping. After sedation, ventilation changes induced by the anesthesiologist, like short hypoxia periods, may also reproduce the arrhythmia. After placing the catheters, there is a good chance that some atrial or ventricular stimulation protocols with different cycle length or extra-stimuli, may reproduce the arrhythmia during the stimulation or after stopping, during the pause. Ventricular stimulation must be attempted with programmed stimulation or burst. Some people try isoproterenol (despite epinephrine seems to be better), but in our experience it may be trick; some times with the sinus rate increasing it may eliminate any sporadic ectopy that could be present; also, with the vigorous myocardial contraction due to isoproterenol, the manipulation of the catheter (and pace mapping) is more difficult or even risky. It seems that isoproterenol works better when it is given as small bolus than continuously (progressive), because there is a better chance that the arrhythmia is induced after the peak effect of the drug, when the sinus rate is slowing down.

Vagal Stimulation

Another very interesting issue is autonomic stimulation to promote cardiac reflex for triggering some arrhythmias. [17,18] This can be important to achieve the morphology in 12 lead ECG of a PVC that eventually becomes completely absent at the time of the procedure in order to proceed with the pace mapping. We are studying the potentiality of vagal stimulation performed by placing a catheter inside the internal jugular, up to the superior wisdom tooth level by using even the RF catheter temporarily detached from the RF generator and connected to a neurostimulator, Figure 3.

In this place, it is usually easy to get an intense vagal stimulation that causes transient asystole, Figure 4-A. Soon after the vagal effect, a reflex sympathetic response occurs usually causing the appearance of PVC, Figure 4-B. Depending on the case, that may be better than the isoproterenol infusion because it triggers the sympathetic response by natural paths. Paradoxically, by causing an important heart rate increase, the isoproterenol may prevent the PVC appearance just because of the diastolic extent reduction.

Pace Mapping

It is a great aid technique pacing point-to-point areas suspected from the ECG PVC morphology. The main objective is to reproduce the morphology of spontaneous PVC in 12-lead ECG through electrical stimulation of a certain point. This step can be accomplished

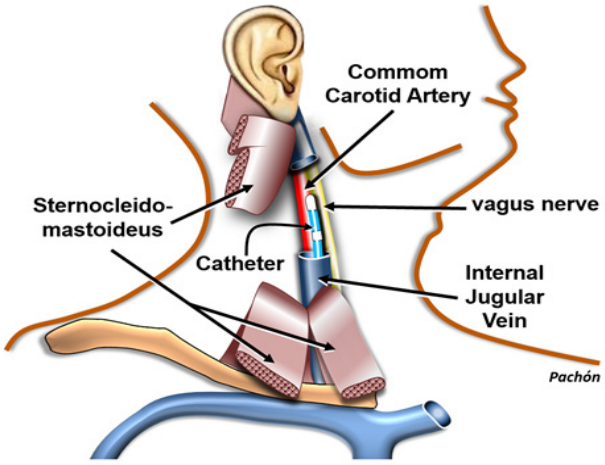

Figure 3: Scheme of the methodology for vagal stimulation during EP studies developed by authors. The RF catheter, temporarily detached from the RF generator and connected to a neurostimulator, is advanced to the internal jugular vein. This position usually has a great proximity with the vagus nerve allowing its stimulation. This maneuver must be only accomplished after being the patient anesthetized.

by direct subjective comparison of the operator or aided with automated computerized systems, Figure 5. A major advantage of this method is that it can be performed in the absence of the arrhythmia since the PVC morphology in a 12-lead ECG technically identical to the ablation ECG, can be compared. An important drawback is that the pace mapping identifies the starting point of the PVC appearance in the myocardium and not necessarily the actual focal origin.[19] Despite being not totally necessary, the use of three-dimensional electroanatomical mapping system and, recently, the rotational angiography may be of great value for mapping assistance.[20]

Computer Aided Pace Mapping

Other area of great interest is to improve the performance and the quality of the pace mapping technique, making it faster and less de-

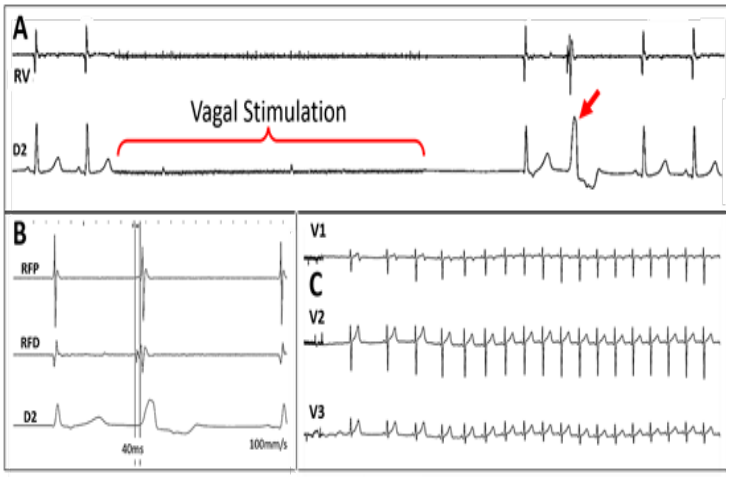

Figure 4: Case of a patient who was symptomatic due to a very frequent monomorphic VPC. However, in the EP laboratory the arrhythmia was completely absent. A: during vagal stimulation there is an immediate asystole followed by a junctional beat and one PVC (red arrow). This response was typically reproducible. All other attempts to reproduce the PVC were unsuccessful. B: The PVC triggered by the vagal stimulation was mapped and a good precocity was obtained allowing the ablation; C: After ablation, vagal stimulations were unable to reinduce new VPCs. Currently, this patient is asymptomatic and has no more arrhythmia.

pendent of the interpretation of the operator. Considering that sometimes we do not have the PVC frequency as desired, pace mapping is the main approach being the technique that allows getting close of the site of origin and save time. There are some reports dealing with automatic template for computerized interpretation of pace mapping.[21]

Ablation of Valsalva Sinus PVCs

A very delicate situation is when PVC is located in the sinus of Valsalva because of the risk of coronary lesion. Only the non-coronary sinus does not originate PVCs as it relates only with the fibrous skeleton of the heart. That means, whenever there are PVCs of this location they are surely originated from the left or right coronary sinus, whose ablations should deal with the risk of coronary injury, Figure 6. One fundamental tip for ablation in the right or left Valsalva coronary sinus is to perform the coronariography immediately before the RF release. A simple and practical way we have proposed is to place the contrast dye in the irrigation system of the ablation catheter. After positioning the RF catheter in the most appropriate mapping place, radiographic contrast product is directly injected through the irrigation system. This should be repeated immediately before each new ablation case the catheter position has been changed. If the contrast shows that we are far from coronary ostium we can ablate without risk. Conversely, if it is found that we are very close to the coronary ostium the ablation must be suspended (Figure 7).

Activation Mapping

It can be performed directly with the RF catheter or through the electroanatomic mapping system. It is certainly the key element to the success of ablation. Generally, the potential that indicate the position of the arrhythmogenic focus with great chance of success precede the QRS surface of the PVC onset in 10 to 60ms,[22] Figure 4-B. The morphology of these potentials is also of great value especially the QS pattern in unipolar recording of the distal pole[23]

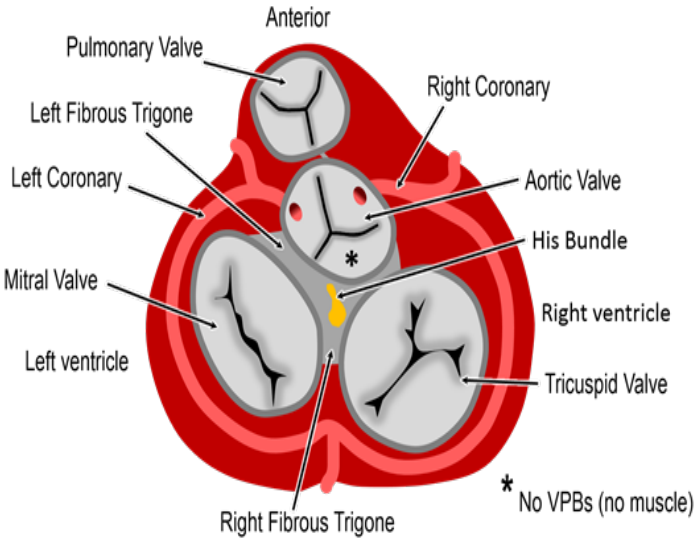

Figure 6: Scheme of the cardiac fibrous skeleton and its relationship with Valsalva sinuses. The non-coronary sinus is related with fibrous tissue only and is the solely one that does not gives rise to PVCs. The coronary sinuses are relatively frequent source of PVCs and the ablation in these places must have special care for avoiding coronary injury.

or the reverse potentials comparing two distal dipoles of the ablation catheter.[24] When myocardium mapping is not quite appropriate in the myocardial the outflow tracts myocardium it is essential to make an inspection on arterial insertions, above the pulmonary and aortic valves,[25,16] as well on the mitral annulus,[8] as these places are often the real origin of these arrhythmias, Figure 1.

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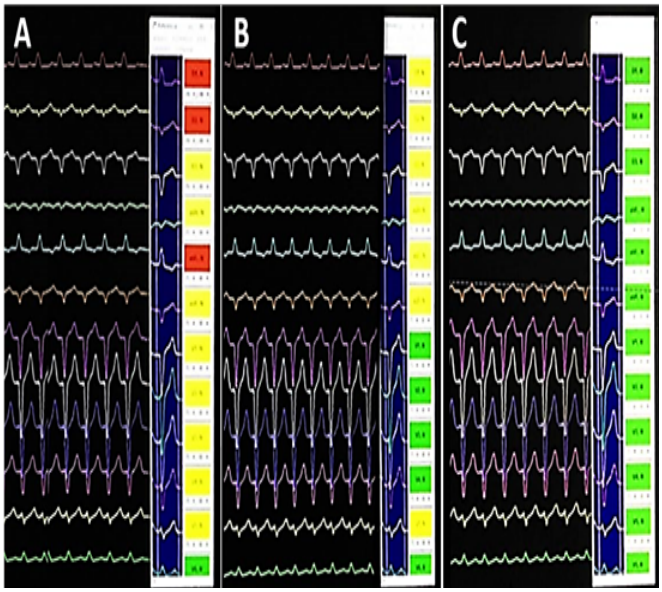

Figure 5: Computerized aid for pace mapping. Pace mapping is extremely useful in the PVC ablation however, it has some disadvantages like the time consuming and a huge dependency of the subjective interpretation of the operator. This software, developed by the authors, as other products on the market, has promoted great agility and efficiency in the pace mapping technique. In A and B there are two examples of pace mapping inappropriate for ablation, however in C the mapping is excellent that is, a place with a high probability of ablation success (all the flags are green).

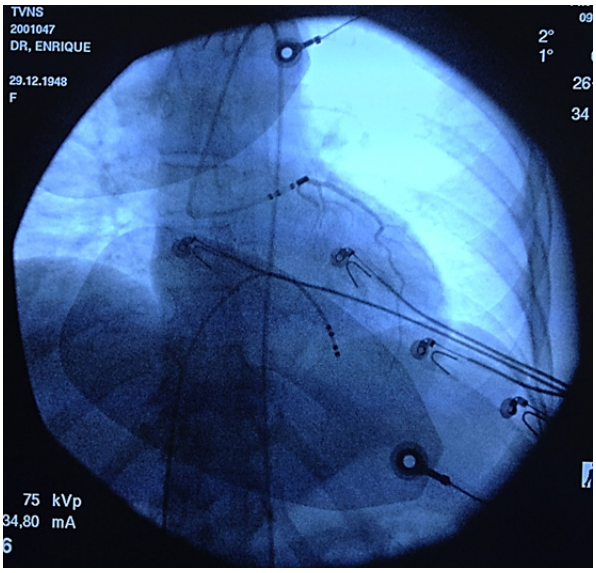

Figure 7: Forbidden PVC ablation. Method proposed and routinely employed by the authors using the irrigation system of the ablation catheter, placed in the best mapping position, by injecting X-ray dye for verifying if it is in a risk position, associated with a coronary ostium. In this example, a young woman had a ventricular tachycardia originated from the left coronary sinus. The best place for ablation was located in the left coronary ostium. The ablation catheter was relocated and the ablation was finally successful but performed outside the ostium, despite being a suboptimal position.

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Advanced Mapping Systems To Guide Atrial Fibrillation Ablation: Electrical Information That Matters

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Abstract

Catheter ablation is an established and widespread treatment for atrial fibrillation (AF). Contemporary electroanatomical mapping systems (EAMs) have been developed to facilitate mapping processes but remain limited by spatiotemporal and processing restrictions. Advanced mapping systems emerged from the need to better understand and ablate complex AF substrate, by improving the acquisition and illustration of electrophysiological information. In this review, we present you the recently advanced mapping systems for AF ablation in comparison to the established contemporary EAMs.

Introduction

Atrial fibrillation (AF) is the most common arrhythmia with an increasing prevalence and a high socio-economical health burden. Catheter ablation (CA) is an established and widespread AF treatment. After the initial discovery and abolishment of focal pulmonary vein (PV) activity as AF triggers,[1-3] CA treatment has undergone considerable improvement over the last years aiming always for better results with faster, safer and easier procedures.

Electrical pulmonary vein isolation (PVI) is the cornerstone of AF treatment.[4-6] In patients with paroxysmal AF, recovered PV conduction is the most common reason for recurrence and can be successfully treated by a new ablation session.[7, 8] In patients with chronic AF though, success-rates are lower and AF triggers from a diseased left atrium (LA) are more common, requiring additional substrate modification, defragmentation or linear ablations.[9,10] Multiple atrial wavelets, macro-reentries, and localized sources (drivers) have been reported to contribute to this substrate.[11, 12]

Achieving electrically continuous, transmural lesions in a beating heart is challenging and requires a reliable three-dimensional (3D) navigation, in order to avoid complications (PV stenosis, perforation, phrenic nerve or esophageal injury). In order to facilitate this task with less radiation than plain fluoroscopy, electroanatomical-mapping systems (EAMs) have been developed, enabling the tracking of intracardiac electrodes in 3D maps and the navigation of catheter ablation.

Conventional mapping systems though cannot adequately detect localized AF drivers due to their sequential spatiotemporal characteristics, their intermittent firing and spatial meandering.[13] For this reason advanced mapping tools have been developed to visualize and better understand the AF-maintaining drivers. These systems have shown promising results for AF ablation and could path the way to a new era of substrate characterization and individual ablation strategies. In this context, the current article aims to review the modern advanced mapping systems for AF ablation in comparison to the established contemporary EAMs.

Contemporary Mapping Systems

All mapping systems are based on non-fluoroscopic visualization of mapping catheters and a 3D reconstruction created by the manipulation of a mapping catheter. Electrical information at map points is recorded and can be used for the color-coded display of the electrical activation sequence known as “activation mapping”, the display of post-pacing intervals known as “entrainment mapping” or the display of unipolar/bipolar electrograms as part of “fractionation” or “voltage mapping”.[14] The most common EAMs for AF ablation are the Carto (Biosense Webster, Baldwin Park, CA, USA) and the EnsiteNavX system (St. Jude Medical, St. Paul, MN, USA).

The latest version of Carto system is based on a hybrid of magnetic and current-based catheter localization technology and enables visualization of multiple catheters simultaneously. Three active magnetic fields generated by a location pad placed underneath the patient act on mini-sensors embedded in the catheter tip providing information about its exact position and orientation, in relation to a reference sensor on the skin. Additionally, six electrode patches positioned at the patient’s back and chest, screen a unique current

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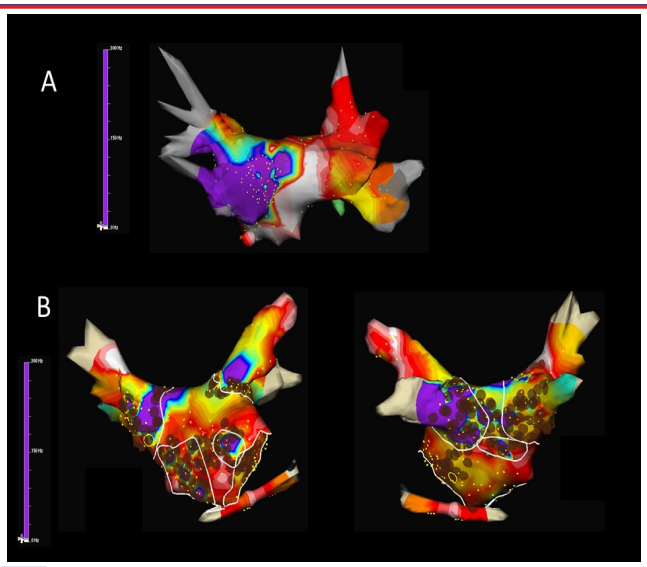

Figure 1: Time-frequency analysis of atrial fibrillation (AF) with Dominant Frequency (DF) maps showing A. a patient with paroxysmal AF in whom DF guidead isolation of the left inferior pulmonary vein antrum lead to AF termination and B. a patient with persistent AF in whom a combined ablation approach with both high-frequency source ablation and circumferential pulmonary vein isolation was performed (Courtesy of Felipe Atienza, Hospital General Universitario Gregorio Marañón, Madrid, ES)

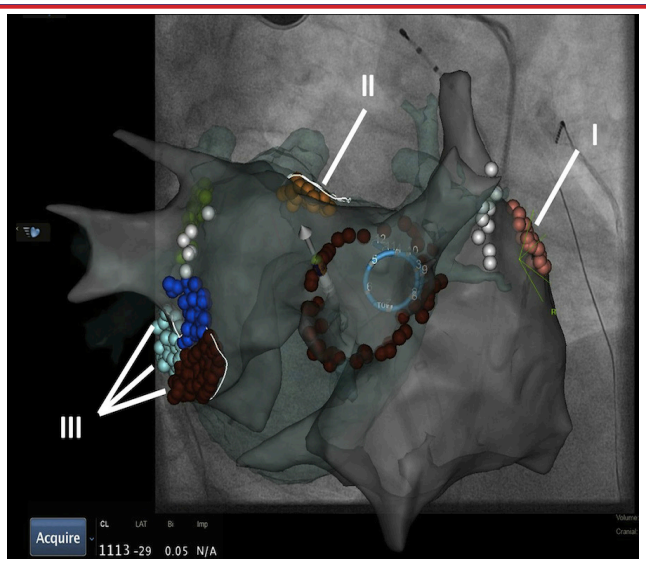

Figure 2: Electroanatomical map (Carto 3, UniVu®) with annotation of AF rotors located by the RhythmView mapping system (Topera) on the right (grey shell, red points; I) and the left atrium (fused with a green 3D CT shell): close to the left atrial appendage (orange, II) and the mitral isthmus region (red, purple, blue, III). A circular mapping catheter (blue) is placed in the right superior pulmonary vein and an ablation catheter is at the posterior wall. The white points show the area of phrenic nerve capture

emitted from different catheter electrodes.[15] Multipolar mapping catheters can be used for fast anatomical mapping (FAM) by registering and reentering 3D models. Respiratory gating is possible through thoracic impedance measurement, but patient movement or dislocation of the location pad may lead to uncorrectable map shifts. In order to enhance recognition of anatomical variations, integration of pre-aquired CT/MRI data or intraprocedural inctracardiac echocardiography (ICE, CartoSound®, Biosense Webster) is possible through merging of the 3D models.[16]

The EnsiteNavX Velocity system is based on an impedance-based tracking technology, capable of tracking intracardiac electrodes as well as tagging points in a high-frequency (8 kHz) electric field produced by six skin electrodes. The 3D-localization of the catheters is calculated based on an impedance gradient in relation to a reference electrode.[17] A process called field-scaling aims to correct for the body's non-linear impedance and the use of intracardiac refrence-catheters reduces motion artifacts. However, dislocation of the reference catheter may lead to uncorrectable map shifts. EnsiteNavX allows for visualization of multiple catheters from different manufacturers and simultaneous collection of anatomical and electrophysiological data from all electrodes of any catheter.[18] Integration of CT/MRI data though requires an extensive registration called fusion.[19]

Both of these EAMs have been proven to reduce radiation and procedural duration[20-22] and in combination with pre-acquired imaging data can lead to less complications and better results.[23,24] Additionally, integration of electrode-tissue contact force data by special catheters (SmartTouch, Biosense Webster or TactiCath, St. Jude Medical) can provide feedback for lesion creation and improve efficacy, reduce risks and procedural parameters.[25-29] The most important contribution of these systems though is the characterization of the AF substrate through fractionation (quality and temporal characteristics of the electrical signals) or voltage mapping (amplitude of electrical signals), which has been the stimulus for further mapping developments. These tools aim to identify additional ablation targets and allow a patient-tailored approach.

Fractionation Mapping

Complex fractionated atrial electrograms (CFAEs) are regarded as surrogates of asynchronous activation of myocyte bundles through a fibrotic myocardium. They are defined as atrial electrograms with low voltage (≤0.15 mV) signals with ≥2 deflections/perturbations of the baseline with continuous deflection of a prolonged activation complex; and/or a very short cycle length (≤120 milliseconds), with or without multiple potentials. The mechanisms of CFAEs creation has been related to factors which perpetuate AF, but it has been also been considered to be passive consequences of near-by rapid AF drivers.[30] Contemporary EAMS integrate automated algorithms that provide CFAEs maps, but this has not been proved superior to conventional CFAE mapping and ablation.[31] Despite the initally encouraging results, recent studies showed a higher rate of resulting atrial tachycardias and failed to reveal a benefit of additional CFAE ablation.[32, 33]

Voltage Mapping

Voltage mapping is based on the correlation of low-voltage areas (<0.5 mV) in the left atrium with endocardial scar and/or structural defects as a substrate that can diminish success rates after AF ablation.[34-38] Supplementary ablation of low-voltage zones as an additional target to PVI serves as an individualized substrate modification (similar to unstable ventricular tachycardias). According to our experience such low-voltage areas are found in 35% of patients with persistent AF and in 10% of patients with paroxysmal AF, most commonly in the septal, anterior, or posterior LA wall. Patients with low-voltage substrate have lower success rates after AF ablation (23% after PVI only) that can be significantly improved by targeting these in a patient-tailored approach (70% after a year). Moreover, this strategy could spare the majority of patients (2/3 of those with persistent AF) from additional ablation lesions and potential complications, without compromising the ablation outcomes.[39] Prospective, randomized clinical studies are needed to clarify the role of a voltage-based AF

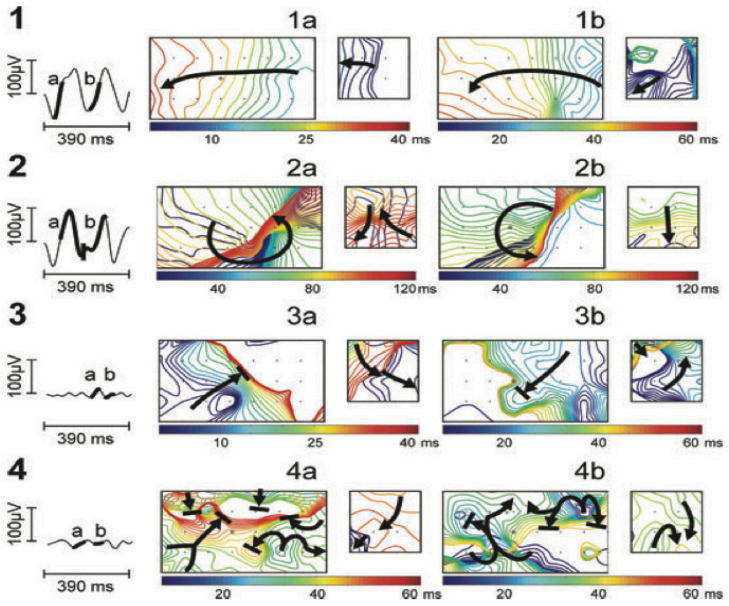

Figure 3: Noninvasive AF mapping using body surface recordings from a uniform grid-torso placed around a patient with persistent AF. On the left, tracings correspond to V1. Panels a and b correspond to wavefront propagation maps of two intervals of the same segment in a color scale. On the left in each panel, maps correspond to the front part of the thorax and on the right, maps correspond to the back. Each electrode position is labelled with a '+' sign and V1 by a circle. Wavefront propagation lines are drawn every 2 ms, drawn blue when appearing first or red when appearing last. Arrows indicate the direction of propagation of each wavefront.[49]

ablation in comparison to established strategies.

Advanced Mapping Systems

Contemporary EAMs have been very valuable for the navigation of AF ablation, but have some limitations. The integrated automated mapping algorithms are susceptible to annotation and interpolation errors that require a manual point-by-point verification of annotated points. This is a time-consuming process that is prone to incorrect judgment regarding signal selection, the window-of-interest and the presence of fragmented/double potentials or areas of very-low continuous potentials. Moreover, spatiotemporal analysis and registration of electrograms on a map as well as the creation of a new map in case of tachycardia change, remains a slow process limited by the speed of signal acquisition. The need to overcome these disadvantages and to improve illustration of the underlying AF mechanisms, has led to the development of advanced mapping systems.

Advanced mapping systems for AF ablation have focused on improving signal quality (high-resolution), acquisition and processing time, precision of annotation and development of automated algorithms that visualize electrophysiologic information. These efforts refer once again to the core principle of electrophysiology: the electrical signals, which guide AF ablation, should be reliable (with high resolution and low noise), appropriately acquired and processed in a timely manner. In this sense, new diagnostic catheters and novel mapping technics have been developed and will be presented here.

Ripple Mapping

Ripple Mapping is a novel technique that displays time-voltage data as dynamic bars on Carto surface shells.[40] Electrograms are visualized as color bars on 3D models, changing colors and dimensions

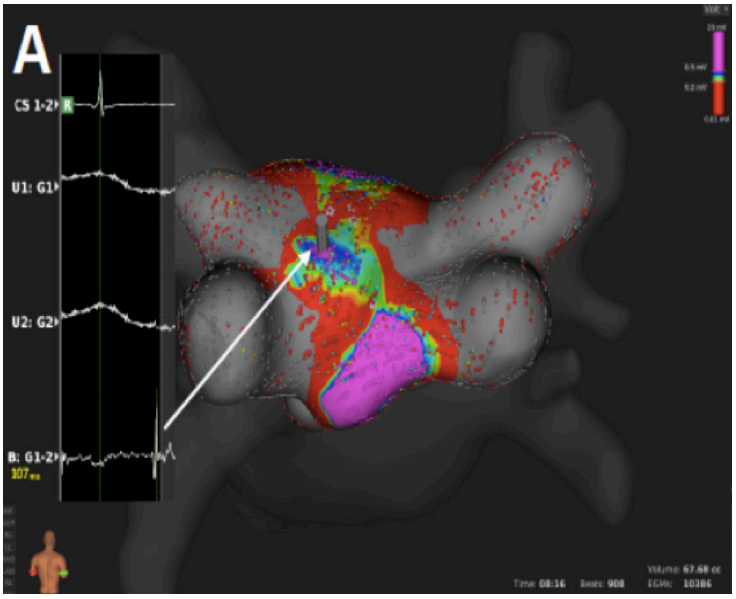

Figure 4A: Voltage base verification of linear lesions: High-density voltage map of the roof region during a redo case with previous box lesion. Note high voltage regions within the box lesion (corresponding local electrograms shown in the box)

according to the voltage-time relationship, time-gated to a pre-selected electrograms (reference). The operator has the impression of a "wave-like" movement of the propagation, without any manual or automatic annotations. This way ripple mapping compensates for isolated annotation and interpolation errors and as recently reported, demonstrates higher diagnostic accuracy for atrial tachycardias compared to conventional activation mapping.[41] Although it is an offline system that requires time for post-processing, ripple mapping has the potential to simplify mapping and minimize operator-dependence. Further evaluation and comparison with other systems is needed to prove if this technology will be integrated in "real-time" clinical practice.

High Dominant Frequencies Mapping

Dominant frequency (DF) maps derive by high-resolution analysis of the Fourier power spectrum and enable the color-coded hierarchical visualization of frequencies in combination with contemporary catheters and EAMs.[42] High DF sites are defined by 20% frequency gradient relative to the surrounding tissue and represent localized reentrant sources (ablation-targets). Multiple DF sites are usually found in a patient with variable distribution (predominantly PV-sites in paroxysmal and more atrial sites for persistent AF) and intra-procedural spatiotemporal stability, which has raised some concern about their role as AF drivers. Ablation of DF sites may result in significant slowing of AF cycle length, reduction of AF inducibility, and AF termination especially in paroxysmal AF patients.[43, 44] The RADAR-AF study compared DF ablation vs. circumferential PVI and found no incremental value for persistent AF but a non-inferiority for paroxysmal AF (Fig. 1).[45] However, more clinical studies are needed to further evaluate the role of DF ablation.

Focal Impulse and Rotor Mapping

In order to improve the identification and abolishment of local reentrant sources a novel computational approach with the concept of focal impulse and rotor modulation (FIRM) has been developed.[46] For this technique, a dedicated 64-pole basket catheter (8 splines with 8 electrodes per spline) is used for panoramic intra-cardiac

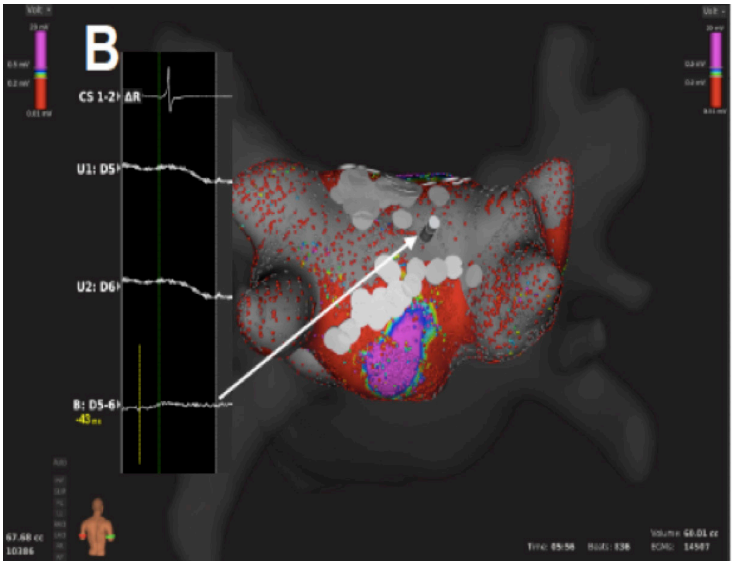

Figure 4B: Voltage base verification of linear lesions: re-map of the same region after additional ablation shows elimination of high voltage potentials

mapping during AF. Automated intra-procedural processing by the RhythmView mapping system (Topera, Menlo Park, CA, USA) enables the depiction of AF propagation maps projected onto grids. These maps are then used to guide ablation of AF drivers (usually 2-3 rotors or focal impulses per patient). Rotors are defined as stable and sustained spiral activation around a center of rotation, whereas focal impulses are defined by centrifugal activation from a source. Target sites are located by their electrode coordinates and radiofrequency ablation with a conventional catheter is usually applied for 15–30 sec up to 10 min, aiming for slowing or termination of AF. Conventional EAMs can integrate tracking of the basket catheter, annotation of target and ablation sites and simultaneous creation of atrial geometries, which may then be used for PV isolation (Fig. 2). PVI with additional direct or coincidental FIRM ablation has been shown to improve mid-term and long-term AF ablation outcome.[46-48] Similar to other technologies though, which are used to supplement conventional AF ablation, additional costs and processing time remain an issue and remain to be proofed for their clinical value.

Non-Invasive Body Surface Mapping

Body surface mapping (BSM) is a non-invasive bedside mapping system that aims to identify AF drivers by using an array of multiple surface electrodes and by projecting this information on a pre-acquired CT/MRI-based 3D model of the atria. Initial research revealed that using a 56-electrode vest around the patient's torso, non-invasive mapping could depict wavefront propagation maps and identify specific patterns like single wavefronts, wave-breakages/splitting or multiple simultaneous wavefronts (Fig. 3).[49] Further development of this kind of mapping led to a 252-electrode vest connected to a special system (ECVUE, CardioInsight Technologies Inc, Cleveland, OH) that records unipolar surface potentials. Biatrial unipolar electrograms are then automatically reconstructed from torso potentials and epicardial activation maps are computed by using the intrinsic deflection-based method. The windows with long ventricular pauses (spontaneous or diltiazem-provoked) are usually randomly selected for AF electrogram analysis. Maps of AF are generated by algorithms with a combination of signal filtering and phase mapping.[50-53] Wave propagation is then depicted color-coded on a beat-to-beat basis and spatiotemporal density maps are analyzed to identify active driver regions (classified as focal or reentrant) and the repetition of this activity. In contrast to focal impulse rotor mapping, AF drivers by BSM are usually (2-3) repetitive reentries clustering in the LA and increase with the duration of continuous AF. Their elimination could lead to AF termination (especially in paroxysmal AF) with a shorter procedural time in comparison to conventional ablation techniques.[54] Despite the need for additional off-line analysis, BSM allows for pre-procedural non-invasive AF mapping and preparation of an individual ablation strategy. Further clinical studies are needed though to elucidate the utility of this system.

High Density Mapping

The concept of high-density mapping refers to the simultaneous acquisition and annotation of multiple electrograms, including activation and voltage information, which are then analyzed by automated algorithms in order to generate precise activation and substrate (voltage) maps. These algorithms were initially applied for macro-reentrant tachycardias, but they have been further developed and adapted for complex arrhythmias like AF, providing us with new insights and a better understanding. In order to achieve this novel mapping catheters have been developed; multiple electrodes serve for fast acquisition of data whereas a smaller electrode size and a shorter inter-electrode distance provide a better signal quality with less noise to far field ratio.

The PentaRay (Biosense-Webster) is a two-dimensional catheter with 20-poles arranged in 5 soft radiating splines (1-mm electrodes separated by 4-mm interelectrode spacing) laid out flat to cover an area with a diameter of 3.5 cm. The multi-branch configuration provides a broader access to information with high resolution.[55] It can be used with conventional EAMs and simplify the identification of focal or microreentry sources, scar borders and critical electrical pathways for the abolishment of macroreentrant tachycardias.[56,57] Recently, 3D high-density maps are made possible by using a specially-designed 64-pole basket array (8 splines with 8 electrodes per spline, 0,4 mm^2 electrode size and 2.5-mm interelectrode spacing) attached to a bi-directional deflectable catheter (IntellaMap Orion® High Resolution Mapping Catheter) in combination with a novel EAM system (Rhythmia Mapping, Boston Scientific, Marlborough, Massachusetts, USA). The Rhythmia system uses a hybrid of magnetic-based tracking for a sensor at the catheter tip and impedance-based tracking for all 64 electrodes for catheter navigation and geometry creation. The greatest advantage of this system is the rapid and automatic acquisition of maps with high spatiotemporal resolution and without the need for extensive manual annotation. Activation maps with thousands of electrograms can be created within minutes.[58-61] Post-processing is not necessary and map-reconstruction (in case of tachycardia change or after lesion deployment) is very fast.

This is accomplished through integrated automated algorithms that meticulously select cardiac beats (based on stability of cycle length, timing, location and respiratory cycle) and filter-out points with discrepancy in comparison to those of close proximity. Far-field components are reduced by combining unipolar and bipolar electrograms. Moreover, the low noise level in the system (0.01 mV) allows the recording of very low-amplitude potentials indicative of scarred atrial myocardium.[62] As a result, the improved differentiation of signals enables depiction of narrow activation waves with high

precision. Adjustment of the window of interest in an activation map can reveal early local potentials or eliminate far-field noise on the map. Similarly, changing the voltage scale can reveal electrical gaps through low-voltage areas or a breakthrough in ablation lines and it can be used to achieve the continuity of lesions (Fig. 4).

To further evaluate the application of this technology, our group has performed feasibility and efficacy studies in patients with supraventricular tachycardias, including AV nodal reentrant tachycardias, atrial flutter and fibrillation.[63, 64] The initial experience of pulmonary vein mapping and ablation in a porcine model has now been expanded to human atria and pulmonary vein ablation.[65,66] Resent studies have provided more confirming results about the use of the mini-basket catheter alone to sufficiently determine PV isolation. Along with improved recording of PV potentials after incomplete ablation, this catheter also registers "PV-like" potentials from neighboring structures. In these cases, pacing maneuvers are helpful to determine PVI and avoid excessive ablation.[67] These results though support the safety of the system and encourage further clinical evaluation.

Conclusions

Contemporary EAMs provided the 3D navigation for AF ablation in order to reduce radiation and improve safety, procedural time and efficacy. Image integration and tools, like fast mapping and contact-force feedback, act complementary towards that goal. Based on EAMs, fractionation and voltage mapping evolved and provided the stimulus for further developments that focused more and more on the visualization and analysis of the myocardial electrical signals.
Advanced mapping systems emerged from the need to better understand and ablate complex AF substrate. These efforts tried to overcome the spatiotemporal and processing limitations of contemporary EAMs and focused on improving the acquisition and illustration of electrophysiological information. Innovative mapping approaches like ripple mapping may someday allow experienced operators to create maps of complex atrial tachycardias without assisting experts. Mapping technics that aim to visualize AF drivers through depiction of dominant frequency areas and characterization of rotors or focal impulses during (intracardiac) or prior (non-invasive) to the procedure, have shown promising results in terms of AF termination and will be further evaluated.[68] The improved electrical signals produced by narrow-spaced catheters and the automated high-density maps may also prove valuable for scar-based ablation strategies.

Characterization and redefinition of AF substrate is a key-element for future mapping systems and personalized AF ablation. Ideally, future mapping-systems would allow visualization of the atrial anatomy and pathophysiology, in order to individualize and monitor lesion formation in a real-time fluoroscopy-free environment, like in the MRI suite.[69-71] Although there is a long way ahead, it remains an exciting time with many improvements and a bright future for AF mapping systems.

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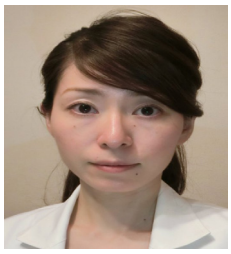

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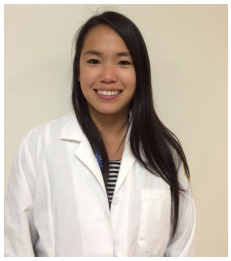

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