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Editorial

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Chasing the Frontiers of Electrophysiology!

Dear Colleagues

Great to see most of you in Chicago at the Annual Heart Rhythm Society meeting. Congratulations to each one of you for your contributions in advancing the field of electrophysiology through your innovations and discoveries. There were several advances in various aspects of the field. Some of the highlights are worth mentioning. We believe that the leadless pacing has completed their full experience. While it is disappointing to see the battery, issue temper the excitement for Nanostim, long term data and safety looks very promising for Micra. Left atrial appendage closure looks solid with excellent safety and efficacy data from Europe. Subcutaneous ICDs have established their role in the clinical tool box successfully and the global experience seems to be positive. New drugs in electrophysiology are rare. It is refreshing to see Etripamil turn out to be a reasonable alternative for the termination of Supraventricular tachycardias. Last but not least there seems to be continued interest in balloon technologies. The outcomes of radiofrequency balloon ablation for paroxysmal AF seems to be promising.

Key note speech by Hugh Evans, the humanitarian Australian who founded the Global Citizen program was very inspiring. We enjoyed the enthusiasm and the level of engagement of the fellows from around the world in the Heart Rhythm Bowl. Congratulations to Michael Gold and George Van Hare on your new roles and contributions.

This issue of the journal has several excellent original contributions and featured reviews. The case reports are quite interesting. We appreciate your contributions and readership.

Have a great summer.
Sincerely

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Early Pulmonary Vein Conduction Recovery After Catheter Ablation Of Atrial Fibrillation

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Abstract

Background: Pulmonary vein electrical isolation (PVI) is an effective treatment for atrial fibrillation (AF). However, recurrence of pulmonary vein (PV) conduction after ablation may limit long-term success. Early identification and treatment of acute PV conduction recovery during initial ablation may have an impact on subsequent clinical results.

Objective: "To" assess the prevalence of acute PV conduction recovery during the observation time after PV isolation for paroxysmal AF, and to evaluate the impact of re-isolation treatment on long-term clinical results.

Methods: 76 patients with paroxysmal AF were randomized to 2 groups to undergo PVI. Group A (Study Group: 38 patients): 30 minutes of observation were given following PV isolation for detection of acute PV-reconnection, with re-ablation of reconnected PVs. Group B (Control Group: 38 patients). Ablation procedure was done either by conventional method or using 3D electro-anatomical mapping. Symptoms, ECG and Holter monitoring were used to evaluate the clinical effectiveness of ablation. Any episode of symptomatic or asymptomatic atrial tachyarrhythmia that lasted more than 30 seconds documented with ECG or Holter monitoring was considered a recurrence.

Results: There was no statistically significant difference in age, sex, AF history, previous AF ablation, structural heart diseases & antiarrhythmic drug history among both groups. In the study group, 14 patients (36.8%) showed no PV reconnection, while 24 patients (63.2%) showed acute PV reconnection within 30 minutes. The LSPV showed the highest rate of acute PV reconnection during the observation period (66.6% of patients showing PV reconnection). AF recurred in only 6 patients (15.8%) in the study group in comparison to 20 patients (52.6%) having AF recurrence post-ablation in the control group. Among 24 patients of the study group, who showed PV reconnection which was re-isolated, only 4 patients (16.7%) had AF recurrence on follow up. In patients who did not show PV reconnection (14 patients), only 2 patients (14.3%) had AF recurrence on follow up.

Conclusions: Re-isolation of recovered PV conduction contributed to the improvement in the success rate of ablation for paroxysmal AF.

Introduction

Atrial fibrillation is a common supraventricular tachyarrhythmia characterized by uncontrolled atrial activation with consequent deterioration of atrial mechanical function. It is the most common sustained cardiac rhythm disturbance, increasing in prevalence with age.[1] It has been well established that pulmonary vein (PV) triggering or driving is the dominant mechanism for paroxysmal atrial fibrillation (AF)[2], and circumferential PV isolation (CPVI) is the main approach for AF elimination.[3] Considerable evidence points to the importance of pulmonary vein (PV) electrical isolation in the treatment of atrial fibrillation (AF) with catheter ablation procedures.[4] However, the recurrence rate of the procedure has been reported up to 30% after initial ablation, and PV conduction recovery accounts for 80% of AF recurrence, according to remapping results during a second procedure.[5] Although it is well recognized that recovery of pulmonary vein (PV) conduction is common among patients who fail atrial fibrillation (AF) ablation, little is known about the precise time course of recurrence.[6] Re-isolation of recovered PV conduction can improve the success rate, making this of great importance to reduce the prevalence of PV re-connection after the initial procedure.[7]

Key Words

Atrial fibrillation, Ablation, Pulmonary veins, Recurrence.

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Aim of the study

This study aims to assess the prevalence of acute PV conduction recovery during the observation time after PV isolation for paroxysmal AF, and to evaluate the impact of re-isolation treatment on long-term clinical results.

Patients and Methods

This study was carried on seventy six patients presenting to the Cardiology department at Ain Shams University Hospitals with atrial fibrillation dedicated for radiofrequency catheter ablation. Patients had pulmonary vein isolation using radiofrequency ablation done in the period from August 2009 till January 2012. Patients were randomly assigned to 2 groups. Group A (Study Group: 38 patients): 30 minutes of observation were given following PV isolation for detection of acute PV-reconnection, with re-ablation of reconnected PVs. Group B (Control Group: 38 patients): the procedure was terminated as soon as PV isolation was achieved, with no time given for observation of PV conduction recovery. Transesophageal echocardiography was performed to exclude left atrial thrombi. Written informed consent was obtained in all cases.

Electrophysiological study

After proper local anesthesia, left subclavian vein puncture was done

for introduction of a decapolar 6Fr catheter in coronary sinus. Left femoral venous puncture was done for introduction of a quadripolar 6 Fr catheter at His region (landmark for trans-septal puncture). Right femoral vein was punctured twice for two long sheaths of 8Fr caliber to be introduced from trans-septal punctures into LA cavity, one for the circular decapolar mapping catheter (Lasso catheter), and the other sheath for ablation catheter. In some cases, 1 trans-septal puncture was only done. 10,000 IU of calheparin were given immediately after successful trans-septal punctures followed by continuous flushing with pressurized heparinized slaine along the sideway of both long sheaths to avoid thrombus formation during this procedure with close follow up of activated clotting time (ACT) to be adjusted to be 300-400 seconds. Selective pulmonary vein angiography was done using 6F 3.5 Judkin's right coronary catheter or multi-purpose catheter.

Ablation Procedure

Conventionally guided catheter ablation:

Ablation was done using open irrigation 3.5 mm-tip ablation catheter in the power controlled mode. Continuous irrigation was achieved using automated irrigation pump (Cool Flow ®, Biosene Webster). Lasso catheter was positioned across the ostium of each PV aiming at recording pulmonary vein potentials (PVPs). The ablation catheter was positioned at the PV ostium or more precisely towards the antral aspect of each PV. Differential CS pacing was usually done for more discrimination of PVPs form LA signals during isolation of left-sided PVs. RF ablation was done segmentally all through the PV ostium aiming at diminishing PVPs in amplitude or making it takes a rounded far-field appearance. RF energy applied was typically 25-30 Watts with external irrigation flow rate of 15-18 ml/min. RF current was applied continuously with repositioning of the catheter tip every 30-60 seconds. "Complete PV isolation" was defined as the elimination of conduction of PV muscle in all pulmonary veins, as judged on the basis of either disappearance or dissociation of PV potentials.

CARTO 3D Electro-anatomical Mapping:

Continuous circumferential lesions were created encircling the left and right PV ostia or antra guided by the CARTO system using a 3.5 mm-tip open irrigation ablation catheter (Navistar™ Thermocool™ Biosene Webster). Integration of CT image into CARTO Mapping System was done. CT image fusion with 3D CARTO map was done in most of the cases ablated by CARTO technique. The CT image was imported into the system using CARTO- Merge ™ technique.

Observation for PV conduction recovery and re-ablation

For cases in Group A: PV conduction recovery was recorded after 30 minutes by re-positioning a decapolar circular mapping catheter in the left superior and inferior PV. Another 30 minutes of observation time were given for waiting and recording the right PV re-connection. At the end of the observation time, all the recovered PVPs were re-ablated aiming at complete re-isolation of the recovered PV. For cases in Group B: The procedure was terminated as soon as PV isolation was achieved, with no time given for observation of PV conduction recovery.

Post AF Ablation Management & Follow Up

Reporting of data was based on a consistent initial post-ablation blanking period of three months after the procedure. Follow up for the patients was done for a duration of 6 months after the procedure to detect long term success rate including the following data: history taking as regards recurrence of the symptoms, surface ECG was taken at 1 day, 7 days, 1 month, 2 months, 4 months, and 6 months after the procedure. Holter monitoring was done in patients with recurrent symptoms to evaluate any arrhythmic events. Cases were always asked to record their ECG when symptomatic.

Any episode of symptomatic or asymptomatic atrial tachyarrhythmia that lasted more than 30 seconds documented with ECG or Holter monitoring was considered a recurrence.

Data Management and Analysis

The collected data was revised, coded, tabulated and introduced to a PC using Statistical package for Social Science (SPSS 15.0.1 for windows; SPSS Inc, Chicago, IL, 2001). Data were presented and suitable analysis was done according to the type of data obtained for each parameter. Student T Test was used to assess the statistical significance of the difference between two study group means. Chi-Square test was used to examine the relationship between two qualitative variables. Fisher's exact test was used to examine the relationship between two qualitative variables when the expected count is less than 5 in more than 20% of cells. $P< 0.05$ was considered significant & $P< 0.01$was considered highly significant.

Results

There was no statistically significant difference in age, sex, AF history, previous AF ablation, structural heart diseases & antiarrhythmic drug history among both groups as shown in [Table 1]. Echocardiographic parameters (LV systolic function, presence of diastolic dysfunction, ventricular hypertrophy, mitral valve disease) were similar in both groups except for left atrial dimensions which were significantly lower in the study group with mean LA 35.5 ± 4.8 mm, ranging from 27-46 mm. In the control group mean LA dimension was 40.2 ± 7.9 mm, ranging from 26-53 mm. This difference was statistically significant with P value of 0.002.

Conventional ablation was done in 34 patients (89.5%) in the study group vs. 32 patients (84.2%) in the control group with no statistical significance. CARTO technique was used in 4 patients (10.5%) in the study group (2 of them were done using CARTO Merge technique) in comparison to 6 patients (15.8%) in the control (all of them were done by CARTO Merge). Regarding ablation strategy, 34 patients (89.5%) were ablated by segmental approach in the study group, 4 patients (10.5%) ablated by circumferential approach. In the control group, in 32 patients (84.2%) segmental approach was used, in 6 patients (15.8%) circumferential approach was used.

Additional lines of ablation were done in 6 patients in the study group (16.7%) in which ablation of cavo-tricuspid isthmus was done in 2 patients, 3 patients had additional ablation along mitral isthmus, & a patient received additional ablation line in SVC for isolation of potentials seen by Lasso catheter situated in SVC. In the control group, 4 patients (10.5%) received additional ablation line. 3 patients received additional ablation line at LA roof. One other patient had ablation along left atrial isthmus between LIPV & mitral annulus. During ablation procedure, 14 patients (36.8%) from the study group developed AF, 6 of which (42.9%) were spontaneously cardioverted to normal sinus rhythm during proceeding ablation, while 8 patients of them (57.1%) required external DC shock delivery. In the control group, 16 patients (42.1%) developed AF during the procedure, 8 of which (50%) were spontaneously cardioverted to normal sinus rhythm during the ablation, while the other 8 patients (50%) needed external DC shock delivery.

Fluoroscopy time was lower in the control group (111.3 ± 40.8

Table 1: showing relation between LA size, PV diameter sum & PV average diameter to AF recurrence in all patients.

	Recurrence of AF						
	No			Yes			
	Mean	±SD	Median	Mean	±SD	Median	P-value
LA (mm)	36.26	5.71	35.50	37.85	6.53	38.00	0.278
PV Diameter Sum	57.27	12.97	55.25	61.33	13.24	61.60	0.337
PV Average Diameter	16.52	2.61	16.07	15.85	1.09	15.63	0.225

Conventional ablation was done in 34 patients (89.5%) in the study group vs. 32 patients (84.2%) in the control group with no statistical significance. CARTO technique was used in 4 patients (10.5%) in the study group (2 of them were done using CARTO Merge technique) in comparison to 6 patients (15.8%) in the control (all of them were done by CARTO Merge). Regarding ablation strategy, 34 patients (89.5%) were ablated by segmental approach in the study group, 4 patients (10.5%) ablated by circumferential approach. In the control group, in 32 patients (84.2%) segmental approach was used, in 6 patients (15.8%) circumferential approach was used.

minutes) compared to the study group (135 ± 32.4 minutes). This difference was highly significant as P value was 0.006. Also total procedural time was lower in the control group (222.6 ± 54.3 minutes) compared to the study group (258.9 ± 74.6 minutes) which was also statistically significant as P value was 0.018.

Results of observation period of PVs in study group

In the study group, 14 patients (36.8%) showed no PV reconnection, while 24 patients (63.2%) showed acute PV reconnection within 30 minutes. The LSPV showed the highest rate of acute PV reconnection during the observation period. PV reconnection occurred in 16 patients (66.6% of patients showing PV reconnection) in LSPV. 4 patients (16.6%) showed PV reconnection in LIPV, 2 patients (8.3%) showed PV reconnection in RSPV. Left common PV showed PV reconnection in 4 patients (16.6%) while no patients had PV reconnection in either RIPV or in right common PV.

Regarding AF recurrence post-ablation, AF recurred in only 6 patients (15.8%) in the study group (in which 30 minutes were given for each PV to detect re-connection) in comparison to 20 patients (52.6%) having AF recurrence post-ablation in the control group. This result was highly statistically significant with P value of 0.001. Among 24 patients of the study group, who showed PV reconnection which was re-isolated, only 4 patients (16.7%) had AF recurrence on follow up. In patients who did not show PV reconnection (14 patients), only 2 patients (14.3%) had AF recurrence on follow up. In patients who did not show PV reconnection (14 patients), only 2 patients (14.3%) had AF recurrence on follow up. This shows that AF recurrence rates did not differ between group of patients who showed reconnection & were re-isolated & those who did not show PV reconnection (P value 0.10).

Complication rates were similar in both groups occurring in 4 patients in each group (10.5%). They all varied between mild pericardial effusion & local bleeding from puncture site after the procedure. One striking complication in one of the control group patients, Lasso catheter (15 mm diameter) which was stuck to postero-medial papillary muscle of MV apparatus with failed all trials to remove the catheter. Patient underwent surgery for removal of the catheter.

Discussion

Catheter ablation of AF is now a realistic therapeutic option for patients with paroxysmal AF.[8] Electrical isolation of all pulmonary veins is the endpoint of ablation.[9] It has been demonstrated that the majority of the patients who fail initial ablation procedure have resumption of PV conduction.[10] The recurrence rate of the procedure has been reported up to 30% after initial ablation, and PV conduction recovery accounts for 80% of AF recurrence, according to remapping results during a second procedure. Re-isolation of recovered PV conduction improves the success rate to 90%, making this of great importance to reduce prevalence of PV re-connection after the initial procedure.[5] A more recent study provided important additional evidence by comparing PV conduction in patients with a successful ablation procedure to those who failed the initial ablation. These investigators showed that in the majority of patients who remain in sinus rhythm; off antiarrhythmic drugs; after AF ablation, no recurrence of PV conduction occurs. In contrast, almost all the patients with AF recurrence show recurrent PV conduction.[11]

In the current study, 14 patients (36.8%) showed no PV reconnection, while 24 patients (63.2%) showed acute PV reconnection within 30 minutes. Among all pulmonary veins recorded (136 vein ostia), 26 veins (19.2%) showed PV reconnection. In the Cheema et al. study, after successful isolation of the PVs, repeat circular electrode recordings from each PV were obtained at 30 and 60 minutes. Recurrence occurred in 13 patients (93%) of the study. Recurrence was observed 30 minutes into the monitoring period in 17 veins (33%) with nine additional veins (17%) showing first recurrence at 60 minutes into monitoring period.[6] This can be explained by the fact that in the current study, the cohort of patients had predominantly paroxysmal AF; in contrast to the Cheema et al. study that comprised predominantly non-paroxysmal AF patients.[6]

Incidence of PV reconnection was higher in the current study if compared to the Wang et al. study. Continuous circumferential lesions were created in the Wang et al. study using CARTO system (Biosense Webster).[12] This step was not performed in our current study as circumferential ablation was done in only 4 patients in study (recheck) group while most of the patients were conventionally

Table 2: showing relation between LA size, PV diameter sum & PV average diameter to AF recurrence in study group patients.

	Recurrence of AF						
	No			Yes			
	Mean	±SD	Median	Mean	±SD	Median	P-value
LA (mm)	35.44	5.08	35.50	35.67	2.88	37.00	0.879
PV Diameter Sum	55.28	14.28	53.50	73.00	18.48	73.00	0.038
PV Average Diameter	16.07	2.62	15.28	16.03	2.05	16.03	0.976

ablated. Although in Wang et al. study additional 30 minutes of observation (reaching total 60 minutes observation) were included in Group C[12] in comparison to the current study in which only 30 minutes of observation were given, but incidence of PV reconnection was higher in the current study.

Regarding the PVs most commonly showing reconnection in the current study, LSPV was the PV that showed highest incidence of reconnection. It occurred in 16 patients (66.6% of patients showing PV reconnection). Then comes the LIPV reconnection which occurred in only 4 patients. Also left common PV reconnection occurred in 4 patients in our study. This is in agreement with the results of Sauer et al. who showed that the left superior PV was the most likely vein to acutely recover conduction compared with the other veins although percentage of LSPV reconnection differed from our study.[13] This also matches with the results of Cheema et al. syudy, when they showed that recurrence of conduction was more commonly observed at 30 minutes in the LSPV as compared to other veins (57% vs 23%, P = 0.02). A first recurrence at 60 minutes was observed in 21% of LSPVs as compared to 15% in other veins (P = 0.63).[6]

Any PV recurrence was also higher in two superior pulmonary veins as compared to inferior pulmonary veins[6] which was the case in the current study in which reconnection occurred more in superior PVs. This finding may be due to impaired catheter stability and energy delivery because of the complex anatomy involving the segment of PV ostium adjacent to the left atrial appendage, where a ridge of tissue dividing the structures is present. This anatomical feature is not present on the right-sided veins and could account for the differential rate of reconnection. Another possibility may be related to the difficulty in ablating the thickened tissue fibers involving this region, which includes the ligament of Marshall that borders the left PV structures.[13]

Follow Up of AF Recurrence Post-ablation

In the current study, AF recurrence rates post-ablation was 14.3% in patients who showed no PV reconnection (2 patients), 16.7% in (4) patients who showed PV reconnection (which was dealt with by re-isolation) with P value 0.100. All cases of recurrence were in the form of AF recurrence with no cases showing post-ablation flutter or atrial tachycardia. In the current study, there was no difference in AF recurrence between patients who showed reconnection and were re-isolated & those who did not show any PV reconnection. This means that observation period is beneficial in any situation whether PVs were reconnected or not, because it will confirm PV isolation (in case of no reconnection) or will raise the attention for the need for re-isolation (in case of reconnection).

This comparison & its results were similar to that done in the Sauer et al. study that compared patients showing reconnection with patients who did not show reconnection. After a single procedure, AF cure was achieved in 119 (56%) of 213 patients who demonstrated acute PV reconnection compared with 124 (59%) of 211 patients without acute PV reconnection observed (P value: 0.97).[13]

Upon comparing the group of patients in which observation time was given for PV reconnection (recheck group), to the group of patients in which no time was given for observation, the current study found that there was a great significant difference between both groups. AF recurrence rates post-ablation was 15.7% in recheck group (with 84.3% of patients free of symptoms), in comparison to 52.6% in control group (with 47.4% of control group patients free of symptoms). This was highly significant with P value of 0.003. Rate of arrhythmia recurrence was nearly the same in patients who were offered additional observational time in both our study & Wang et al. study, especially in the group in which 30 minutes of observation were given, exactly like protocol of our study group.[12]

Table 3: showing relation between LA size, PV diameter sum & PV average diameter to AF recurrence in study group patients.

	Recurrence of AF						
	No			Yes			
	Mean	±SD	Median	Mean	±SD	Median	P-value
LA (mm)	37.72	6.58	36.00	38.50	7.21	39.50	0.730
PV Diameter Sum	61.64	8.52	64.40	56.66	7.39	61.60	0.180
PV Average Diameter	17.51	2.42	17.10	15.77	.56	15.63	0.052

Fluoroscopy time was lower in the study group (111.3 ± 40.8 minutes) compared to the control group (135 ± 32.4 minutes). This difference was highly significant as P value was 0.006. Also total procedural time was lower in the study group (222.6 ± 54.3 minutes) compared to the control group (258.9 ± 74.6 minutes) which was also statistically significant as P value was 0.018.l

PV conduction recovery was the dominant cause of AF recurrence after the initial ablation procedure and accounted for 80% of AF recurrence. PV conduction recovery after the initial PV isolation procedure could be classified into acute recovery and chronic recovery, according to the time it occurred. It is postulated that their respective mechanisms differ from each other. Acute PV conduction recovery might be attributable to discontinuous or non-transmural lesions and chronic PV conduction recovery might be caused by the restoration of a few atrial myocardium cells which survived initial ablation.[12]

Theoretically, re-ablation of recovered PV conduction could produce trans-mural lesions, reduce living atrial tissues along lesion lines, and thus contribute to lowering of the prevalence of chronic PV conduction recovery and improving long-term success rate.[12] The follow up results of the current study showed that the success rate in the study (recheck) group was significantly higher than that in control group. The results of the Wang et al. study also showed that the prevalence of acute PV conduction recovery varied according to different observation time spent on evaluating it. Theoretically, the longer the observation time was, the higher the prevalence of PV re-connection would be. Unfortunately, it was impossible to spend unlimited observation time on evaluating PV re-connection, so it was advisable to set a limited window of observation.[12]

The results of the current study are of potential clinical importance. These findings, combined with the results of prior studies, which have shown that the outcome of AF ablation correlate strongly with PV isolation, provides evidence to support incorporation of a 30- to 60-minutes monitoring period into AF ablation protocols.[11]

Conclusions

The prevalence of acute PV conduction recovery was not low after PV isolation, which mostly occurred within 30 min after initial isolation. LSPV was the PV that showed highest incidence of reconnection. It occurred in 66.6% of patients showing PV reconnection.

Observational time (30 minutes) given for detection of acute PV reconnection was of great benefit. Re-isolation of all veins that demonstrated early reconnection improved the long-term single procedure outcomes of AF ablation. The results of this study suggest that better strategies to permanently isolate the pulmonary veins are needed.

Conflict Of Interests

None.

Disclosures

None.

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Clinical Role Of Dominant Frequency Measurements In Atrial Fibrillation Ablation – A Systematic Review

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Abstract

Introduction: Experimental data strongly supports a role for high-frequency sources in the perpetuation of atrial fibrillation, it follows that identification of areas exhibiting spectra containing high dominant frequencies (DF) may represent perpetuating sources and targeted elimination might terminate AF. The aim of this review is to present and critically appraise the literature on DF studied in association with AF ablation.

Methods And Results: A systematic review was done including the PubMed (MEDLINE), Cochrane Central Register of Controlled Trials (Central), Scientific Electronic Library Online (SciELO), and HighWire Press databases. The searches were made by combining the terms "Dominant Frequency", "Atrial Fibrillation", and "Catheter Ablation" and their translations for the English and non-English based databases. Ten articles were selected from a total of 327 articles found after the initial search. The ablation strategy varied, most studies performed pulmonary vein isolation alone or associated with complex fractionated atrial electrogram ablation with or without an additional intervention. The use or not of DF sites as ablation target was distinguishable between the articles. Four articles ablated DF sites as a major intervention or in addition to a traditional approach. The remaining 6 articles assessed DF sites pre and post ablation and associated these data with clinical outcome.

Conclusions: No prior study has systematically comprised information for clinical use of DF. The current literature supports global DF as a useful marker of ablation outcome; however direct intervention targeting DF appears premature with mixed results and too few studies.

Introduction

Atrial fibrillation (AF) is the most common supraventricular arrhythmia in clinical practice with both increasing prevalence and incidence in a global pattern.[1] Catheter ablation is an accepted, widely employed therapy with good outcomes in paroxysmal AF and less optimal outcomes in persistent AF.[2] Empiric approaches, such as pulmonary vein isolation (PVI), ablation lines, and electrogram based approaches have been used with reasonable efficacy.[3] 'Targeting' approaches have traditionally used feature extraction of electrocardiogram signals recorded during AF. The most widely employed technique is ablation of complex fractionated atrial electrograms (CFAEs).

Fractionated electrograms are believed to represent sites of reentry that facilitate maintenance of AF.[4] CFAEs are defined as low-voltage fractionated electrograms with a cycle length <120 ms.[5] Studies have suggested that CFAEs can potentially characterize areas with wavefront collision, functional conduction block, wave break and wave fusion.[6] These sites with CFAE appear temporo-spatially stable[7] and ablation at these sites may also result in AF termination.[7]-[9]

Key Words

Dominant Frequency, Atrial Fibrillation, Signal processing, Catheter ablation, Systematic Review.

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However, lack of standardization and the frequent use of the mean cycle length (CFEmean) as a poor surrogate for CFAEs, has led to conflicting data and favoring a simple, empiric circumferential ablation.[2] An alternative targeting method is identification of the spatial distribution of excitation frequencies during AF by spectral analysis of intracardiac electrograms.[10] This method is referred to as Dominant Frequency (DF) in the literature. Unlike CFAE, that is most often presented as a time domain feature of the electrograms (the mean cycle length); DF approaches contemplate the frequency contents of the electrograms. Dominant frequency is defined as the highest magnitude sinusoidal component of the electrogram and is found by decomposing the electrograms into a finite number of sinusoidal constituents and finding the one with the highest magnitude.

The DF is quantified in hertz and is variable between electrograms recorded at different anatomic sites.[9] Despite the differences between the DF and CFAE, some experimental studies have claimed that high DF activity at the posterior left atrium is the cause of fractionation of wave fronts in its immediate surroundings, resulting in CFAEs.[11]

Theoretically, DF indicates the source of fibrillatory activity by recognizing the signal with a higher frequency compared with its surroundings[2]; it appears to be associated with perpetuating rotors in pre-clinical studies.[12], [13] As experimental data has strongly supported a role for high-frequency sources in the perpetuation of AF, it follows that identification and elimination of areas exhibiting spectra containing high dominant frequencies (DF) may represent

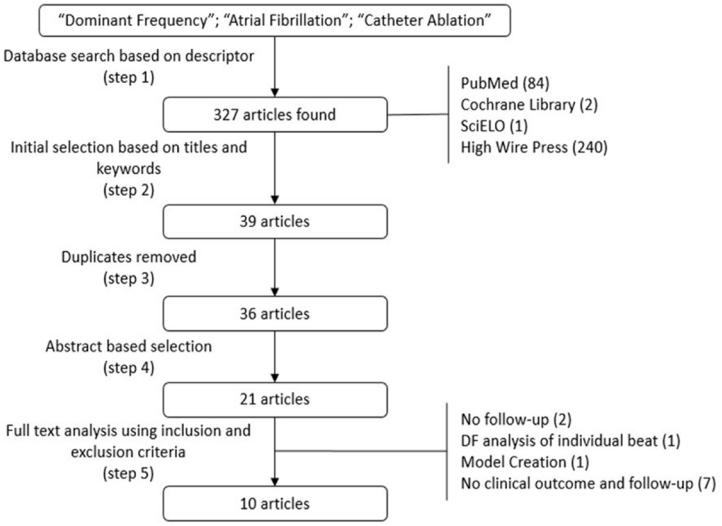

Figure 1: Steps followed for the systematic review.

perpetuating sources, might terminate AF.[9],[14] The aim of this review is to present and critically appraise the literature on DF studied in association with AF ablation.

Methods

The databases used for this review include PubMed (MEDLINE), Cochrane Central Register of Controlled Trials (Central), Scientific Electronic Library Online (SciELO), and HighWire Press. The searches combined the terms "Dominant Frequency", "Atrial Fibrillation", and "Catheter Ablation" for the English based databases. The same terms and their translations were used for the non-English based databases. Articles published in English, Portuguese, and Spanish were accepted to this review. Randomized clinical trials, non-randomized clinical trials, cohort studies, case-control studies, and others interventional and observational studies were included. Guidelines, editorials, review articles, meta analysis and poster presentations were excluded.

For an article to be included in this review it must have met all the following criteria: (1) Assessment of intracardiac DF for LA or RA or both; (2) Reported ablation outcomes; (3) The DF measurements must be correlated to outcomes in any way; (4) a follow-up period of ≥ 6 months must be present. Articles linking DF to geometry, signal processing or spatiotemporal parameters without clinical correlations were excluded from this review. The number of participants and publication data was not used as exclusion criteria.

This review was based on the following steps: Database search based on descriptor (Step 1); Initial selection based on titles and keywords (Step 2); Duplicates removal (Step 3); Abstract based selection (Step 4); and Full-text analysis using inclusion and exclusion criteria (Step 5). The methodology used in this review is summarized in [Figure 1].

Studies passed through the fifth step were selected for data extraction. Relevant information related to study design, type of population, follow-up period, DF assessment, ablation procedures (strategy, use of DF sites for ablation, and anatomic regions assessed), outcome periods (short and long term), complications, and correlations between DF assessment and clinical prognosis were assessed.

Results

A total of 327 articles were identified at the initial step (84 from PubMed, 2 from Cochrane Library, 1 from SciELO, and 240 from HighWire Press). Thirty-nine potential articles remained after Step 2. Duplicates were removed in Step 3 and, 21 articles resulted after abstract selection in Step 4. The selection in Step 5 identified 10 articles which passed through quality assessment and data extraction. The reasons for exclusion of the 11 studies are listed in [Table 1].

Table 1: List of excluded articles and respective reasons.

Author and year	Title	Exclusion
Bencsik et al 2009	Acute effects of complex fractionated atrial electrogram ablation on dominant frequency and regulatory index for the fibrillatory process	No follow-up.
Biviano et al 2015	Atrial electrogram discordance during baseline vs reinduced atrial fibrillation: Potential ramifications for ablation procedures	No clinical outcome and follow-up.
Garibaldi et al 2012	Predicting catheter ablation outcome in persistent atrial fibrillation using atrial dominant frequency and related spectral features	No follow-up.
Grzeda et al 2009	Complex fractionated atrial electrograms: Properties of time-domain versus frequency-domain methods	Model creation.
Lee et al 2011	Relationship among complex signals, short cycle length activity, and dominant frequency in patients with long-lasting persistent AF: A high-density epicardial mapping study in humans	No clinical outcome and follow-up.
Lin et al 2012	A Prospective, Randomized Comparison of Modified Pulmonary Vein Isolation Versus Conventional Pulmonary Vein Isolation in Patients with Paroxysmal Atrial Fibrillation	DF analysis of individual beat.
Salinet et al 2014	Distinctive patterns of dominant frequency trajectory behavior in drug-refractory persistent atrial fibrillation: Preliminary characterization of spatiotemporal instability	No clinical outcome and follow-up.
Takahashi et al 2006	Organization of frequency spectra of atrial fibrillation: Relevance to radiofrequency catheter ablation	No clinical outcome and follow-up.
Takahashi et al 2008	Characterization of Electrograms Associated With Termination of Chronic Atrial Fibrillation by Catheter Ablation	No clinical outcome and follow-up.
Tuan et al 2011	Regional fractionation and dominant frequency in persistent atrial fibrillation: Effects of left atrial ablation and evidence of spatial relationship	No clinical outcome and follow-up.
Yokoyama et al 2009	Paroxysmal atrial fibrillation maintained by nonpulmonary vein sources can be predicted by dominant frequency analysis of atriopulmonary electrograms	No clinical outcome and follow-up.

DF = Dominant Frequency

From the 10 selected studies, 1 was a randomized controlled trial (RCT)[15], and 9 were non randomized studies (NRS).[16]-[24] There were six studies with paroxysmal and persistent AF patients[15]-[18],[20],[21], and 4 studies with only persistent AF patients.[19],[22]-[24] One article was from 2006[18], two from 2009[16],[20], two from 2010[19],[23], two from 2011[22],[24], one from 2013[17], and one from 2014.[15] There were 3 studies which classified AF as persistent and long-lasting or long-standing persistent[17],[19],[24], and 2 studies which classified AF as paroxysmal and non-paroxysmal.[20],[21] The sample size varied among the articles with 40 the smallest[21] and 232 the highest[15] study population.

The ablation strategy varied; studies reported PVI alone or associated with CFAE ablation with or without an additional intervention such as empiric linear lesions. Four articles involved ablation of DF sites as a major intervention or in addition to an empiric approach[15]-[17],[22], one of which was a randomized clinical trial.[15] The remaining six articles assessed DF sites pre and post ablation and associated DF values with clinical recurrence.

The shortest mean follow-up was 9±6 months.[18] The regions selected for DF measurements varied, however, all articles involved LA assessment of DF. Five studies also measured DF in the RA.[15],[16],[20],[21] In addition, three articles assessed DF extracted from the atrial component of lead V1 of the 12-lead electrocardiogram (ECG).[18],[23],[24] We empirically divided studies into outcomes that reported DF values as markers of interventional success and studies that targeted high DF sites with the aim to improve procedural outcomes. [Table 2] and [Table 3] present the selected articles according to whether high DF was used as an ablation target.

Dominant Frequency Values as a Marker of Procedural Success

In the following studies, DF values were employed as markers of procedural success rather than as targets for ablation. We describe the results of studies reporting outcome associated with DF values.

With a sample size of 84 patients, Lemola et al 2006[18] performed a circumferential PVI (CPVI) or an electrogram-guided ablation (EGA) in persistent AF and paroxysmal AF groups and correlated the changes in DF with clinical outcome. They simultaneously analyzed the spectral component of atrial activity from lead V1 with electrograms at the base of the left atrial appendage (LAA), on the anterior left atrial wall, and coronary sinus (CS). In both ablation approaches, EGA or CPVI significantly decreased the mean DF in the LAA and in the CS. Contrary to another similar study[23], termination of AF during ablation did not appear related to the percent DF reduction in the LA, CS or V1 values. In persistent AF patients who underwent EGA, a greater decrease in DF values in the CS and V1 was associated with freedom from recurrent AF.

In 2009, Lo et al aimed to associate different parameters with the prediction of AF termination and long-term outcome.[20] In their work, a PVI and a linear ablation at the anterior roof and lateral mitral isthmus were performed in 83 patients with an additional CFAE approach if AF was not terminated. Although smaller LA size and lower RA mean DF were the only parameters that independently predicted AF termination, other parameters such as lower mean DF at LA and RA, and lower max RA DF were also associated with acute AF termination. In addition, a larger LA diameter and presence of RA ectopy were independent predictors of late AF recurrence.

Similarly, in 2011, in order to determine if electrical and structural remodeling measurements influence outcomes in AF ablation, Yoshida et al[24] performed a PVI followed by a CFAE ablation in 79 persistent or longstanding persistent AF patients. Additional linear ablation was performed if AF persisted after PVI. Electrograms recorded prior to ablation in the LAA, and CS, and surface lead V1 were used for analysis. Patients who did not achieve AF termination had significantly higher DF in the LAA and lead V1. In a multivariate analysis, DF in the LAA was associated with AF termination. After a mean follow up of 14 ± 7 months, patients with AF recurrence had a higher DF recorded in the LAA than patients without recurrence (6.8 ± 0.7 Hz vs. 6.3 ± 0.7 Hz; P=0.03).

In a prior study from 2010, the same group examined change in DF from surface lead V1 atrial activity and the CS electrograms during the ablation procedure of persistent AF patients (PVI + CFAE)[23] and correlated with acute and long-term clinical success. Ablation terminated AF in 39 patients and 61 patients required cardioversion. The mean percentage decrease in DF was 9.8% ± 8.8% in V1 and 10.0% ± 6.8% in the CS. A decrease ≥11% in DF (V1) and AF termination during ablation procedure were both independent predictors of freedom from recurrent atrial arrhythmias after a single procedure. Also, the percent decrease in DF of AF was significantly correlated with the RFA duration directed applied to CFAE sites.

In 2012, Okumura et al[21] identified CFAEs and DF characteristics from responders and non responders, relative

Table 2: List included of articles that did not target dominant frequency.

Author and year	DF definition	Types of Population	Ablation	Clinical correlation	Areas assessed	Follow-up
*Lemola et al 2006	The frequency of the highest peak in the periodogram (0.5-60Hz)	Paroxysmal (49) and Persistent (35) AF.	CPVA EGA	Acute decrease in the DF of AF after EGA was associated with a favorable clinical outcome in patients with persistent AF.	V1, CS	9 ± 6 months
*Lin et al 2010	DF gradient >20%	Persistent (20) and Long-lasting Persistent (30) AF.	PVI + Linear Ablation + CFE + Non-PV Ectopies	Presence of an intra-LA DF gradient predicted the SR maintenance rate.	LA	11 ± 6.5 months
*Lo et al 2009	The normalized largest peak identified in the spectrum of 2-30Hz	Paroxysmal (33) and Non-paroxysmal (52) AF	PVI + Linear Ablation + CFAE	Lower mean LA DF, lower mean RA DF, and lower max RA were associated with acute AF termination.	LA, RA, PV	13 ± 8 months
*Okumura et al 2012	The largest peak frequency of the resulting spectrum (3-30Hz)	Paroxysmal (24) and Non-paroxysmal (16) AF	CPVI	Higher DF in the LA, non-paroxysmal AF and longer AF duration were independent predictor of AF recurrence.	LA, RA, PV, CS	12.3 months
**Yoshida et al 2010	The frequency of the highest peak in the periodogram (0.5-20 Hz)	Persistent (100) AF	APVI + CFAE	>= 11% decrease in DF had the highest accuracy in predicting freedom from atrial arrhythmias.	V1, CS	14 ± 3 months
**Yoshida et al 2011	The frequency of the highest peak in the periodogram (0.5-20 Hz)	Persistent (42) and Long-standing Persistent (37) AF	PVI + CFE + Linear Ablation	DF in LAA was associated with AF termination.	LAA, V1, CS	14 ± 7 months

AF = Atrial Fibrillation; APVI = Antral Pulmonary Vein Isolation; CFE = Complex Fractionated Electrograms; CFAE = Complex Fractionated Atrial Electrograms; CPVA = Circumferential Pulmonary Vein Ablation; CPVI = Circumferential Pulmonary Vein Isolation; CS = Coronary Sinus; DF = Dominant Frequency; EGA = Electrogram-Guided Ablation; LA = Left Atrium; LAA = Left Atrial Appendage; NRS = Non Randomized Study; PV = Pulmonary Vein; PVI = Pulmonary Vein Isolation; and RA = Right Atrium. (*Prospective study, **Prospective and Retrospective study)

to AF termination during the procedure and patients with and without AF recurrences during follow-up. From the 40 patients, 19 were CPVI responders and 21 were CPVI non-responders. In the non-responders group, the DF from the LAA, LA body, and CS were significantly higher than the CPVI responders. The recurrent AF group presented significantly higher prevalence of non-paroxysmal AF patients (66.7% vs. 28.6%), longer mean AF duration (97.3 vs. 42.3 months), and higher mean DF in the LA body (6.89 ± 0.71 vs. 6.14 ± 0.85 Hz) in comparison to the non-recurrent AF group in a mean follow-up of 12.3 months. In addition, they found that those parameters (higher DF in the LA, non paroxysmal AF and longer AF duration) were independent predictors of AF recurrence.

Lin et al (2010)[19] performed PVI and linear ablation in 50 persistent AF patients and examined the effects of ablation on the patterns of DF distribution. Additional CFAE ablation was performed if AF was not terminated. Non-PV ectopy was later focally ablated in all patients. AF termination and clinical outcome were not assessed in 10 patients because the endpoint was not reached after PVI. As a result, AF terminated in 19 of the 40 patients and termination was significantly higher in patients with higher DF gradient recorded across the LA (DF max was >20% of the average DF in the LA) when compared to patients with lower DF gradient (<20% of the average DF). The isolation of DF max sites resulted in a final procedural AF termination rate of 71% after all continuous CFAE were eliminated. The DF gradient was predictive of long-term success.

Dominant Frequency as a Modifiable Target for Ablation

In the studies described below, high DF sites mapped within the atria were targeted for ablation and outcomes were associated with this strategy.

Initially, in 2009, Atienza et al[16] performed a catheter ablation of all DFmax sites prior to PVI in 50 patients to evaluate the safety and long-term outcome of ablation DFmax sites. In total 50 paroxysmal and persistent AF patients participated in this study. They associated higher probability of remaining free from atrial arrhythmias and fibrillation with ablation of DF sites. Recurrences of AF were higher in patients with remaining DF sites after the procedure (50% vs. 77%; P=.05). In their work, a predictor of a better outcome for persistent AF patients was found to be the presence of an LA-to-RA gradient before ablation. Moreover, ablation of DF sites and paroxysmal AF were independent predictors of long-term AF freedom.

The same group tested the hypothesis that targeted ablation of high DF sites referred to as high frequency source ablation (HFSA) would be as effective as empiric PVI procedures. In 2014, Atienza et al[15] reported a non-significant improvement in recurrence of AF or AT at 1 year in the HFSA arm in paroxysmal AF (79% vs. 81% for AF, and 72% vs. 76% for AF/AT, respectively) and in persistent AF (65% vs. 69% for AF, and 63% vs. 67% for AF/AT, respectively). Similarly, the time to the first recurrence after a single procedure and after redo procedures did not differ in both paroxysmal and persistent AF patients. It was highlighted that a number of patients from the HFSA groups (18 in the HFSA alone and 26 in the CPVI + HFSA) were spared from ablation due to safety concerns (HFS located inside LAA, and proximity to structures) and that additional ablation lines in the control group may have increased efficacy. Nonetheless, a high DF target strategy appeared no better than empiric PVI in both paroxysmal and persistent patients.

Kumagai et al 2013[17] studied 50 patients of which 18 exhibited procedural AF termination. Of those, 14 had PVI only, three had additional high DF ablation, and one had PVI + DF ablation + CFAE, which was the only persistent patient to achieve termination. Eight of the 14 paroxysmal patients demonstrating AF termination had high DF sites ablated during within the PVI circles and three patients at LA septum. Overall, 11 of 18 patients reached AF termination due to ablation in high DF sites in this study. Only DF sites ≥8 Hz were considered for ablation. In total, 31 high-DF sites were ablated in paroxysmal AF and 130 in persistent AF. Also, LA-to-RA DF gradient in patients with AF termination was not significant compared with patients without AF termination after the procedure.

Verma et al 2011[22] performed PVI after DF-guided ablation in 30 persistent AF patients based on retrospective observations of 20 AF patients group who underwent previous CFAE-based ablation and later compared with 30 case-matched patients from a control PVI group. Only two patients achieved AF termination with DF

Table 3: List of articles that ablated on dominant frequency sites.

Author and year	DF definition	Types of Population	Ablation	Clinical correlation	Areas assessed	Follow-up
*Atienza et al 2009	DFmax ≥20% of its surroundings	Paroxysmal (32) and Persistent (18) AF.	DFmax + CPVI	Independent predictors of freedom of AF were ablation of DFmax sites and paroxysmal AF.	PV-PLAW, LA, CS, RA	9.3 ± 5.4 months
§Atienza et al 2014	DFmax ≥20% of its surroundings	Paroxysmal (115) and Persistent (117) AF	CPVI only HFSA only CPVI + HFSA	Freedom was seen in 79% of CPVI and 81% of HFSA in paroxysmal AF, and in 65% of CPVI and 69% of CPVI + HFSA in persistent AF patients at 1 year.	LA, CS, RA	12 months
*Kumagai et al 2013	DF ≥ 8Hz with RI >0.2	Paroxysmal (23) AF, Persistent (9) AF and Longstanding Persistent (18) AF.	PVI PVI + DF PVI + DF + CFAE	AF terminated by ablation at high-DF sites (9.9 ± 0.7 Hz) in 11 of 18 patients.	LA, RA, CS	12 months
**Verma et al 2011	Group I: DF ≥ 8Hz with RI >0.2 Group II: DF higher than the mean atrial DF with RI >0.2	Persistent (80) AF	CFAE-based DF + PVAI Control PVAI	After 1 year, DF + PVAI resulted in freedom in 17/30 patients (57%) off antiarrhythmic therapy after 1 procedure.	LA	12 ± 2 months

AF = Atrial Fibrillation; CFAE = Complex Fractionated Atrial Electrograms; CPVI = Circumferential Pulmonary Vein Isolation; CS = Coronary Sinus; DF = Dominant Frequency; HFSA = High-Frequency Source Ablation; LA = Left Atrium; PVAI = Pulmonary Vein Antral Isolation; PV-PLAW = Pulmonary Veins-Posterior Left Atrial Wall; PVI = Pulmonary Vein Isolation; RA = Right Atrium; RI = Regularity Index. (*Prospective study, **Prospective and Retrospective study, § Randomized Controlled Trial)

ablation alone and two others patients reached AF termination after additional PVI. The remaining 26 required cardioversion. After a mean of 12 ± 2 months, 17/30 patients (57%) from the DF + PVI group achieved AF freedom without drugs after the first procedure which was not significantly different from the control PVI group which achieved 60% AF freedom. On retrospective analysis of the CFAE-based group, AF termination occurred in regions where high DF (8-25 Hz) overlapped with CFAE (characterized by a mean cycle length of 40-120 ms). They observed that 89 ± 8% of the high DF regions overlapped with CFAE, however only 48 ± 27% of the CFAE areas overlapped with high DF regions.

Discussion

In this systematic review, we examined the clinical use of DF in regard to catheter ablation for atrial fibrillation. No prior study has systematically reviewed this topic to evaluate the relevance of DF in the clinical field. Since the late nineties, experimental studies have speculated on the potential use of high DF sites for ablation[9], [25], [26] given the strong experimental association with AF perpetuation. The mechanism of persistent AF in humans remains elusive but recent data strongly supports maintenance by rotors with high DF.[25] From the analysis of the presented clinical articles, two major findings can be described: (1) measured DF appears to correlate with acute and chronic procedural outcomes. (2) Ablation on DF sites did not convincingly improve procedural success. Other findings include: (1) high mean DF across the LA at the beginning of ablation is associated with poor outcome, (2) decrease in DF value in CS and V1 during the procedure is associated with less recurrence, (3) reduction ≥11% in surface ECG derived DF during the ablation procedure is associated with freedom from AF recurrence in persistent AF, and (4) higher pre-ablation intra-LA DF gradient is predictive of long-term SR maintenance.

Global DF as a Marker

From the analyzed articles, it is clear that there is a correlation between DF and ablation outcome. Theoretically, high DF indicates the source of fibrillatory activity by recognizing the signal with a higher frequency compared with its surroundings[27], it appears to be associated with perpetuating rotors. It follows that a reduction in the fibrillatory activity should occur when this value reduces and observational studies appear to support this. Therefore, DF behaves as a marker of ablation success, with a reduction in both surface and intracardiac (LA and CS) measures indicative of better outcome. Some studies presented higher termination when ablating CFAE areas adjacent to high DF values[19], [21] this correlation between CFAE and DF indicates that the intraprocedural reduction of DF may present a useful marker of optimal ablation as an alternative to AF termination, although this potential has not been examined prospectively.

High DF Sites as a Target for Ablation

The data presented by the second group of articles were somewhat contradictive. Ablating high DF sites prior to CPVI presented beneficial results for both paroxysmal and persistent patients in an early work by Atienza et al in 2009[16]; however, no such conclusion could be inferred from the RCT performed by the same group in 2014.[15] Supporting this, additional high DF-based ablation on PVAI of 30 persistent AF patients did not improve on outcome as indicated by Verma et al 2011.[22] Moreover, Kumagai et al in 2013[17] reported lower AF termination in patients that combined high DF-guided and CFAE ablation after PVI. The discrepancy of these results might be related to certain differences in studies characteristics. For high DF definition, two articles[15], [16] based their maximum DF value in comparison to its surroundings, therefore their inclusion criteria did not involve a previously defined value. While the other two[17], [22] defined a cutoff value of 8Hz for high DF ablation, this isolates the possibility of recognizing lower amplitude DF sites with the same influence on neighboring tissue that sites with DF ≥8Hz might be expected to have. The absence of a control group in three of the four studies[16], [17], [22] impairs the validation and comparison of their results. These four studies were quite heterogeneous in demographics, two studies had a mean population age of 55 ± 9 years[15], [16] and the other two of 64.8 ± 11.1 years.[17], [22] In addition, Verma et al had higher mean AF duration of 7.4 years[22], higher than the 60.9 ± 67.6[17], 19.9 ± 11 months[16], and 4.13 years[15] years from the remaining three studies. The comparison of the results from those articles might not be justified since age and AF duration were associated with worse procedural outcomes.[24]

Why does ablation of high DF sites not provide better results?

This apparent paradox might be explained by understanding the limitations of frequency analysis. First, a reduction in globally measured DF is associated with good clinical outcome but it does not follow that ablation of specific high DF sites results in the same. The dilemma of DF use lies on its variability due to changes in amplitudes, and morphology, which could be the effect of noise and far-field potentials.[27] Complexity of the signal morphology, as present in CFAE, and relative amplitude can affect the power spectrum and therefore the DF value, the morphology of discrete, narrow electrograms will have minimal impact on DF value, however low amplitude, broad CFAE electrograms will impair reproducibility of DF measurement and are less reliable.[28] Bipolar electrograms and signal duration ≥2 seconds are recommended to reduce those influences, as well as signal processing prior to fast Fourier transform (FFT), averaging multiple signals, and evaluation of power spectrum consistency.[29] Most studies follow those recommendations but vary considerably in the duration of signal examined and present data as a single value that is not representative of the time variant signal. For example, the two studies authored by Atenzia[15], [16] appear to show conflicting results, however the electroanatomic mapping system and processing of DF values were entirely different in the two studies and may go some way to explaining the discrepancy. Thus, targeting high DF is vulnerable to many confounding factors, not limited to signal processing issues but also bystander collision, pivot of wave fronts as well as meandering driver sources; indeed, it is quite conceivable that collision between two driver wave fronts will result in a higher DF value than either driver alone. However, it can be understood that if one driver is eliminated the overall DF drops due to a reduction in the collision and therefore reduction in global DF can quite readily be a marker of source reduction both directly and indirectly. Trying to target high DF may not yield the same result as both measurement error and confounding ablation of collision sites will not impact sources. In addition, in the case of meandering rotors, the shift in the observed frequency due to relative motion of the catheter and the rotor (Doppler Shift) can complicate the interpretation of high DF sites.[30] Even in the case of presence of a stationary rotor and neglecting the targeting error due to catheter navigation inaccuracies, the ablation at the pivoting center of the rotor may only decrease the rotation rate of the rotor, the required ablation strategy for rotors is unknown.

Put simply, these data indicate that DF can be used as a marker to predict outcome and recurrences; however, targeting this marker might not be the solution to increase ablation success with current signal processing techniques. High DF at specific site might be an indicator of a high frequency driving source, or it might be passive and just result of collision or overlap of different wave fronts.[31]

Future Considerations

Despite the disappointing results of targeting there remains good evidence that DF is a reflection of intraprocedural substrate change, as such it may provide a marker of the need for additional substrate ablation after PVI, and as such, a marker of optimal substrate ablation, avoiding proarrhythmia and complications associated with attempting to ablate until SR is achieved. Furthermore, contemporary signal processing techniques should be investigated to differentiate collision, nonstationary phenomena and anchored sources of AF perpetuation. Research using analysis of wavebreak and longer recording periods will attempt to resolve this issue to allow more specific targeting and avoid bystander regions. More work needs to be done to improve the accuracy of DF measurement and site differentiation.

Study Limitation

Not all studies presented full representation of the atria, some presented only a specific region or 'global' metric from surface ECG or CS. Therefore, we could not provide a direct quantitative comparison of data and the results were provided in a qualitative manner. Restricted to the design of our study, no statistical calculation and summary from demographics were provided. However, important information was provided relevant for this review. No exclusion was done based on quality assessment, for this reason, the results and conclusion presented from the analyzed articles can be biased and may not represent the optimal situation. Some studies presented a small sample size[16]-[19], [21], [22] that reduces the external validity of their results. In addition, most studies used the same individual as a control for itself in a retrospective comparison[17]-[21], [23], [24] which also alters the validation of the results.

Conclusions

No prior study has systematically comprised information for clinical use of DF. Our systematic literature review supports DF as a useful marker of ablation outcome; however direct intervention targeting DF appears premature with mixed results and too few studies. Further research is warranted to explore this relationship Further research is warranted to explore this relationship and the development of more selective ablation procedures to avoid unnecessary complications and improve the outcome of targeted approach. Current DF methodology and targeting is insufficient to be used as a clinical tool but shows great promise as signal processing methods evolve.

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Conflict Of Interests

None.

Disclosures

None.

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Mechanistic Insights Into Durable Pulmonary Vein Isolation Achieved By Second-Generation Cryoballoon Ablation

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Abstract

Background: The mechanism explaining the efficacy of cryoballoon ablation (CBA) for atrial fibrillation has not been clarified.

Methods and Results: We compared lesion characteristics between patients in whom pulmonary vein isolation (PVI) was performed by CBA (n=56) and those by contact force (CF)-based RF ablation (n=56). We evaluated the 3-dimensional PV morphology before and after cryoballoon inflation. After PVI, a 3D left atrial voltage map was created. Pacing (10 mA and 2 ms) was performed within the low voltage area from the ablation line, and electrically unexcitable ablated tissue was identified. ATP-provoked dormant conduction after PVI occurred in 9 of the 224 (4%) PVs in the CBA group and in 13 of the 224 (6%) PVs in the CF group (P=0.3935). The inflated balloon stretched the PV from the original PV ostial surface by 5.2±3.3 mm, but at sites with (vs, sites without) residual PV potential/dormant conduction, the extent of the PV distension was reduced (2.6±3.4 mm vs. 5.3±3.3 mm, P<0.0001). The unexcitable ablated tissue around the PVs was significantly wider in CB patients than in CF patients (16.7±5.1 mm vs. 5.3±2.3 mm, P<0.0001).

Conclusions: Use of the cryoballoon significantly distends the PV. Without this extensive distention, PVI may not be successful. CBA seems to yield wide unexcitable ablation zones. These factors seem to explain the durability of CBA lesions.

Introduction

Cryothermal energy has emerged as an alternative ablation energy that does not issue in the clot formation and excessive tissue damage that occur with radiofrequency (RF) energy-based catheter ablation.[1] Although cryothermal energy is a milder and safer form of energy than RF energy, pulmonary vein isolation (PVI) performed with a second-generation cryoballoon has been highly successful in cases of paroxysmal atrial fibrillation (AF) and comparable to PVI performed by point by point-based RF ablation[2]–[6] or even contact force (CF)-based RF ablation.[7],[8] Despite the efficacy of cryoballoon ablation (CBA), however, some patients suffer recurrence of the AF, due mainly to PV reconnections or to non-PV triggers.[9],[10] Thus far, the mechanisms explaining durable and non-durable lesion formation around the PV ostium by means of second-generation CBA have not been fully investigated. Because establishing good balloon surface-to-tissue contact is essential for successful CBA of AF, we investigated, by means of 3-dimensional (3D) geometric imaging, how the inflated balloon surface contacts the 4 PVs. We then characterized lesions created around the PV ostia by CBA and those created by CF-based ablation to clarify the mechanism responsible for the efficacy of CBA.

Key Words

atrial fibrillation, cryoballoon ablation, pulmonary vein isolation, pulmonary vein distension.

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Material and Methods

Study Patients

The study involved 112 consecutive patients treated for AF (symptomatic paroxysmal AF [n=88] or persistent AF [n=24]) at Nihon University Itabashi Hospital between September 2014 and December 2015. The patient series comprised 72 men and 40 women with a mean±SD age of 63.8±7.7 years and median duration of AF of 18 months (interquartile range, 6–48 months). Patients were blindly (but not randomly) assigned to 1 of 2 ablation procedures: PVI performed by means of second-generation CBA (CBA group, n=56) and PVI performed by means of CF-based RF catheter ablation (CF group, n=56). Written informed consent was obtained from all patients. All antiarrhythmic drugs were withdrawn for at least 5 half-lives prior to the procedure. Transesophageal and transthoracic echocardiography were performed 1 day before the ablation procedure with an ACUSON Sequoia C256 echocardiography system (Siemens Medical Solutions USA, Inc., Malvern, PA). LA diameter (LAD) and maximum LA volume (by the prolate ellipsoid method) were determined, and the left ventricular ejection fraction (LVEF) was determined by means of M-mode echocardiography (Teichholz method). Multi-slice computed tomography was performed with a 320-detector row, dynamic volume scanner (Aquilion ONE; Toshiba Medical Systems, Tokyo, Japan) in all patients for 3D reconstruction of the left atrium (LA) and PVs before ablation.

Electrophysiologic Study and Ablation

Electrophysiologic study was performed in all patients under conscious sedation achieved with dexmedetomidine and fentanyl.

After vascular access was obtained, single transseptal puncture was performed, and intravenous heparin was administered to maintain an activated clotting time of >300 seconds.[11],[12]

CBA

In all patients who underwent CBA, 2 SL0 long sheaths (St. Jude Medical, Inc., St. Paul, MN, USA) were inserted into the LA via the puncture hole.[11] The 3D geometry of the LA and PVs was reconstructed with an EnSite NavX mapping system (St. Jude Medical) from data obtained with a 20-pole circular mapping catheter (4-mm interelectrode spacing; Inquiry AFocus II EB catheter; St. Jude Medical) or a 10-pole mapping catheter with 5-mm interelectrode spacing (Snake, Japan Lifeline, Inc., Tokyo, Japan) through 1 of the 2 SL0 sheaths. An exchange length (0.035 inch) guidewire was introduced into the left superior (LS) PV, over which another SL0 sheath was exchanged for a 15Fr deflectable sheath (Flexcath, Medtronic, Inc., Minneapolis, MN, USA). An Artic Front Advance 28-mm cyroballoon (CB-Adv) (Medtronic) with an Achieve inner lumen mapping catheter was placed in the LA through the steerable 15Fr sheath. The CB-Adv was then inflated and advanced successively to each PV ostium to establish optimal PV occlusion, determined by the absence of contrast leakage. To avoid a vigorous wedging of the balloon inside the PVs, we used the —proximal-seal| technique for all RSPV and LSPV, i.e., withdrawing the inflated cryoballoon until a small leak was observed and then performing a small repositioning of the cryoballoon were applied.[13] Cryoenergy was delivered to each PV after occlusion was established. Ablation of each PV antrum was performed with a 180-s application followed by a 120-s or 180-s application. Continuous monitoring of the phrenic nerve during ablation of the right superior and inferior PVs (RSPV and RIPV, respectively) was systematically performed by pacing the right phrenic nerve from the superior vena cava.[11] After each CBA procedure, PVI was confirmed with the 20-pole circular mapping catheter. If residual PV potentials were revealed, additional cryoenergy was delivered.

CF-Based RF Ablation

In all patients who underwent CF-based ablation, extensive encircling ipsilateral PVI was performed, guided by a double Lasso catheter and the 3D geometric map reconstructed with the CARTO mapping system (Biosense Webster, Inc., Diamond Bar, CA), as previously reported.[12] The point-by-point ablation method was used by a CF-sensing irrigated tip catheter with 2-5-2 mm spacing (Thermocool Smart Touch; Biosense Webster) under VisiTag system guidance.[12] RF energy was delivered at a maximum power output of 25–30 W and a target CF of 10–20 grams with a force-time integral of > 400 gs. The upper temperature limit was set to 43°C at a saline irrigation rate of 17–30 mL/min (CoolFlow Pump; Biosense Webster). PVI was confirmed with the Lasso catheters. If the PV remained connected, additional touch-up CF-guided ablation lesions were created until PVI was achieved.

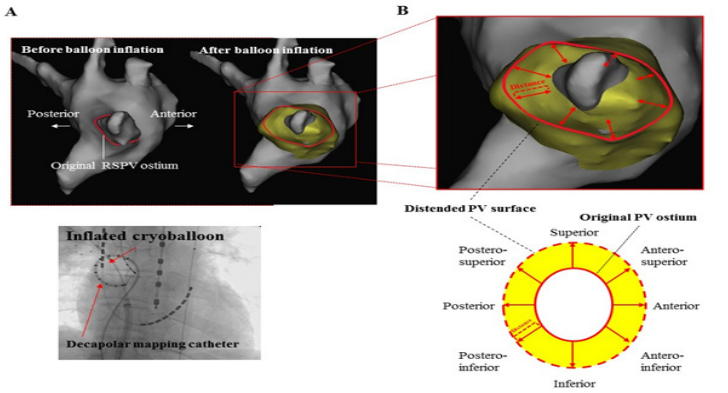

Figure 1: Representative 3D maps created with the use of a mapping catheter before and after inflation of the cryoballoon. The example here is of the RSPV ostium (A). Maps were used to measure the extent of PV distension (B). After inflation of a 28-mm cryoballoon, we maneuvered the decapolar mapping catheter around the balloon, fluoroscopically verifying contact between the balloon and the PV (A, lower panel). 3D, 3 dimensional; PV, pulmonary vein; RSPV, right superior PV.

Creation of 3D Images of the PV Ostium After Inflation of the Cyoballoon

For 21 of the 56 patients who underwent CBA, we created 3D images of the distended PV ostium after inflating the cyoballoon. Upon completion of the CBA procedure, the Snake mapping catheter was advanced into the LA through the SL0 sheath. The balloon was again inflated, and we created the 3D geometry of the distended PV by carefully manipulating the mapping catheter around the inflated balloon surface, which was now in contact with the endocardium at the target PV ostium [Figure 1]. To minimize distortion by the mapping catheter, we created the 3D geometric image of the expanded PV surface during pullback of the mapping catheter, which we performed in a step-by-step manner from different directions.[14] At each PV, we measured the amount of balloon-induced distention at the PV ostium by measuring the distance between the original PV surface and the surface of the distended PV at the 8 segments: the superior, antero-superior, anterior, antero-inferior, inferior, postero-inferior, posterior, and postero-superior segments [Figure 1]. Finally, we excluded the diameter (2mm) of the tip of the mapping catheter from the distance between the original PV surface and surface of the distended PV, and used that distance for the analysis, because

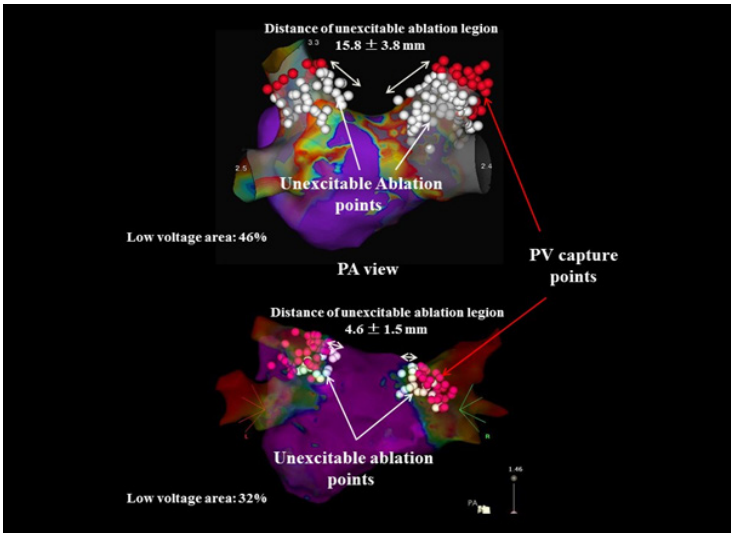

Figure 2: Assessment of low voltage areas and unexcitable ablation lesions around the PV ostium created by CBA and CF-guided radiofrequency catheter ablation. Shown are low voltage maps after CBA (upper panel) and after CF-guided ablation (lower panel) (A). The low voltage area was slightly larger after CBA than after CF-guided ablation. The width of unexcitable tissue along the ablation line was significantly wider after CBA than after CF-guided ablation (B). White dots indicate absence of capture, and red dots indicate capture within the low voltage zone of the ablated PV ostium. CBA, cryoballoon ablation; CF, contact force; PV, pulmonary vein.

the catheter tip further distended the ostia beyond that of the CB by 2mm.

Identification and Measurement of Low Voltage Areas and Unexcitable Scar Tissue

For each patient, after complete CF-based PVI or completion of 2 (or 3) cryoenergy applications at each PV, a 3D LA voltage map was created, and the percentage of the low voltage area (<0.5 mV), i.e., the ratio of the low voltage area to the total PV-LA surface area (defined by the surface area of the total LA and the distal segments of the PVs 10 mm from each PV ostium) was calculated. After placement of the circular mapping catheter distally within the PV, pacing (10 mA, 2 ms) was performed by the ablation catheter (or the mapping catheter) with 2-mm interelectrode spacing within the low voltage area from the ablation line to the distal segments of the PVs, and we identified whether pacing captured the distal PV tissues or not by the circular mapping catheter. Electrically unexcitable regions were defined as sites where there was no pace capture [Figure 2]. We measured the distance from the edge of the low voltage area to

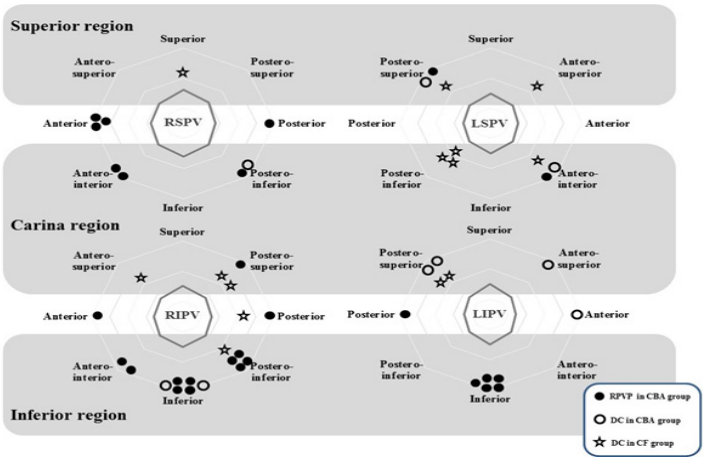

Figure 3: Location of residual PV potentials and dormant conduction provoked by ATP after CBA and CF-guided radiofrequency ablation. RSPV, right superior PV; RIPV, right inferior PV; LSPV, left superior PV; LIPV, left inferior PV; CBA, cryoballoon ablation; CF, contact force; PV, pulmonary vein.

the center of the tag at the unexcitable region in each of the PV segments (except the inferior segment) shown in [Figure 2]. We did not include the RIPV or left inferior (LI) PV because of the difficulty in identifying sites of capture within the short sleeve of each of these PVs.

Ensuring Complete PVI

In patients who underwent CBA, if residual PV potentials around the PV antrum were identified on the 3D LA voltage maps and Lasso catheter recordings despite a total of 3 cryoenergy applications, touch-up RF ablation was performed at acute PV conduction sites with a 4-mm irrigated tip Safire BLU Duo ablation catheter with 2-5-2 mm spacing (St. Jude Medical).

In all patients, 30 minutes after PVI, adenosine triphosphate (ATP) (30 mg) was administered intravenously by bolus injection to provoke dormant PV conduction.[12] Sites of dormant PV conduction were verified with the circular mapping catheter. Sites of residual PV potential and/or breakthrough sites, i.e., sites of dormant PV conduction, were categorized according to the PV segment in which they were revealed. RF energy was applied to the conduction gaps until the dormant PV conduction disappeared. Cavo-tricuspid isthmus ablation was performed when typical atrial flutter was induced by burst atrial pacing or observed clinically.

Post-Ablation Follow-Up

All patients' antiarrhythmic drugs were resumed after the procedure but then stopped after a 3-month post-ablation blanking period. All underwent routine follow-up examinations at our outpatient clinic 2 weeks after ablation, 1 month after ablation, and at 1-to-3-month intervals thereafter for at least 6 months. Twenty-four-hour Holter monitoring was scheduled between 3 and 6 months after ablation. An ECG event recorder was used if a patient reported cardiac symptoms. All documented AF episodes of >30-s duration on the standard ECG, ECG event monitor, or 24-hour Holter recording were considered a recurrence.

Statistical Analysis

Continuous variables are expressed as mean±SD or median values and interquartile ranges. Differences in continuous variables between the CBA group and CF group were analyzed by unpaired t-test or Mann-Whitney U-test, as appropriate. Differences in the extent of distention between the 4 PVs and between PV segments were examined by analysis of variance (ANOVA). Differences in categorical variables were analyzed by chi-square test. P <0.05 was accepted as statistically significant. All statistical analyses were performed with JMP 10 software (SAS Institute, Cary, NC).

Results

Patient and Procedural Characteristics

Patient characteristics and transthoracic echocardiographic variables are summarized per group in [Table 1]. There was no significant difference in clinical characteristics, LAD, or LVEF between the CBA group and the CF group.

Residual PV Potentials After CBA and Dormant PV Conduction Provoked by ATP

A total of 2.2±0.8 cryoenergy applications (for a total freezing time of 328±98 s for each PV) successfully isolated 198 of the total 224 (88%) PVs. The average nadir balloon temperatures were -50.3±6.2 degrees for the RSPV, -49.2±4.9 degree for the LSPV, -44.4± -6.0

Table 1: Clinical Characteristics of Patients Per Study Group

	CBA group (n=56)	CF group (n=56)	P value*
Age (years)	64.3±9.8	63.3±10.9	.6371
Sex ratio (M/F)	35/21	37/19	.6933
Duration of AF (months)	12 (5–36)	24 (6–60)	.3494
Body mass index (kg/m²)	23.8±4.1	24.3±4.3	.4646
AF type			
(Paroxysmal/Persistent)	46/10	42/14	.3570
Hypertension	26 (46)	29 (52)	.5706
Heart failure	6 (11)	3 (5)	.4898
Diabetes mellitus	12 (21)	6 (11)	.1975
Echocardiographic measures			
Left atrial diameter (mm)	39.2±6.6	39.7±5.4	.6752
LVEF (%)	67.7±9.5	67.4±8.1	.9018
Left atrial volume (mL)	40.4±17.2	46.5±18.9	.0744
CTI ablation	23 (41)	20 (36)	.5600

Values are shown as mean±SD, median and interquartile ranges or n (%) unless otherwise indicated. CBA cryoballoon ablation; CF contact force-based radiofrequency ablation; AF atrial fibrillation; LVEF left ventricular ejection fraction; CTI cavotricuspid isthmus.*per Student t-test, Mann-Whitney U-test, chi-square test, or Fisher's exact test, as appropriate.

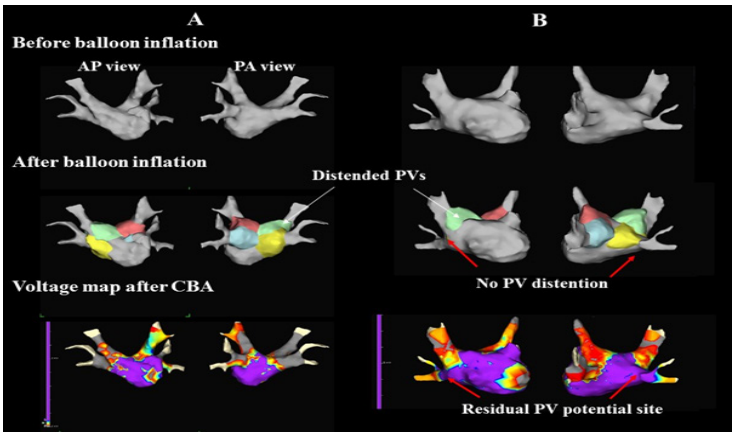

Figure 4: Representative 3D PV distention maps without and with residual PV potentials after cryoballoon ablation. In cases without residual PV potentials (A), balloon inflation concentrically distends the ostia of all 4 PVs (middle panel), resulting in good circumferential ablation lesions, as manifested by a low voltage zone (lower panel). After balloon inflation (B), the ostia of the RSPV, LSPV, and LIPV are evenly distended, but the RIPV ostium is distended mainly in the postero-superior direction (middle panel), resulting in residual PV potentials in the antero-inferior and inferior segments of the RSPV and RIPV (lower panel). Note that the left atrial dimension is larger in the case with residual PV potentials than in the case without it. Abbreviations are as shown in [Figure 3].

degrees for the RIPV, and -42.6±5.1 degrees for the LIPV (P<0.0001 by ANOVA). Complete isolation of all 4 PVs was achieved upon the initial attempt in 38 (68%) of the 56 patients in this group. In the remaining 26 (12%) PVs in 18 (32%) patients, the 3D voltage map and circular mapping catheter recording revealed residual potentials in 28 PV segments (median, 2 [1–2] sites per patient), and these required touch-up ablation to achieve complete PVI. Distribution of the PV segments with a residual potential is shown in [Figure 3]. Fifteen (54%) of the 28 sites with a residual PV potential were located in the inferior region of the RIPV or LIPV In comparison to patients without residual PV potentials, patients with residual PV potentials were younger (59.1±11.5 vs. 66.7±8.0 years, P=0.0053), had a higher body mass index (25.6±4.9 vs. 22.9±3.3 kg/m2, P=0.0166), were more likely to have persistent AF (39% [7/18] vs. 8% [3/38], P=0.0085), and had a greater LA volume (49.1±20.3 vs. 36.3±13.4 mL, P=0.0063) and lower LVEF (63.3±8.7 vs. 69.7±9.3 %, P=0.0175). In contrast, in the CF group, PVI was achieved for all 224 PVs, i.e., for all 56 patients.

After PVI, ATP (30 mg) provoked dormant PV conduction in 9 (4%) of the 224 PVs (in 9 [16%] of the 56 patients) in the CBA group and in 13 (6%) of the 224 PVs (in 8 [14%] of the 56 patients) in the CF group (P=0.3935). The sites of dormant conduction are shown in [Figure 3]. The sites of dormant conduction showed no regional predilection in the CBA group, but in the CF group, sites of dormant conduction were located mainly in the carina regions of the right and left PVs (amounting to 9/14 [64%] PV segments with dormant conduction).

Cryoballoon-Produced PV Distention

As noted above, a PV distention map was created for 21 patients in the CBA group. Representative 3D images of the PV and LA before and after cryoballoon inflation are shown in [Figure 4]. Overall, the inflated balloon stretched the PV ostium surface by 5.2±3.3 mm.

Regionally, the inflated balloon distended the RSPV, LSPV, and RIPV ostia mainly in the postero-superior direction (as defined by the 3 segments showing the greatest distention), but it distended the LIPV ostium in the superior direction. Distention was significantly less in the opposite segments, i.e., in the anterior, antero-inferior, and inferior segments of the RSPV (4.3±3.1 mm vs. 6.5±3.5 mm in the posterior, postero-superior, and superior segments, P=0.0003), LSPV (4.1±2.8 mm vs. 7.3±3.3 mm, P<0.0001), and RIPV (3.0±2.8 mm vs. 6.3±3.0 mm, P<0.0001), and the antero-inferior, inferior, and postero-inferior segments of the LIPV (2.7±2.4 mm vs. 7.4±2.6 mm for the antero-superior, superior, and postero-superior segments, P<0.0001) [Figure 5]. The residual PV potential/dormant PV conduction was found in 25 (3.7%) of the 672 PV segments (21 patients×4PVs×8 PV segments) in the 20 PVs (24% of the 84 PVs), which was strongly associated with contrast leakage before CBA (18 [90%] PVs vs. 5 [8%] in the 64 PVs without it, P<0.0001). The number of residual PV potential/dormant PV conduction sites differed between segments and increased in the following order: 1 (0.6% of the 168 PV segments [21 patients×8 PV segments]), 5 (3.0%), 7 (4.2%), and 12 (7.2%) segments in the LSPV, RSPV, LIPV, and RIPV, respectively (P=0.0084). Importantly, the extent of PV distension was decreased in the PV segments showing residual PV residual PV potential/dormant PV conduction (2.6±3.4 mm vs. 5.3±3.3 mm, P<0.0001).

Low Voltage and Unexcitable Scar Areas

Representative examples of the PV ablation lesions and ablation points linked to unexcitable tissue are shown in [Figure 2]. We examined 17 RSPVs and 15 LSPVs (2 LSPVs were without pace capture) in 17 CBA group patients and 19 RSPVs and 14 LSPVs (5 LSPV were without capture) in 19 CF group patients. The low voltage area on the 3D LA map was significantly greater in the CBA group patients than in the CF group patients (44.5±15.2% vs. 36.3±5.4%,respectively, P=0.0350), and unexcitable tissue along the ablation line around the PVs was significantly wider in the CBA group patients than in the CF group patients (16.7±5.1 mm

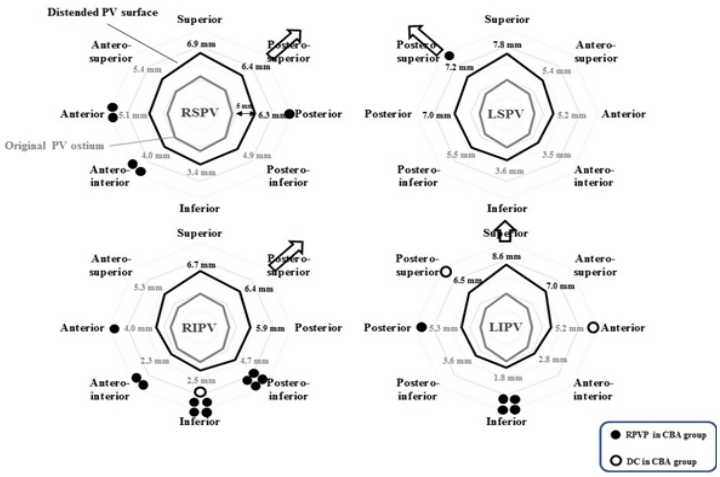

Figure 5: Extent of PV distention after cryoballoon inflation and its relation to residual PV potential/dormant conduction in the various segments of the RSPV, RIPV, LSPV, and LIPV. Black lines indicate the extent of PV distention in the various PV segments, and gray lines indicate the mean diameter of original PV ostium. The PV distention was greatest at 3 of the 8 PV segments, and the measurements are shown in black; the remaining measures of PV distention are shown in gray. Open arrows indicate the main direction of PV distention. Abbreviations are as shown in [Figure 3].

vs. 5.3±2.3 mm, respectively, P<0.0001). Regional differences in unexcitable tissue along the ablation line were noted in the CBA group (P<0.0001 by ANOVA for RSPV and LSPV), but there were no differences between PV segments in the CF group (RSPV; P=0.8194, LSPV: P=0.1183) [Figure 6].

Complications and 1 Year Outcomes

Transient phrenic nerve palsy occurred during RSPV ablation in 3 patients (5%) in the CBA group. No other complication was observed in either group. The AF recurrence rate at a median of 12 months was equivalent at 11% (6/56 patients) in the CBA group and 18% (10/56 patients) in the CF group (P=0.4187).

Discussion

Results of our investigation into the mechanism explaining the success of CBA in treating AF can be summarized as follows: First, the incidence of ATP-provoked PV dormant conduction after CBA was as low as that after CF-based RF ablation, although touch-up ablation was necessary in 32% of patients who underwent CBA. Second, the inflated balloon stretched the PV ostium by 5.2±3.3 mm, but there were regional differences in the PV distension between the LSPV, RSPV, LIPV, and RIPV. Third, the sites of residual potential or dormant conduction were located in PV segments in which distention resulting from inflation of the cryoballoon was moderate rather than extensive. Fourth, the low voltage area resulting from CBA was significantly greater and the unexcitable tissue along the cryoenergy-produced ablation line was significantly wider than those resulting from CF-based RF ablation.

Residual PV Potentials after CBA and Dormant PV Conduction After CBA vs. CF-Based RF Ablation

Previous studies have shown that the efficacy of CBA for paroxysmal AF is similar to that of point-by point RF ablation, but in some patients undergoing CBA, touch-up ablation is required for complete PVI. In our study, touch-up ablation for residual PV potentials was required to complete the PVI in 26 (12%) of the 224 PVs in 18 (32%) of the 56 patients. Touch-up ablation after CBA has been reported for 0–17% of PVs.[15]-[19] In our study, patients with residual PV potentials were relatively young, had a relatively high body mass index and large LA volume, and were likely to have persistent AF. In addition, we meticulously identified residual PV potentials using 3D voltage map, and we looked for PV potentials not only inside the PV but also in the PV antrum. These patient characteristics and our procedure might account, at least in part, for the incidence of touch-up ablations in our patient series.

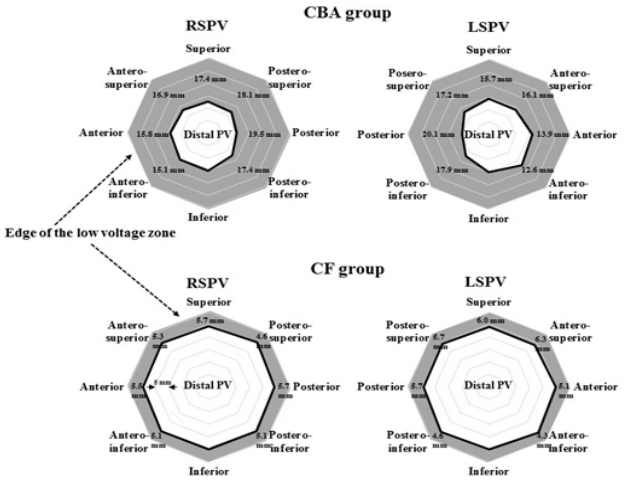

Figure 6: Width of unexcitable ablation lesion in each PV segment of the RSPV and LSPV after CBA and CF-based ablation. Gray areas indicate unexcitable ablation lesions from the edge of the low voltage area on the 3D voltage map. Abbreviations are as shown in [Figure 3].

The incidence of dormant PV conduction provoked by ATP in our CBA group was lower but statistically comparable to that in our CF group (4% vs. 6% of PVs). The low incidence of dormant PV conduction we encountered after CBA is well in line with previously reported incidences of 2%–8%.[17]-[19] Dormant conduction in our point-by-point RF group was relatively low because we used not only CF but also the VisiTag module, which includes catheter stability information. We reported previously that use of this module reduced the commonly reported incidence of dormant conduction.[12], [20], [21]

Characteristics of Lesions Created by CBA

This study clarified the mechanism explaining good lesions achieved with CBA. Although lesion durability has been documented, a detailed explanation has not been provided.[2]-[6] Adequate CBA occlusion with good balloon-tissue surface contact is important for successful PVI. In theory, extensive, concentric PV distention achieved with the cryoballoon should result in good balloon-tissue surface contact, and we believe that the extensive distention (approximately 7 mm) observed in our study patients was responsible for the creation of ideal ablation lesions around the PV. Nonetheless, our data showed that regional heterogeneity was noted in each PV. The inflated balloon stretched the PV surface in the postero-superior direction in the RSPV, LSPV, RIPV and in the superior direction in the LIPV, resulting in lesser PV distention on the opposite sides. The lesser PV distention was significantly associated with an increased number of residual PV potentials/dormant PV conduction sites.

Similarly, sites requiring touch-up ablation and sites of dormant conduction after CBA are often found in the inferior PVs, especially in the inferior segments of the RIPV.[15],[17]-[19] In the chronic phase, these sites have been reported to be the common sites of PV reconnection.[9],[10],[26] Recently published studies[17]-[19] have suggested that this may be due to malalignment of the cyoballoon, and thus poor balloon-tissue surface contact, in relation to the PV ostium. Therefore, even if PV occlusion by cryoballoon and acute PVI succeed, the lesser PV distention sites can potentially lead to future PV reconnections.

We found that the low voltage area after CBA was significantly larger than that after CF-based RF ablation. Recent studies of CBA have also documented wide and antral ablation lesions.[10],[22]-[24] Nevertheless, the authors assessed only the border line between the ablated and non-ablated regions, and therefore, actual ablated regions within the PV have not been known. We identified the actual ablated regions where PV sleeve tissues were not captured by pacing within the low voltage areas. Unexcitable ablation tissue in the RSPV and LSPV was nearly 3 times longer (16.7 mm) than that (5 mm) achieved by CF-based RF ablation. In fact, the widths of unexcitable ablated tissues that we measured match the reported widths derived from pathological assessment (14±7 mm).[25] Interestingly, PV segments with the widest unexcitable scars were well matched with PV segments showing the greatest PV distention (i.e, the superior, postero-superior, and posterior segments) [Figure 5] and [Figure 6], suggesting that extensive PV distention with good balloon-tissue contact results in wider lesions. These ablated lesion characteristics may explain why CBA-based PVI that persists in

the chronic phase was reported in approximately 70% of previously isolated PVs regardless of whether the arrhythmia recurred,[9],[10],[26] and this percentage is significantly higher than the recently published percentage yield of RF ablation.[26]-[29]

Clinical Outcomes

Clinical AF recurrence at a median follow up of 12 months was detected in only 6 (11%) of the 56 patients in our CBA group but in 10 (18%) of the 56 patients in our CF group. Recent studies comparing CF-guided RF ablation with CBA have shown statistical equivalence between the 2 technologies.[7],[8] CBA produces wider lesions which however are not more effective than the more narrow lesions produced by CF-guided RF ablation. This may relate to the fact that even focused lesions may eliminate triggers and that transmural continuous lesions around the PVs may not be necessary in all cases.[9],[10],[26]

Limitations

Our study was limited by the size of the patient groups, considering the fact we performed distension assessments in approximately half of the study patients, because of the tedious and time-consuming nature of the assessment. Nonetheless, the subsequent acute and chronic outcome after CBA are similar to other reports, suggesting that our results will be applicable to analysis of CBA performed for other conditions. Measurement of PV distension after cryoballoon inflation may include an artefact since the measurement of distension was not performed using an absolute geometrical/spatial reference. We did not analyze CBA lesions and PV reconnection sites in the chronic phase. Although some differences can be expected in the chronic phase, the trends should be similar to those in the acute phase.[10], [26]

Conclusions

PV distension produced by cryoballoon inflation appears to be greater in the postero-superior direction than in the antero-inferior direction. Unsuccessful PVI appears to occur when PV distention is relatively inextensive. Overall, CBA lesions appear to be more durable at the posterior and superior aspects of the PV ostia than at the floor of the RIPV. CBA results in wider ablation lesions and unexcitable ablation zones than those resulting from CF-guided RF ablation. This may explain the high efficacy of CBA for paroxysmal AF.

Conflict Of Interests

None.

Disclosures

None.

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Thermal Field In Cryoablation Procedures For Pulmonary Veins Isolation: Importance Of Esophageal Temperature Monitoring

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Abstract

Background: Cryoablation procedures for pulmonary vein isolation have proved to be a successful treatment of atrial fibrillation, but exposure of surrounding organs to excessively low temperatures is potentially dangerous. Hence the importance of monitoring esophageal temperature and at the same time predicting the thermal field induced by the procedure, so as to provide clinicians with a valuable tool to make critical decisions.

Methods and Results: We formulated a mathematical model for computing the temperature in the relevant region and used numerical simulations to interpret recorded clinical data. The temperature at the outer esophageal surface can be much lower than the luminal one. Observing the esophageal lumen cooling rate at the early stage of the procedure it is possible to forecast whether temperature is bound to reach dangerous values; the same quantity has a correlation with the steepness of the transesophageal thermal gradient.

Conclusions: Monitoring the time evolution of luminal esophageal temperature is of fundamental importance not only to realize but also to predict well in advance critical developments of the procedure.

Introduction

Atrial fibrillation (AF) is the most common arrhythmia in the Western countries and is associated with an increased mortality compared to people in sinus rhythm. Catheter ablation is an established treatment to achieve and maintain sinus rhythm in patients with recurrent AF. Pulmonary vein isolation (PVI) is the cornerstone of any ablation procedure and may be achieved with different energy sources, but radiofrequency and cryoenergy are those more widely used. Both techniques are aimed at producing lesions at PV ostia or antra to achieve the disconnection of the veins from the rest of the left atrium.[1],[2],[3]

Several studies have shown that radiofrequency ablation (RFA) and cryoablation (CA) have comparable results in terms of efficacy and safety.[4], [5], [6], [7], [8] FIRE and ICE is the most recent randomized trial comparing the efficacy of the two treatments.[9]

Here we refer specifically to ablations performed by means of a cryoballoon. Till recently CA was claimed to be safer than RFA concerning ETL occurrence, but then cases of fistulae have been reported with increasing frequency.[10],[11],[12],[13] Such complications have been described in many experimental studies revealing an extreme variability of patients' reaction.[14],[15],[26],[17],[18],[19],[20],[21],[22],[23]

Key Words

cryo-ablation, pulmonary veins isolation, atrial fibrillation, esophageal lesion, esophageal temperature monitoring, thermal field computation.

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ETLs are most likely to occur when the patient's esophagus is particularly close to the posterior atrial wall (Sánchez-Quintana [24] presents helpful anatomical studies). Theoretical mathematical models for atrial RF ablation have been formulated and implemented .[25],[26]

The main scope of the present paper is to formulate a mathematical model for CA, which allows computing the whole thermal field in the relevant region. We validate the outcome of numerical simulations on the basis of experimental data, pointing out some important facts concerning the necessity of monitoring luminal esophageal temperature (LET).

Based on numerical simulations we infer some criteria for the correct interpretation of LET measurements, emphasizing the role played by the thermal gradient and by the cooling rate detected at the early stage of the procedure. The importance of the latter quantity has been recently emphasized by Deiss et al.[27]

Methods

Mathematical model

Let us introduce the model geometrical setting. Critical geometrical parameters affecting the thermal field during CA are the esophagus thickness, its distance from the left atrium, and the epicardial fat layer (EFL) thickness. These parameters may vary considerably. Therefore, a mathematical model can only refer to an average situation. Of course, the model can be adapted to specific cases when information on the actual location of the relevant organs is available.

Nevertheless, since the thermal diffusivity of the involved tissues is within a rather narrow range, even computing the thermal field for a standard case may give a significant hint of what we can expect when e.g. the esophagus happens to be closer to the heart.

Since we are facing a great anatomical diversity, it makes sense to select a simplified geometry (a strategy also adopted by Berjano [25], Berjano and Hornero[26]), capturing the thermal field in the region of interest with reasonable approximation. The esophagus is represented by a straight cylinder E, whose lumen is in close contact to the probe, in consideration of the fact that it presents a constriction in correspondence of the LA (nice pictures can be found at https://www.med-ed.virginia.edu/courses/rad/gi/esophagus/anat01.html).

The heart is an immobile cylinder H [Figure 1], surrounded by a fat layer and separated in two halves by a septum of negligible thickness parallel to the blood flow, impervious to blood and pervious to heat [Figure 1]. Heart pulsations can be averaged out during the time of one application (equivalent to two of three hundreds heartbeats) so that blood flow can be taken stationary. Each half of the cylinder H has two chambers H1 (atria) and H2 (ventricles) having different thickness. We further simplify geometry, with no substantial alteration of the thermal field, considering a scheme in which two PVs merge (namely those that are going to be occluded by the cryo-balloon). Thus, we sketch blood supply to the left atrium by means of three vessels: one large, VP1, two small, VP2, VP3. We put VP1 as close as possible to the cylinder E in order to maximize esophageal exposure to the cryo source. How to sketch blood outflow and inflow in other chambers is immaterial from the point of view of the thermal behavior, so in our geometrical scheme we put just one duct VA leaving the left ventricle and two (VB1, VB2) assuring blood flow through the right chambers. A flat velocity profile determined by the imposed discharge is assumed at each cross section to avoid the unnecessary complexity of fluid dynamics.

The idealized elements described so far are placed in a cubic box, whose side is 20 cm long. The initial temperature is assumed to be 37°C everywhere, as well as the temperature T_B of the blood perfusing the organs.

Of course, this setting is quite sketchy, but it captures the basic elements, as far as thermal conduction is concerned.

We considered two sets of geometrical parameters representing non-exceptional anatomical structures, but combined in such a way to imply rather different thermal behaviors. Clearly, the presence of much thicker EFL, like in obese patients, would act as a very effective thermal shield for the esophagus. Among the papers consulted to choose the anatomical data, we quote Xia[28] and Bertaso[29],

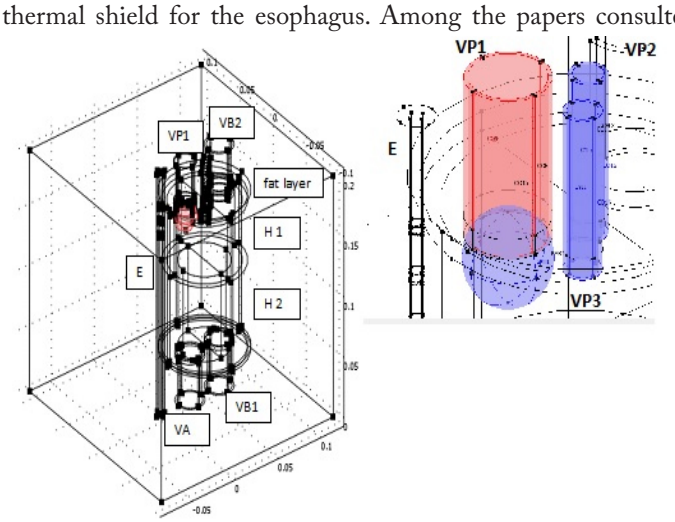

Figure 1: Sketch of the geometrical setting (left) and detail of the balloon region (right).

SET 1 (largely safe conditions): esophagus thickness 3mm, EFL thickness 3mm, esophagus-balloon surface distance 1.10 cm;

SET 2 (border to critical): esophagus thickness 2.5mm, EFL thickness 1mm, esophagus-balloon surface distance 0.65cm.

Let us now sketch the equations governing heat transport. For the blood flowing through H, transport is due to diffusion and convection:

(see [Table 1] for density ρ_B, specific heat c_B, and thermal conductivity k_B), where Δ is the Laplace operator and v is blood velocity, supposed uniform over cross sections). In the composite domain esophagus + connective + heart + EFL we use Pennes equation, also known as the bioheat equation

$$\rho_B c_B \frac{\partial T}{\partial t} + \rho_B c_B v \frac{\partial T}{\partial x} - k_B \Delta T = 0$$

where **ρ**, c, k take the corresponding value listed in [Table 1] (from Berjano[25] and Berjano and Hornero[30]), T_B is equal to 37°C, and ω(T) is the temperature dependent blood perfusion rate, given as

as long as it is positive, and zero otherwise, with ω_0 as in [Table 1] (from Holmes[31]).

$$\rho c \frac{\partial T}{\partial t} - k\Delta T = -\omega(T)\rho_B c_B (T - T_B)$$

There is no general agreement on the value to be given to the ratio ω_1/ω_0. Following Lakhssassi [32] we take ω_1/ω_0 =1.

In equation (2) we have neglected the source term expressing the

$$\omega(T) = \omega_0 + \omega_1 \frac{T - T_B}{T_B}$$

metabolic heat production, estimated to be 1÷2 W/kg at rest.

In simulations we have used a 23mm diameter balloon at uniform temperature T_c = –70°C.

Two situations have been considered:

- 5 min cooling (a time never exceeded in the procedure)
- 4 min cooling, followed by the recovery of the baseline temperature in the balloon during the next 30 sec (this kind of simulation is important to understand how some of the relevant tissues keep cooling for a while after interruption of refrigerating gas).

LET measurements

Cryo-ablation procedures were performed at the Coronary Unit at the Hospital of Massa, Italy (June-October 2015) with a cryo-balloon Arctic Front Advance (Medtronic, Inc, Minneapolis, MN, USA). LET was recorded by means of the catheter Esotherm (FIAB SpA, Vicchio, Italy) with three olive shaped stainless steel rings bearing a thermocouple and connected to the Esotest monitor (FIAB SpA, Vicchio, Italy). The probe was positioned with fluoroscopic guide into the esophagus at the level of the cryo-balloon. Data were recorded by means of a data logger. Procedures followed the standard

Table 1: Tissues thermal properties

	ρ	c	k	ω_0
	(Kg m^{-3})	(J kg^{-1} K^{-1})	(W m^{-1} K^{-1})	(s^{-1})
Esophagus	1000	3700	0.4	$3\cdot10^{-3}$
Connective	1000	3200	0.4	$6\cdot10^{-4}$
Fat	900	2200	0.2	$5.5\cdot10^{-4}$
Heart	1200	3200	0.7	0.017
VA. VB	1000	3200	0.4	-
Blood	1000	4180	0.54	-

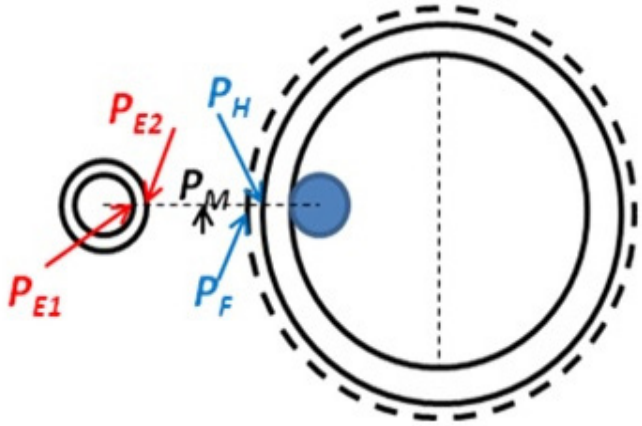

Figure 2: Cross sectional view through the balloon showing points P_{E1} (internal esophageal wall), P_{E2} (external esophageal wall), M (median point between esophagus and fat), P_F (fat boundary facing esophagus), P_H (external atrium wall).

protocols of Apuane Hospital (Massa). Data were collected from a random set of nine de-identified patients, not specifically enrolled for the present study.

Results

I) Simulated time temperature evolution in some selected point of interest.

In [Figure 2] we illustrate the set of points which are relevant to our simulations.

First group of simulations: balloon temperature –70°C. Duration of cooling 300 sec.

Concerning the geometrical parameters in SET 1, the temperature at the points shown in [Figure 2] is plotted vs. time in [Figure 3].

In the chosen geometry, computed LET (identifiable with the curve P_{E1}) exceeds the esophageal external temperature by only 2.5°C.

We observe that the transesophageal thermal gradient reached after 5 min is in this case rather moderate: 0.8°C/mm.

One more remark is about the maximal speed of temperature variation, which in P_{E1} is very small (0.02°C/s), as well as in P_{E2}(0.03°C/s), in comparison with the much larger one in P_H(0.5°C/s). However, if the esophagus runs closer to the heart the LET variation will be definitely faster. Actually, there is a clear correlation between the LET descent rate at the early stage and its expected evolution later. Such a feature is confirmed by the simulation run for the parameters in SET 2 [Figure 4], which emphasizes the great influence of the reduction of the fat layer thickness and of the esophagus-balloon distance.

Numerical results show that SET 2 is border to critical concerning the external esophageal wall. Much smaller LET values, even below

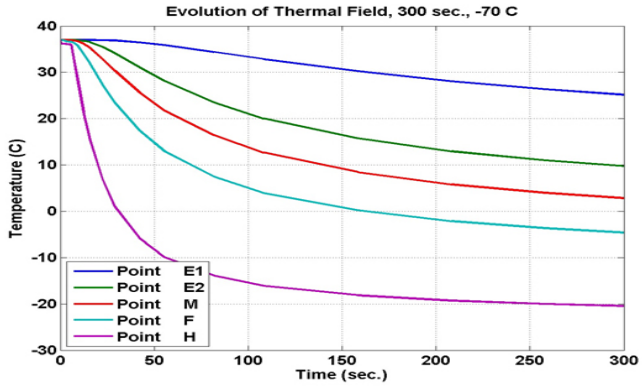

Figure 4: Cooling curves, balloon temperature –70°C, duration of cooling 300 sec. The geometrical parameters are the ones of SET 2. The respective temperatures after 240 sec are 28, 12, 7, -2, -20. P_{E1} max cooling rate: 0.06°C/s. P_{E2} max cooling rate: 0.22°C/s.

zero (down to an astonishing –12°C reported by Fürnkranz[16]), can be reached in the clinical practice if conditions are particularly unfavorable. In [Figure 4] we may notice the remarkable fact that while LET stays in a non-alarming range (terminal value 26°C), the external esophageal temperature drops to 10°C (the transesophageal thermal gradient is now 6.4°C/mm). The maximal cooling rate of the external esophageal wall is 0.22°C/s, and we find a much larger value when approaching the fat layer (0.65°C/s).

Second group of simulations: balloon temperature –70°C, duration of cooling 240 sec followed by the return of the balloon temperature to 37°C in 30 sec.

We report simulations for the parameters in SET 1 only. [Figure 5] emphasizes that LET, that equals 34°C at time 240 s, is not yet increasing 160 s after the suspension of gas supply. Likewise, temperature in P_{E2} decreases by one more degree. This is in agreement with the observation of Fürnkranz[20], where a decrease of 1.5°-2°C was found after interruption. For the parameters in SET 2 nadir

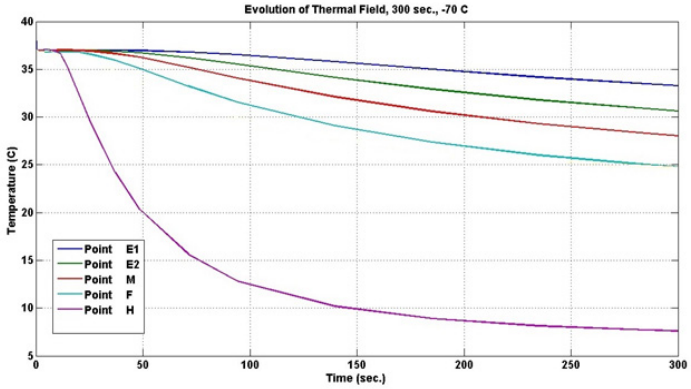

Figure 3: Cooling curves, balloon temperature –70°C, duration of cooling 300 sec. The geometrical parameters are the ones of SET 1. The respective temperatures (°C) after 240 sec are: 34, 32, 29, 26, 8. P_{E1} max cooling rate is 0.02°C/s. P_{E2} max cooling rate 0.03°C/s

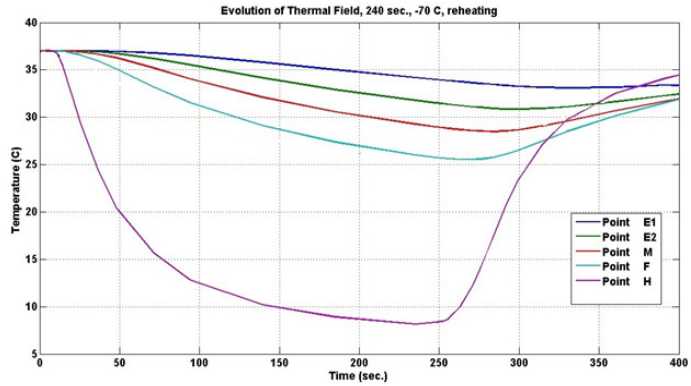

Figure 5: Cooling at -70°C for 240 sec. Then return of the balloon temperature to 37°C in 30 sec. Temperature of distal organs keep decreasing for several seconds. Parameters as in SET 1

temperature is expected to be ~3°C lower than the one at time 240 s (based on experimental observation).

On the contrary, temperature in P_H reacts almost immediately to reheating owing to the proximity to the balloon.

II) Measured temperature profiles during cryo-ablation procedures

The figures below show some representative LET-vs time curves related to 13 PVIs performed on nine patients. All the 36 PVI procedures were successful, but we chose to omit the ones showing negligible temperature variations. For a better reading of the data, we just plotted the temperature of the coldest of the three sensors on the probe. We group the curves in two categories: 9 in which LET stays in a safe range [Figure 6] during the standard cooling time (240s), and 4 that have been interrupted earlier because LET had attained abnormally low values [Figure 7], where dots indicate the switch off

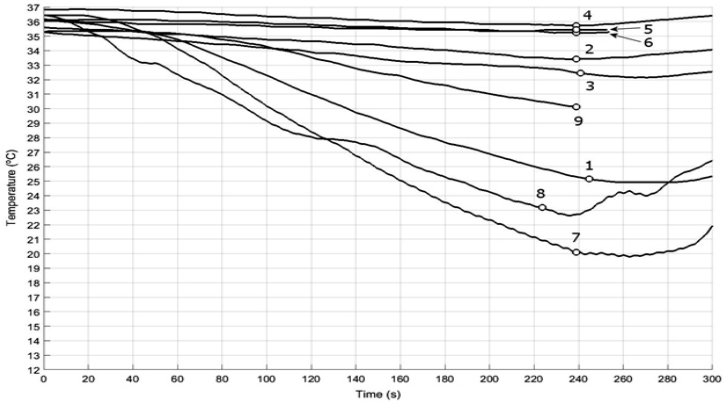

Figure 6: LET time course in 9 procedures exhibiting a normal behavior.

time). The remaining 23 data not plotted were in category 1. Three of the nine patients were subjected to marked esophageal cooling. Particularly important data are reported in [Table2] and [Table3] according to their category (L = Left, R = Right, S = Superior, I = Inferior, MCR = Max Cooling Rate).

Discussion

Model targets

Since the minimal esophageal temperature is reached at the external esophageal wall, one of the main targets in our investigation of the thermal field during CA for PVI was to evaluate the difference between the internal and external esophageal temperature. Moreover, we wanted to emphasize the relationship between LET decrease rate at the early stage of the procedure and the later onset of a steep

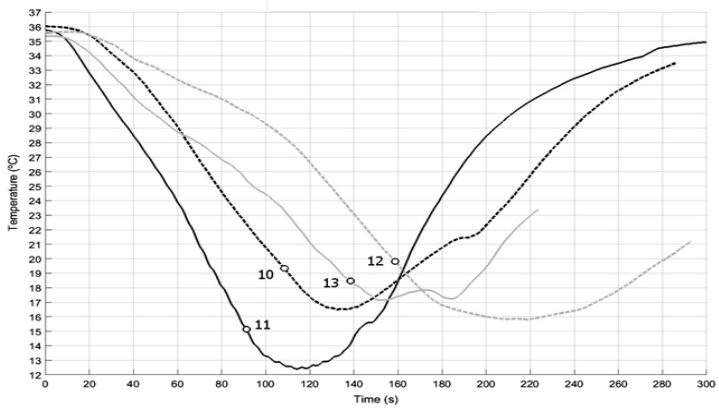

Figure 7: LET time course in 4 procedure with fast cooling and consequent early interruption.

transesophageal thermal gradient. Indeed the possibility of predicting such a gradient is a valuable help in the selection of a threshold LET preventing ETL. Such a feature has been discussed quite recently by Deiss et al.[27] Finally, the mathematical model allows evaluating the size of discrepancies that may occur between measured and actual LET.

Main findings

The model indicates that the difference between internal and external esophageal temperature turns out to be as large as 16°C in a seemingly not critical case [Figure 4]. This fact has received a confirmation in an experiment performed on dogs.[33] Clearly even larger thermal gradients are achieved when the esophagus is closer to the left atrium, incrementing the difference between the measured LET and the periesophageal temperature in a dangerous way. Despite the fact that [Figure 4] refers to a specific geometry (SET2), we can anyway use it to reasonably describe such a situation by interpolating between the curves corresponding to points P_{E2}, P_M, P_F, thanks to the similarity of the thermal diffusivity of the involved tissues. For instance if the esophagus is 2.5mm closer to the atrium, LET can be read with good approximation along curve P_{E2} instead of P_{E1}. In such a way, we realize that even quite a small displacement of the esophagus towards the cryo-balloon can have dramatic consequences on LET. Similarly, we can have an idea of what happens by perturbing the geometry of SET2 in other ways (thinner esophagus and/or atrium wall, reduced thickness or absence of the fat layer, etc.).

Still referring to [Figure 4], we remark that points closer to atrium

Table 2: First category of recorded data (patients exhibiting safe LET evolution)

Curve	Basal temp.(°C)	Vein	LET at 240 s (°C)	MCR (°C/s)	Nadir temp. (°C)	Nadir time (s)
1*	36.1	LSPV	25.1	0.06	24.9	253
2†	35.6	RSPV	33.4	~0.01	33.4	240
3†	35.3	RIPV	32.4	~0.01	32.1	265
4‡	36.8	LIPV	35.7	< 0.01	35.7	240
5‡	36.2	LSPV	35.2	< 0.01	35.2	240
6‡	36.0	LIPV	35.4	< 0.01	35.4	240
7§	36.5	LSPV	20.1	0.1	19.8	264
8||	36.5	LIPV	23.0 (after 225 s)	0.08	22.6	257
9¶	35.2	RIPV	30.1	0.03	Not recorded	

* LET evolution compatible with the predicted P_{E1} curve in [Figure 4]† Mild esophageal cooling. LET basically coincident with the P_{E1} curve in [Figure 3]‡ Negligible esophageal cooling§ LET behavior intermediate between the curves P_{E1}, P_{E2} in [Figure 4], indicating that esophagus was at shorter distance from heart than in the theoretical case (estimated difference 1-2mm)| LET behavior intermediate between the curves P_{E1}, P_{E2} in [Figure 4], indicating that esophagus was at shorter distance from heart than in the theoretical case (estimated difference 1-2mm)¶ LET behaves like the P_{E2} curve in [Figure 3] (the estimated sensor-balloon distance is ~3mm less than the one in SET1)

Table 3: Second category of recorded data (patients with risky LET evolution)

Curve	Basal temp.(°C)	Vein	LET at switch off (°C)	Switch off time (s)	MCR (°C/s)	Nadir temp. (°C)	Nadir time (s)
10*	36.0	LSPV	19.5	110	0.24	16.5	135
11†	35.6	LIPV	15.3	105	0.31	12.5	129
12‡	35.5	LSPV	20.0	160	0.18	15.8	210
13§	35.4	LIPV	18.5	140	0.18	17.1	152

** LET behavior intermediate between the curves P_{E2}, P_M in Figure 4. Alarming MCR. † LET behavior similar to P_M in Figure 4. Dangerous MCR. External esophageal wall may have approached 0°C ‡ LET behavior like P_{E2} in Figure 4 § LET behavior like P_{E2} in Figure 4

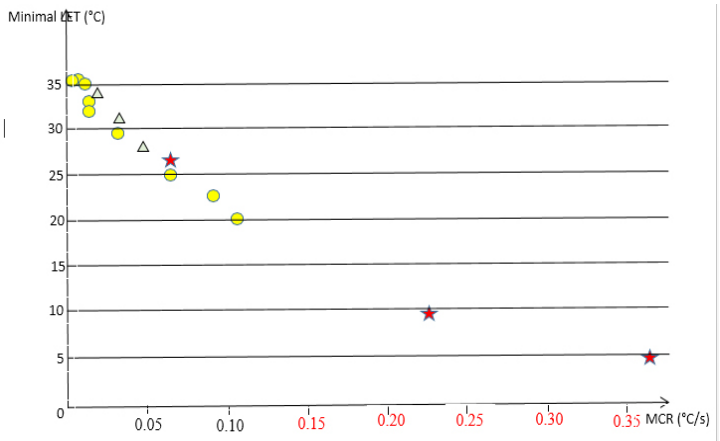

Figure 8: ° Experimental, deduced from Fig.6 *Predicted (cooling curves E1, E2, M, data as in SET2, Fig.4: min.temp.=temp.at 240s - 3°C) ΔPredicted (cooling curves E1, E2, M, data as in SET1, Fig.4)

also exhibit a faster initial cooling rate. Thus, we can say that, for the reasons explained above, calculating the initial slope of the LET cooling curve allows to predict dangerous situations. This looks to be a good criterion to establish whether the procedure is at risk, alerting the clinician about the possibility to abort it at an earlier stage, much before esophageal injuries can arise and still with a good chance of success. The quoted paper by Deiss et al[27] addresses such an issue with great clarity, plotting minimal measured LET vs. max cooling rate. We have reported our own results in [Figure 8] with the purpose of comparison. In [Figure 8] circles represent the clinical data of [Figure 6] (procedures completed in the standard time), triangles and stars are predictions according to simulations in [Figure 5] and [Figure 4], respectively. Concerning the latter case, the reported temperatures are obtained subtracting ~3°C from the values attained after 240s, which is a typical decrease after switch off encountered in critical cases as suggested by the results in [Figure 7]. The agreement between our [Figure 8] and the corresponding figure of Deiss et al[27] is excellent. Based on our theoretical and clinical investigation, we realized that MCRs exceeding 0.15°C/s are associated with the possible attainment of dangerous temperatures, suggesting the consequent interruption of gas supply to the cryoballoon. This confirms the similar conclusion by Deiss et al[27] (the threshold there identified is 8.5°C/m~0.14°C/s).

We have performed several more simulations in order to show the influence of some of the parameters (e.g. cardiac output, perfusion rate, etc.). We do not report all these results, but we want to discuss two more aspects emerging from the calculation performed in the considered geometries, regarding the real meaning to attach to the LET measure. First of all, the value detected by a thermocouple is actually the temperature at the welding point on the metallic sensor. Owing to the large thermal diffusivity of stainless steel (~4.10-6m2/s) temperature is rather uniform throughout the metallic body, and we can assume it to be the mean temperature over the luminal cross section. However, it is legitimate to ask what the real thermal excursion is over the esophageal cross section at which the nadir temperature is attained. The answer is rather surprising: in the fairly safe conditions of SET1 it equals 3.5°C, meaning that that the detected LET may differ from the actual nadir temperature by almost 1.8°C. Another possible source of error can come from an incorrect longitudinal deployment of the probe. Still for SET1 we have calculated that if e.g. the probe misses the coldest point by 2cm the detected LET will be 2°C above the nadir. Of course, all such discrepancies widen in cases that are more critical. Thus, clinicians have to know that these errors may sum up, in an amplified way in critical cases, giving a false impression of safety.

Model validation

The LET time course during CA has not been reported frequently in the literature. The cooling curve shown in Ahmed et al[14] is in very good agreement with the LET time behavior predicted in [Figure 4] (point P_{E1}), which is a first confirmation about the model validity. Let us now proceed with the comparison of numerical simulations with the clinical data collected at Apuane Hospital.

Some general remarks are necessary to understand the origin of possible discrepancies between theory and practice.

- The balloon temperature never reaches the theoretical value of -70°C, but it stabilizes to values between -40°C and -60°C, depending on the patient, possibly producing much milder LET variations.
- LET measures during the reheating stage frequently exhibit a short stasis or even a momentary temperature regression, not predicted by the model. In our opinion, this corresponds to the phase of balloon extraction, which is performed after some time, when the balloon has returned to a harmless temperature. After removal, the low temperature blood in the operated pulmonary vein resumes circulation, and the phenomenon is detected (with some delay) by the thermal sensors.
- Balloon orientation and PV morphology can have some influence on LET evolution.

Theoretical curves must be shifted to be adapted to actual patient's baseline temperature.

In view of such considerations we may assert that in the first category (70% of cases) the all detected LET curves [Figure 7] agree with the model predictions [Figure 3]-[Figure 4] and that anyway the model allows at least to interpret abnormal cases of category 2 [Figure 8] in terms of deviations from standard geometry. The 23 data not shown are also compatible with our mathematical model, modifying data to allow e.g. a larger distance of PVs from the posterior left atrial wall.

Conclusions

We have formulated a mathematical model that is able to predict LET behavior during cryo-ablation procedures for the majority of cases. However, its main utility is that it can give some information of clinical interest in the cases exhibiting abnormal esophageal cooling. For instance, it indicates that there exists a critical threshold for MCR during the early stage of the procedure, while LET is still in a quite safe range, warning the clinicians that a dangerous situation is going to develop.

Such a threshold has been identified as 0.15°C/s. By the way, we remark that excessive esophageal cooling occurred in one third of the patients, revealing that deviations from "normality" is not rare.

The model elucidates additional interesting features, emphasizing the influence of some critical physiological parameters, such as EFL, atrium and esophagus thickness. The external esophageal temperature can be much lower that LET and can reach dangerous values even if LET is far from an alarm threshold. The model has been implemented for safe or border-to-safe geometries, but it also allows interpreting critical LET evolutions due to a reduced esophagus-balloon distance, even providing an indirect measure of such a quantity. Finally, the model predictions fit remarkably well the data recorded during CA procedures performed at the Apuane Hospital (Massa, Italy), as well

as those found in the literature (most notably Ahmed et al[14] and Deiss et al[27]).

Conflict Of Interests

None.

Disclosures

Antonio Fasano is R&D manager at FIAB, Italy. Luca Anfuso is researcher at FIAB, Italy.

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Focal Atrial Fibrillation from the Superior Vena Cava

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Abstract

We report the case of a 66 year-old male who underwent catheter ablation for drug-refractory paroxysmal atrial fibrillation (AF) at our institution. Radiofrequency catheter ablation was performed using a three-dimensional electroanatomical mapping system. During ablation of the pulmonary veins (PV), right atrial ectopics were noted to repeatedly trigger AF and atrial tachycardia (AT). After PV isolation, mapping of the right atrium revealed that the superior vena cava (SVC) was in AF, while both atria were in an organized AT. Segmental ablation was performed around the SVC ostium, resulting in vein isolation and immediate restoration of sinus rhythm, while the SVC remained in AF. This case highlights the importance of the SVC in some AF patients as a potential source for non-PV triggers. SVC isolation can be safely achieved in most cases to improve outcomes.

Introduction

Pulmonary vein (PV) isolation is the most frequently used ablation strategy in patients with paroxysmal atrial fibrillation (AF). However, in a significant proportion of patients non-PV triggers may play a role in AF initiation, and several studies suggest that ablation of non-PV triggers, in addition to PV isolation, significantly improves long-term outcomes.[1]-[4]

Case presentation

A 66 year-old male with a 3-year history of paroxysmal AF was referred for catheter ablation. His past medical history included hyperlipidemia and benign prostate hyperplasia. Previous transthoracic echocardiography revealed a normal left ventricular size and systolic function (LVEF 60-65%) with normal left atrial size (3.2 cm). He did well on Metoprolol and Digoxin until recent months, when he started experiencing more frequent episodes, especially with exercise.

The patient presented to the electrophysiology laboratory in sinus rhythm. The procedure was conducted under general anesthesia and mapping and ablation was aided by EnSite NavX system (St. Jude Medical, Minneapolis, MN). During ablation of the PVs the patient went into AF, triggered by right atrial ectopics with earliest activation recorded at the distal crista catheter [Figure 1]. Eventually, the AF organized into a regular atrial tachycardia (AT) (CL 320 ms), also earliest at the distal crista, positioned at the superior vena cava (SVC)-right atrium (RA) junction. After completion of PV isolation, the catheters were withdrawn back into the RA and the Lasso catheter was advanced into the SVC. Interestingly, the SVC was found to be in AF, while both atria remained in AT [Figure 2].

A decision was made to isolate the SVC. High-output pacing to delineate the course of the phrenic nerve revealed significant close proximity to the region of planned ablation. Therefore, using an irrigated ablation catheter with force sensing capabilities (TactiCath, St. Jude Medical, Minneapolis, MN), radiofrequency energy was applied around the SVC ostium distant to the course of the phrenic nerve, starting at the posterolateral region. After only five 20-second contiguous lesions (25 Watts), SVC isolation was achieved, resulting in termination to sinus rhythm, while the SVC remained in AF [Figure 3]. No acute SVC reconnection was demonstrated with Adenosine 12 mg IV or with Isoproterenol infusion up to 12 mcg/min, and no other non-PV triggers were identified. After 7 minutes, AF within the SVC spontaneously terminated. After spontaneous AF termination within the vein, presence of dissociated SVC firing was documented and exit block was further demonstrated by pacing from the Lasso catheter [Figure 4].

Discussion

Myocardial sleeves may extend from the RA to the SVC[5] and several studies show that the SVC is an importance source of non-PV triggers in paroxysmal AF.[6]-[8] Myocardial extensions in the SVC harbour ectopic pacing cells that can depolarize by means of abnormal automaticity or afterdepolarization, creating the substrate for atrial arrhythmias, such as AT or AF.[9]

This case shows that, in addition of being a source of AF-triggering ectopies, the SVC may contain enough myocardial tissue to sustain AF within the vein. The coexistence of AF within the SVC and organized AT in both atria suggests a discrete breakthrough area between the vein and RA, confirmed in this case by the quick SVC isolation after limited segmental ablation. This resulted in immediate termination of the AT and no reinduction of atrial arrhythmias despite atrial pacing and high-dose isoproterenol.

Electrical disconnection of the SVC can be effectively achieved in most cases by segmental or circumferential ablation.[9],[10] Potential risks of SVC isolation derive from the vicinity of structures such as

Key Words

Atrial fibrillation, Superior vena cava, Non-pulmonary triggers, Catheter ablation.

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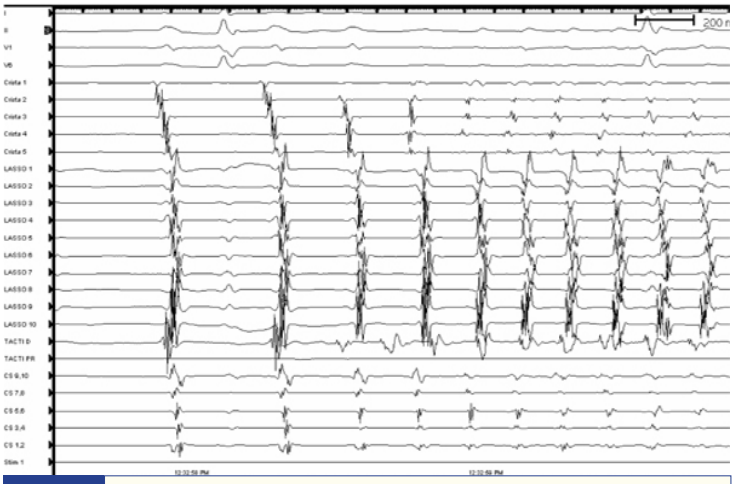

Figure 1: AF initiation triggered by atrial premature depolarizations earlier at the distal crista catheter, positioned at the RA-SVC junction.

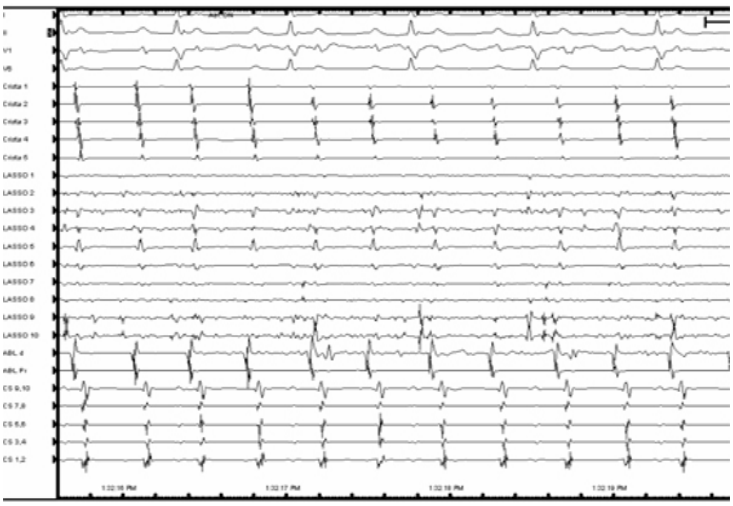

Figure 2: Intracardiac recordings with the Lasso catheter advanced into the SVC, the ablation catheter in the RA and the crista catheter along the RA free wall with the tip in the SVC-RA junction. AF can be observed in the SVC, while both atria are in an organized AT.

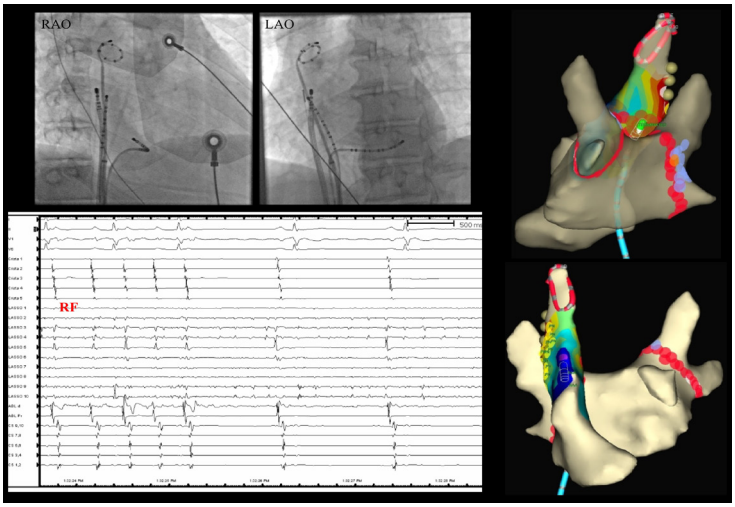

Figure 3: SVC isolation by segmental ablation at the vein ostium. Isolation resulted in immediate AT conversion to sinus rhythm, while the SVC remained in AF. The red dots represent radiofrequency lesions and the yellow dots represent areas of phrenic nerve capture with high-output pacing.

the sinus node and the phrenic nerve. Before ablation the course of the phrenic nerve should be carefully delineated with high-output pacing and zones with diaphragmatic capture must be avoided to prevent phrenic nerve palsy.

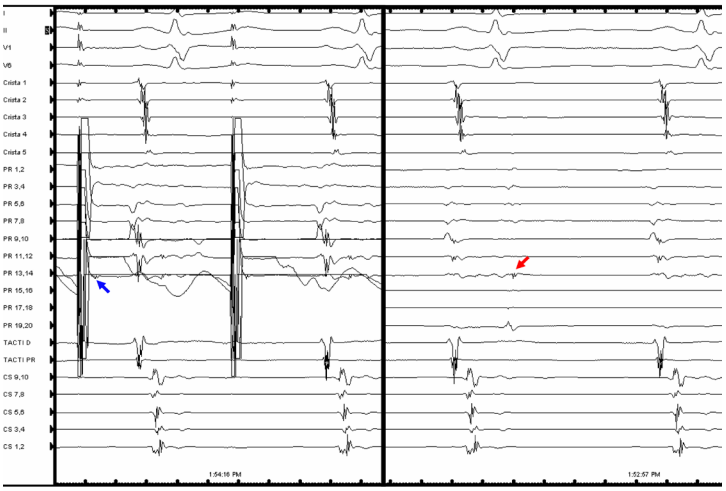

Figure 4: Exit block in the SVC demonstrated by pacing from the Lasso catheter (left panel, sleeve capture marked with blue arrow) and by the presence of spontaneous dissociated potentials in the SVC (right panel, red arrow).

Conflict Of Interests

None.

Disclosures

None.

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Giant Left Atrial Appendage Aneurysm Mimicking Mediastinal Mass and Associated with Incessant Atrial Arrhythmias

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Abstract

Left atrial appendage aneurysm (LAAA) is a rare entity. Clinical manifestations include arrhythmias and systemic embolization. We show here an example of a large and ectopic LAAA mimicking a mediastinal mass on chest X-ray and presenting with incessant atrial arrhythmias. Subsequent investigations leading to the correct diagnosis are described.

Summary

A 50-year-old man was transferred to our institution with a diagnosis of incessant supraventricular tachycardia (SVT) not responding to medical treatment. Past medical history included pericarditis at age 23 and paroxysmal atrial fibrillation (AF) at age 42. He described progressive shortness of breath over the preceding two months (NYHA class III/IV at presentation), orthopnea and paroxysmal nocturnal dyspnea. Physical exam revealed regular tachycardia, elevated central venous pressure and positive Kussmaul sign. Electrocardiogram showed regular SVT at 150 beats per minute [Figure 1]. Intravenous amiodarone was started, with subsequent return in sinus rhythm. The admission chest X-ray demonstrated a well-defined mediastinal enlargement at the aortopulmonary window [Figure 2], and was also notable for pericardial calcifications. Transthoracic echocardiogram was performed but limited due to poor echogenicity. There was mild biventricular dysfunction, without significant valvular disease.

Chest CT scan was performed and showed a dilated left atrial appendage extending in the anterior mediastinum [Figure 3]. There were also important pericardial calcifications. A cardiac MRI demonstrated low normal left ventricular ejection fraction (53%). A giant and ectopic left atrial appendage aneurysm (LAAA) was confirmed, measuring 8 cm and travelling upward into the superior mediastinum, with suspected herniation through a partial pericardial agenesis [Figure 4] and Movie 1 and 2. No thrombus was seen.

Electrophysiological study showed an eccentric retrograde conduction demonstrated with isoproterenol infusion, but only non-sustained tachycardia was induced. A left anterolateral concealed accessory pathway with poor conduction capacity was suspected, for which catheter ablation was performed through a retrograde approach. Despite early success from the ablation procedure, early recurrence of SVT mandated the resumption of antiarrhythmic drugs (flecainide and diltiazem) with subsequent good control and the patient was discharged home 3 days later. Follow-up visits are planned before considering a second ablation procedure by transseptal approach if required.

Key Words

Left atrial appendage, Atrial arrhythmias, Mediastinal Mass.

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Discussion

LAAA is a rare entity. It can be congenital or acquired, usually as a consequence of mitral valve disease with elevated intra-atrial pressure. Congenital LAAA can be intrapericardial or extrapericardial when the left appendage herniates through a congenital defect of the pericardium. In most cases, only surgery or autopsy can confirm the integrity of the pericardium. In our case, suspected herniation through a partial pericardial agenesis is supported by the extra-anatomical location of the LAAA in the superior mediastinum. The reported clinical LAAA manifestations are systemic embolization (18%) and supraventricular arrhythmias (60%).[1] Surgical resection

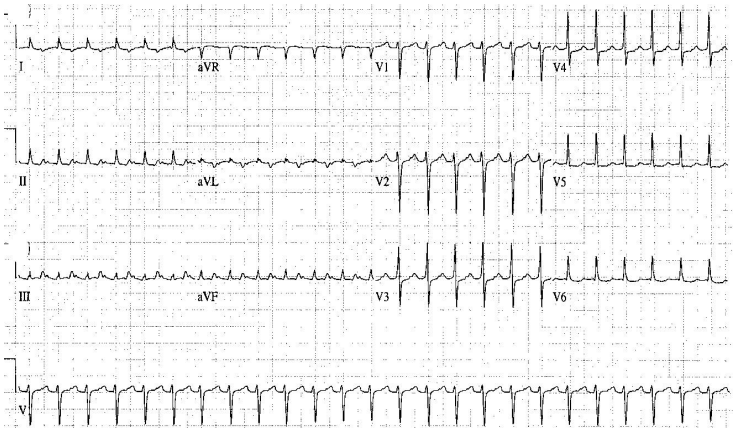

Figure 1: Initial ECG showing narrow complex tachycardia. The visible P wave (long RP tachycardia) is suggestive of either a reciprocating tachycardia using a retrograde accessory pathway or an atrial tachycardia.

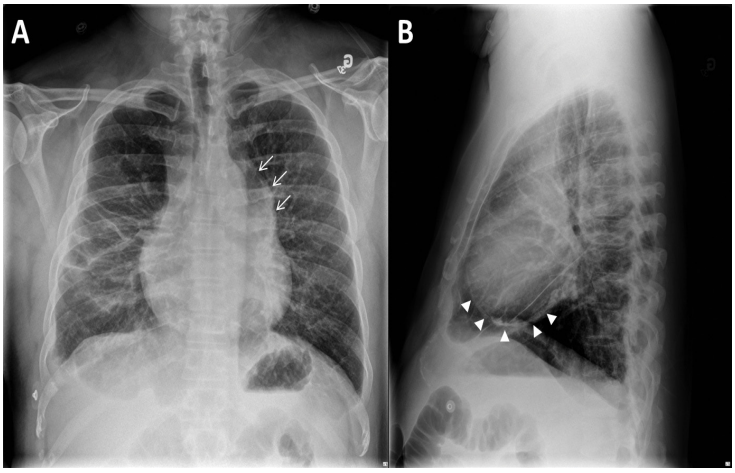

Figure 2: Chest X-Ray showing enlarged mediastinum at the aortopulmonary window due to left atrial appendage aneurysm LAAA (A, arrows), and curvilinear pericardial calcifications (B, arrow heads) inferiorly.

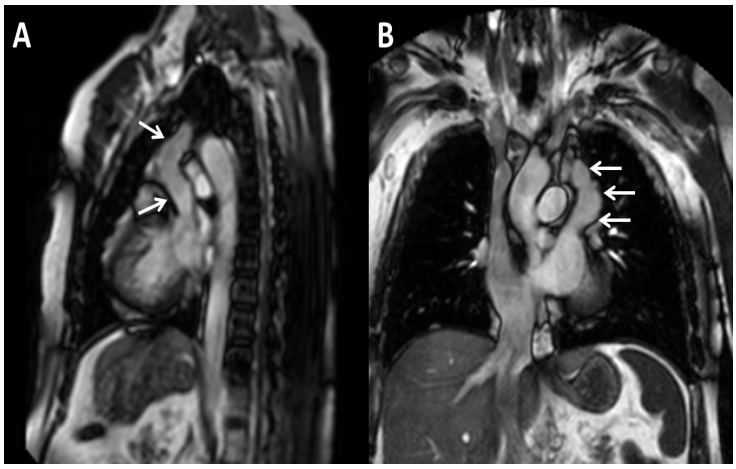

Figure 4: Cardiac MRI balanced steady-state free precession (b-SSFP) sequence in left two-chamber (A) and coronal (B) views showing the left atrial appendage aneurysm (arrows) extending upward in the anterior and superior mediastinum, causing the abnormal cardiac contour seen on chest x-ray.

of the LAAA is usually the preferred treatment, as it eradicates the potential embolic source as well as most atrial arrhythmias. Some authors favor surgery even in asymptomatic patients to prevent the potentially morbid and fatal complications associated with AF and systemic embolization.[2] Surgery was not performed in the current case since electrophysiological study has identified another mechanism for the atrial arrhythmias, which were subsequently controlled with antiarrhythmic drugs.

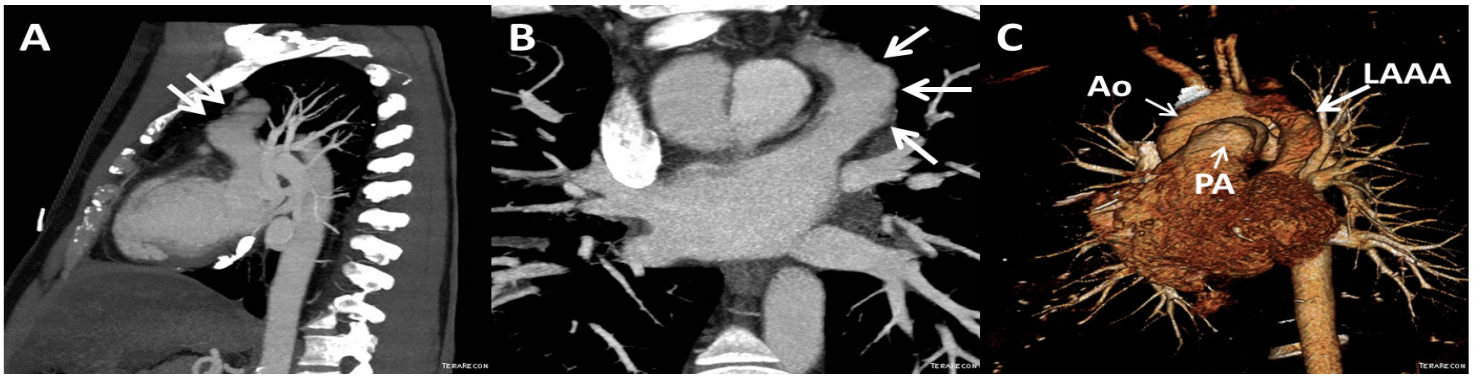

Figure 3: Contrast-enhanced chest CT in sagittal (A), and coronal (B)maximum intensity projections (MIP) showing the left atrium and left atrial appendage aneurysm (arrows). Panel A also shows inferior pericardial calcifications. (C) 3D volume rendering reconstruction showing the LAAA in relation to other cardiac structures. Ao: aorta; PA: pulmonary artery.

Conflict Of Interests

None.

Disclosures

None.

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A Novel De Novo Mutation In Lamin A/C Gene In Emery Dreifuss Muscular Dystrophy Patient With Atrial Paralysis

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Abstract

We present a 26 year old female Indonesian patient with full spectrum Emery Dreifuss Muscular Dystrophy (EDMD) characterized with contracture of elbows, heel cord and pelvic muscle wasting and weakness and atrial paralysis, as rare cardiac findings in EDMD . A novel de novo pathogenic heterozygous missense mutation (NM_170707.3: c.122G>T, p.Arg41Leu) in exon 1 was detected. Preventing atrial paralytic patients from systemic embolism is important. Early diagnosis, intervention, targeted management and counseling are necessary for a better health and life quality of individuals with EDMD.

Introduction

Emery Dreifuss Muscular Dystrophy (EDMD) is a rare genetic disorder, characterized by early contractures, slowly progressive muscle wasting and variable cardiac conduction defects. The disease was firstly describe as X-linked muscular dystrophy, but later autosomal dominant and autosomal recessive forms were reported.[1]-[4] Lamin A/C (LMNA) gene on 1q21.2-q21.3 is responsible for autosomal-dominant form of EDMD. Mutation in this gene played role in skeletal and cardiac muscular defects.[2]-[3] In the past three decades, atrial standstill phenotype is rarely reported to develop in all forms of EDMD inheritance.[5]-[8]

Case Report

We present a 26 year old female patient with some episodes of presyncopal states and contracture of elbows, knees, heels with muscle wasting. At age 7, she was seen to have mild contracture of knees and heels. When she was 12, she required wheelchair to travel distances greater than 10 meters. The first cardiac abnormality was noted at the age 18. She presented to the physician due to palpitation. Holter monitoring showed low amplitude P waves and first degree AV-block with ventricle premature complex.

Recent physical examination, contracture of elbows, knees and heels are obviously seen [Figure 1a] and [Figure 1b]. High level of creatinin kinase was found (709 U, normal < 167 IU). Electrocardiography (ECG) showed conduction abnormality (absence of P-waves) as depicted in [Figure 2]. Transthoracic echocardiography showed atrial enlargement and no 'A' wave in the Doppler mitral flow pattern correspond to atrial mechanical standstill. The diagnosis of atrial paralysis was further supported when we found no atrial electrical activity in the right atrial appendage, interatrial septum and lower right atrial during DDDR implantation procedure. The ventricle was easily paced with 0.5mA and the mode was changed into single ventricle pacing system (VVIR). Six month after PPM implantation she was admitted to another hospital due to embolic stroke.

No other family members were reported to be affected with the same abnormalities. Based on the clinical features, Sporadic Autosomal Dominant form of EDMD was suspected. Therefore, molecular analysis of the LMNA gene was warranted. Sanger sequencing of all coding exons and surrounding splice sites of the LMNA gene was performed as described below. The genomic DNA reference sequence was NM_170707.3. PCR of exon one was performed using primers ACTCCGAGCAGTCTCTGTCC (forward) and GCCCTCTCACTCCCTTCC (reverse). One hundred nanograms of DNA solution (1 µL) were added into PCR mixture, which contained 12.5 µL ReadyMix formulation (2x) of KAPA2G Fast PCR master mix (KAPA Biosystems), 1 µL of primers working solution, and 10 µL of H_2O. Amplification was performed using PCR System 9700 (Applied Biosystem) with the following protocol. PCR was initiated by 10′ denaturation at 95°C, followed by 35 PCR cycles (30" 95°C, 30" 60°C, 60" 72°C) and 7′ final elongation at 72°C. Sequence result was compared to published reference sequence using Mutation Surveyor software version 5.0 (Applied Biosystems Genetic Analyzers, MegaBACE, and Beckman CEQ electrophoresis systems). In exon one, a missense mutation has been detected, changing a CGC codon (coding for arginine) into a CTC (coding for leucine); c.122G>T, (p.Arg41Leu)) (nomenclature according to the

Key Words

Emery-Dreifuss Muscular Dystrophy, Atrial Paralysis, Mutation Lamin A/Cl.

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HGVS guidelines; http://www.hgvs.org/mutnomen/) [Figure 3]. To our knowledge, this mutation has not been reported before. Carrier testing with the same protocol as mentioned above were performed and revealed that the mutation had occurred de novo.

Discussion

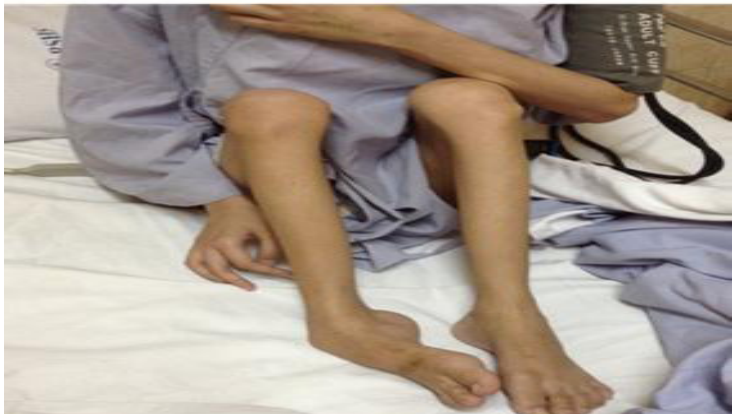

Figure 1a: Patient shows muscle wasting and contracture of knees and heels.

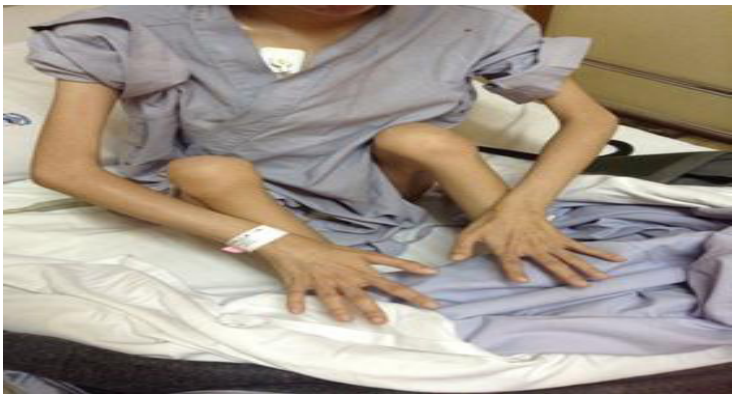

Figure 1b: Patient shows contracture of elbows.

Most clinical features of our patient, who had contracture of elbows, heel cord, pelvic, muscle wasting and weakness and cardiac junctional rhythm, are consistent with those described in the EDMD literature.[1]-[3] In addition, our patient showed atrial paralysis that is rarely reported to develop in EDMD. In the past three decades, only five EDMD patients including our case were reported to develop atrial paralysis (see [Table 1]).[5]-[8]

Lamin A/C gene consists of 12 exons that produce at least four types of RNA via alternate splicing including lamins A,A**δ**10, C and C2. Lamin A and C are intermediate filament proteins that form a helical dimer through their rod domains. Lamin A and C differ in the length and aminoacid sequence of their carboxyl terminals, but the initial 566 aminoacids (5' and rod domain) of both lamins are identical. The lamin A/C protein is expressed in the nuclear envelope of many tissues, primarily in skeletal and cardiac muscle.[9] The mutations in this gene lead to several laminopathies through

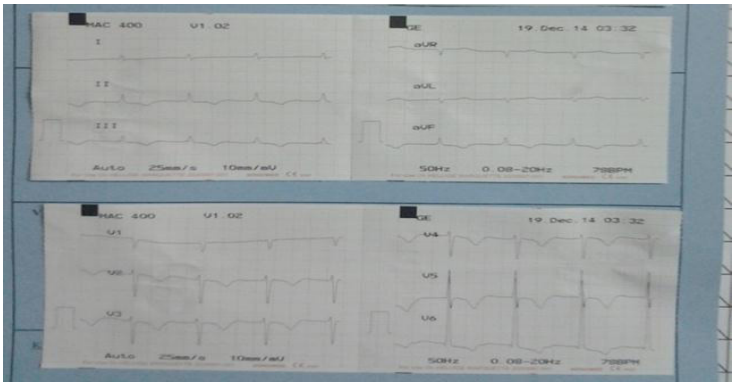

Figure 2: Electrocardiogram showed persistent junctional bardycardia rhythm (absence of P-waves).

defects in mechanical integrity of cells, alteration in regulation of tissue-selective transcription, and defect in cell proliferation.[9]-[10]

Atrial paralysis is histopathologically described as replacement of normal atrial muscle with non-functional fibrous tissue.[11] Regarding LMNA function, this cellular change was hypothesized as a result of structural changes in nuclear envelope due to mutated lamin that leads to decreased nuclear stability and impaired nuclear-cytoskeletal coupling. This condition results in a higher susceptibility to nuclear rupture and cardiomyocyte apoptosis and will likely to be replaced by fibrosis in later stages of the disease. This may provide a possible substrate for conduction block and re-entrant arrhythmias.[12],[13]

So far, 24 mutations in the Lamin A/C gene have been reported.[3]-[5],[12],[14]-[18] The particular mutation detected in our patient (c.122G>T, (p.Arg41Leu)) has not been reported before. This mutation is located in **α**-helical central rod domain of lamin A and C protein structure [Figure 4]. Felice et al suggested that mutation in the rod domain of the lamin A/C gene may cause the full clinical spectrum of EDMD-AD which comparable to our patient.[18] However, Fatkin et al suggested that missense mutation in the tail region of Lamin A and C cause EDMD while rod mutations cause isolated myocardial disease.[14] Atrial paralysis is less documented in the literature. Tabel 1 shows the comparison between atrial paralysis patients with different mutations. The development of atrial paralysis starts in the late late third to fourth decade in all of age in all patients. We are trying to

Table 1: Summary of clinical features and genomic study in EDMD patients with atrial paralysis

Patient	Age	Sex	Muscular findings	Cardiac findings	Inheritance	Genetic study	Reference
1	29	Male	Severe skeletal dystrophy (Contracture of elbows,hips, rigid spine, wide spread muscular hypotrphy)	Atrial paralysis, VVIR PM	AD-EDMD	LMNA C1583G mut (exon 9)	Sanna et al,2003
2	24	Male	Mild muscular involvement	Atrial paralysis, VVIR PM	XL-EDMD	STA 29 bp deletion	Boriani et al,2003
3	32	Male	Severe skeletal dystrophy (wasting humeral muscles, elbows contracture, thinning lower legs, and distal muscle weakness)	Atrial paralysis, VVIR PM	Atrial paralysis, VVIR PM	Unknown	Marshall et al, 1992
4	26	Female	Severe skeletal dystrophy	Atrial paralysis, VVIR PM	Familial (possibly autosomal dominant)	Unkown	Wozakowska-Kaplon et al,2011
5	26	Female	Severe skeletal dystrophy (contracture of elbows, knees, heels with muscle wasting)	Atrial paralysis, VVIR PM	AD-EDMD	LMNA G122T (exon 1)	Present case

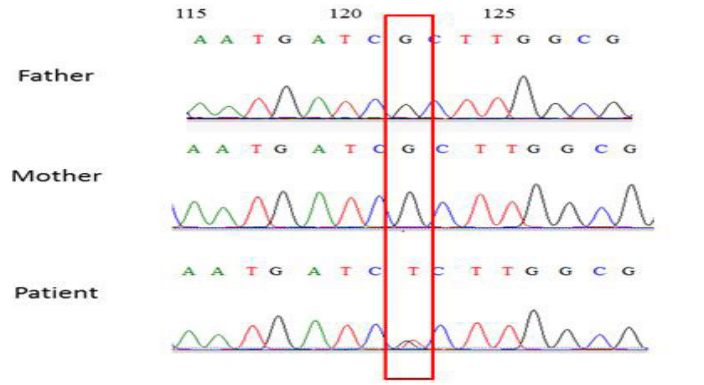

Figure 3: Electropherogram of molecular analysis in the trios sample. The patient's electropherogram shows the heterozygous missense c.122G>T,(p.Arg41Leu) mutation. Father and mother shows wild type (red box).

delineate the genotypes responsible for the atrial paralysis phenotype. In five EDMD patients with atrial paralysis (unfortunately two patients were genotypically unknown), the genomic positions were diverse. Two patients (patients 1 and 5) carried a mutation in the LMNA gene but in the different genomic position. Patient 1 carried a mutation in the carboxy-terminal tail domain of lamin A protein and Patient 5 (our case) carried a mutation in the central rod domain. Both patients had severe muscular dystrophy. We conclude that there is no clear correlation in hypothetical domain-specific phenotype related to EDMD manifestations.

Atrial paralysis and other forms of bradyarrhythmias carry significant risk of systemic embolism in EDMD with cardiac

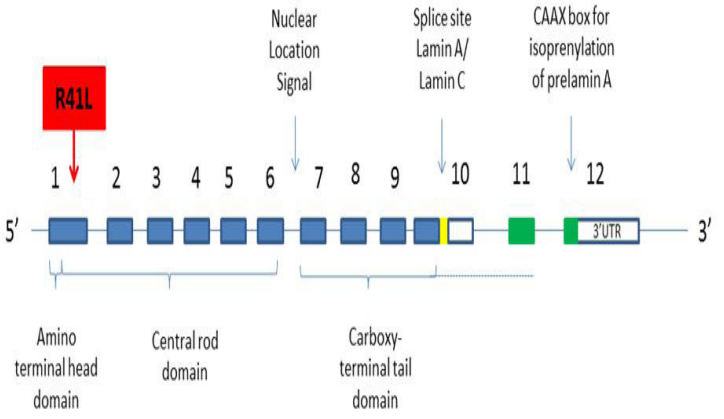

Figure 4: Illustration shows mutation in our patient (red box) is located in the central rod domain on the schematic of the genomic organization of the LMNA gene. The nuclear location signal, the splice site for the different generation of lamin A and lamin C, and the CAAX box for the isoprenylation of prelamin A are indicated by arrows. Blue areas indicate the sequences identical for both lamin A and lamin C. Regions coding for lamin C specific amino acids are indicated by yellow box. Regions coding for prelamin A specific amino acids are indicated by green box.

involvement.[13] Therefore, anticoagulation therapy is highly recommended.

In summary, we report a novel mutation in LMNA gene following autosomal dominant form of EDMD with atrial paralysis as a rare feature. Prevention from systemic embolism is important in EDMD patients with atrial paralysis. Functional analysis study for the future is needed to determine genotype-phenotype correlation. Early diagnosis, intervention, targeted management, and counseling are necessary for a better health and life quality of individuals with EDMD.

Conflict Of Interests

None.

Disclosures

None.

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Smartphone-Based Arrhythmia Detection: Should We Encourage Patients to Use the Ecg in Their Pocket?

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Abstract

The detection of atrial fibrillation (AF) is important for stroke prevention in patients with AF. This paper aimed to investigate the current landscape of smartphone-based arrhythmia detection and monitoring. The current technology can be divided into smartphone-based photoplethysmography (PPG) and smartphone-based single-lead electrocardiograms (ECGs). Our literature review concluded there are currently no validated PPG applications for the detection of arrhythmias available to the general population. However, an initial validation study indicates that the current development in Cardiio Rhythm PPG application, when made available, could provide an accurate and reliable means to detect AF in patients at risk of developing AF. The smartphone-based single-lead ECG devices are more promising. Multiple studies have shown the AliveCor smartphone ECG to be a reliable and accurate means of detecting atrial fibrillation. A drawback is that this device strictly provides data and is not capable of making a diagnosis of atrial fibrillation. The recorded ECG needs to be sent to a physician or medical professional for further review. In conclusion, these devices show promise in arrhythmia assessment, managing patients with AF, and diagnosing AF early in high risk patients. Caution should be used when assessing data provided by these devices, as validation in a real-world setting is still underway.

Introduction

By the year 2015, 64% of American adults owned a smartphone, which is a 35% increase from the spring of 2011.[1] These devices have become ensconced into our lives, and their utility is ever expanding. Once used for merely communication, smart phones have come to replace the wrist watch, provide camera and navigation functions, and allow easy access to the Internet. More recently, they have become powerful tools in monitoring our health. There are smartphone-enabled glucometers, blood pressure cuffs, oximeters, and even heart monitors. This will present a new challenge to physicians, namely the interpretation of diagnostic information captured on smart phones, in particular cardiac arrhythmias.

Atrial fibrillation (AF) is a common arrhythmia, affecting more than 2.7 million Americans.[2] This arrhythmia is associated with significant morbidity, carrying a 4- to 5-fold increased risk for ischemic stroke.[3] AF is often silent, with patients occasionally presenting with stroke as the first manifestation of the arrhythmia.[4] Other patients have troubling symptoms such as palpitations or dizziness, but traditional monitoring has been unable to define an arrhythmia. Periodic sampling of heart rate and rhythm could be helpful to establish a diagnosis in these conditions. Smartphone monitoring of AF could also prove useful in patients with known AF. Symptomatic episodes could be documented which might alter the patient's regimen of rhythm control or rate control medications. Furthermore, the costs for treating AF are extremely high, accounting for greater than 6.5 billion dollars annually.[5] An investigation into the use of relatively inexpensive smart phones as a monitoring device for AF is attractive.

The purpose of this manuscript is to investigate the current landscape of smartphone-based arrhythmia detection and monitoring. We will discuss the current technologies, and the methods used to validate them. It is our hope to provide practicing clinicians with the background information necessary to critique smartphone-based event monitoring.

Smartphone Technology

Currently, the methods of using a smartphone to detect and monitor atrial fibrillation can be divided into two groups. The first group simply uses a downloadable application and hardware that already exists on modern smartphones, the camera and lamp. The second group uses a pair of external electrodes, either built into the case or as a stand-alone -unit that communicates with an application downloaded to the phone.

The requirement of purchasing additional hardware is a possible barrier to use. As discussed, methods of using a smartphone to screen for atrial fibrillation are being developed that use a downloadable application, without the need of additional hardware. These applications use the phone's camera and lamp, in effect turning the phone into a photoplethysmographic (PPG) sensor [Figure 1]. The phone's lamp illuminates the user's finger, and a signal recorded through the phone's camera is then processed through an algorithm. The algorithm analyzes the regularity of the pulse waves.

Key Words

Atrial fibrillation, Technology, Stroke prevention.

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One such stand alone smartphone PPG application currently in development is Cardiio Rhythm, developed by Cardiio (Cambridge, MA, USA, [Figure 1]). The accuracy of this application to detect atrial fibrillation was shown in an outpatient clinic in 1013 patients with known hypertension, diabetes mellitus, and/or aged >65 years.[6] Immediately following completion of a single-lead ECG (using the AliveCor device discussed below), 3 PPG waveforms were acquired sequentially from each patient using an iPhone 4S (Apple Inc) running the Cardiio Rhythm smartphone application (Cardiio Inc). Each PPG waveform recording lasted 17.1 seconds and was classified automatically by the Cardiio Rhythm smartphone application as "Regular" or "Irregular." A diagnosis of AF was produced if at least 2 of 3 PPG waveform recordings from a single patient were classified as "Irregular." The approach for detecting the presence of AF was based on a lack of repeating patterns in the PPG waveform because of the irregular rhythm of AF. When a diagnosis of AF was made by the Cardiio Rhythm application, the AliveCor automated AF detection algorithm, or both, a full 12-lead ECG was performed within 15 minutes of the initial screening. Two blinded cardiologists over-read the single-lead ECG printouts to provide a reference diagnosis by using standard criteria. They found that the diagnostic sensitivity and specificity of Cardiio Rhythm for AF detection was 92.9% (95% CI 77-99%) and 97.7% (95% CI 97-99%) respectively, suggesting that the application provides an accurate and reliable means to detect AF in patients at risk of developing AF. A disadvantage of the dependence on regularity of rhythm to define atrial fibrillation is that PVC's or PAC's may cause irregular rhythm.

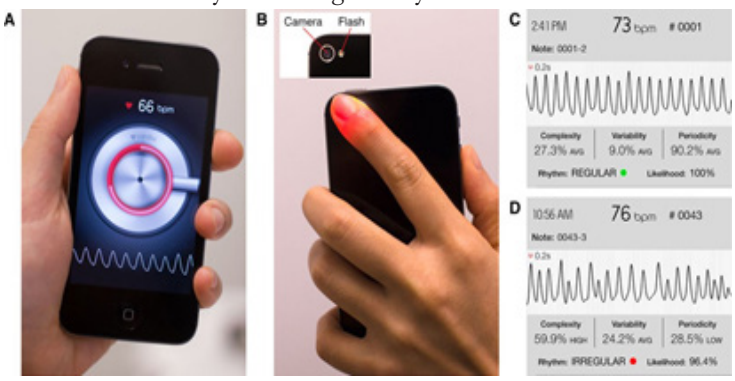

Figure 1: Cardiio Rhythm Application

A: Smartphone interfaceB: Camara and Lamp (flash) required for waveform gatheringC: Example regular waveform output as captured by the device.D: Example irregular waveform output as captured by the device.

One of the more recent smartphone-enabled health devices include smartphone-based event monitors which combine external ECG sensors with a smartphone application. One such device is the AliveCor Heart Monitor, a smartphone-based heart monitor that is capable of recording a single-lead ECG. This device received US FDA approval in 2012. The AliveCor Heart Monitor is smaller than a credit card, and consists of two metal electrodes. A bipolar lead I is created when the two metal electrodes are touched by the patient's right and left hands. The ECG electrical signals are then converted to an ultrasonic FM sound signal, and transmitted to a smartphone on which the AliveCor Kardia App has been installed. The tracings can be reviewed on the smartphone, electronically stored, or electronically sent for review by the user's provider[Figure 2].

AliveCor has developed three FDA-cleared detectors or algorithms for use in the device.[7] These detectors approximate ECG Lead I,

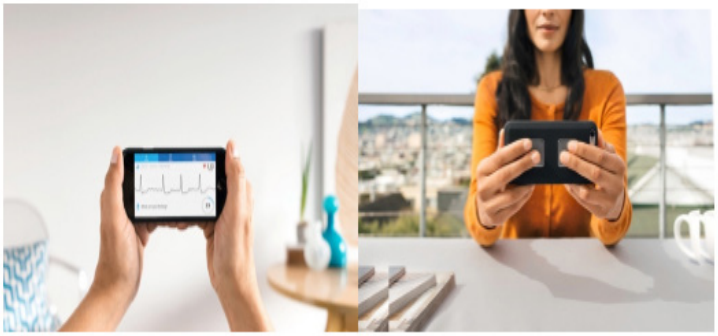

Figure 2: AliveCor Kardia Application (LEFT) and demonstration of finger placement for the AliveCor single-lead ECG (right)

with the patient placing fingers from each hand on the respective electrodes. The rhythm is labeled as "normal" when the patient's heart rate is between 50-100 beats per minute, there are no or very few abnormal beats, and the shape, timing, and duration of each beat is considered normal. The rhythm is labeled as "unreadable" when the detector indicates there was too much interference for an adequate recording, whether from too much movement, or poor contact between the electrodes and the patient's skin. The rhythm is labeled as "Possible AF Detected" when the device detects the presence of atrial fibrillation, and has been shown to do so with 98% sensitivity and 97% specificity when comparing it with a contemporaneous 12-lead ECG interpreted by a cardiologist.[8] AliveCor notes that this device provides data and is not capable of making a diagnosis of atrial fibrillation. The recorded ECG can then be sent to a physician or medical professional for further review.

Smartphone Studies

The accuracy of the AliveCor device has been investigated by multiple studies.[8]–[10] The sensitivity and specificity of the AliveCor device was assessed by Lau et al.[8] They sought to assess and enhance the initial AF detection algorithm, as well as to assess the accuracy of the device as a tool for the detection of AF by comparing it with a simultaneous 12-lead ECG interpreted by a cardiologist. In order to assess the initial algorithm and further enhance it, 109 patients (39 with AF)were recruited. Following a 12-lead ECG, each patient had a single lead (Lead I) iPhone ECG which was later presented to two cardiologists blinded to the 12-lead diagnosis. The actual rhythm was determined by the 12-lead ECG interpreted by a third cardiologist. Following unblinding, the algorithm was optimized by increasing the weighting of absence of P waves, and applied to the same dataset. To validate the optimized rhythm, a total of 204 patients, including 48 in AF, were recruited. Data were collected in the same manner with blinding to the 12-lead diagnosis, and analyzed in the same way. They reported a high sensitivity (98%), specificity (97%), and accuracy (97%) of the optimized AF detection algorithm to detect AF.

The cost-effectiveness of using the AliveCor device to screen for AF was investigated in the Screening Education And Recognition in Community pharmacies of Atrial Fibrillation to prevent stroke in an ambulant population aged ≥65 years study (SEARCH-AF) by Lowres et al[9].Pharmacists performed pulse palpation and iECG recordings collected by the AliveCor device. In their investigation (n = 1000), the automated AF detection algorithm showed a sensitivity of 98.5% and a specificity of 91.4% when compared to an over-read performed by a cardiologist. Using treatment/outcome data from a

United Kingdom cohort of 5,555 patients with incidentally detected asymptomatic AF, they determined the cost-effectiveness would be $4,066 per Quality Adjusted Life Year gained and $20,695 for preventing one stroke.

The effectiveness of the AliveCor device in identifying AF was investigated by Williams et al.[10] A total of 99 patients were recruited to the study. In their study, sensitivity was reported to be 90-93% and specificity was 76-86% when compared to 12-lead ECG.

The usability and accuracy of the AliveCor device for AF screening in a hospital population with an increased risk for AF was investigated by Desteghe et al.[11] A total of 445 hospitalized patients in cardiology or geriatric wards were recruited for the study. A single-lead ECG captured by the AliveCor device was compared to a full 12-lead or 6-lead ECG recording. In this setting, they reported the device to have a sensitivity of 81.8% and a specificity of 94.2%. Including device patients (pacemaker or ICD), in the analysis resulted in a sensitivity of 36.8%and a specificity of 96.1%.

While these studies succeeded in establishing the sensitivity and specificity of the device, no study to date has yet to investigate the utility of a mobile health intervention in affecting clinical outcomes. The iPhone Helping Evaluate Atrial Fibrillation Rhythm through Technology study (iHEART)[12] is a single center, prospective, randomized controlled trial which seeks to accomplish this goal. In this study, a total of 300 participants with a recent history of atrial fibrillation will be enrolled. Participants will be randomized 1:1 to receive either the iHEART intervention, receiving an iPhone with an AliveCor Mobile ECG and behavioral altering motivational text messages, or usual cardiac care for 6 months. Outcomes assessed will include the difference in recurrent AF detection rate over the six-month study period between the control group and the iHEART intervention group, as well as the time-to-treatment for those treated for recurrent AF.

Summary

Application-based smartphone arrhythmia detectors provide a low barrier to use, as they require no additional hardware beyond a smartphone. However, there are still questions as to whether these applications are reliable. In fact, there are currently no validated PPG applications for the detection of arrhythmias available on the Apple App Store or the Google Play Store. The Cardiio Rhythm application, mentioned above, is still in the developmental stages and not available for download to the general population. That being said, an initial validation study indicates that the Cardiio Rhythm application, when made available, could provide an accurate and reliable means to detect AF in patients at risk of developing AF.

Smartphone accessory-based arrhythmia devices currently offer a validated means of monitoring atrial fibrillation. The AliveCor device mentioned above has received FDA approval and has undergone multiple studies to investigate its accuracy. In the United States, the device is available over the counter and is marketed directly to the general public with a manufacturer suggested retail price of $99.00 (US). Multiple controlled studies have shown the device to be a reliable and accurate means of detecting atrial fibrillation. However, it is important to note that sensitivity is greatly decreased in patients with an implantable device and is not recommended for patients with pacemakers or ICDs. The detection of AF by the AliveCor device is not diagnostic, and positive findings of new AF should warrant a confirmatory ECG. The utility of this device will be further investigated by the iHEART study, which seeks to compare the AliveCor device to the current standard of care in a real world setting.

These devices show promise in arrhythmia assessment, managing patients with AF, and diagnosing AF early in high risk patients. Caution should be used when assessing data provided by these devices, as validation in a real-world setting is still underway. That being said, these devices may be more reliable than symptom recognition, leading to quicker follow-up with a confirmatory ECG or other testing.

Conflict Of Interests

None.

Disclosures

None.

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Pulmonary Vein Isolation With The Multipolar nMARQ™ Ablation Catheter: Efficacy And Safety In Acute And Long-Term Follow Up

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Abstract

Pulmonary vein isolation (PVI) is an established therapy for atrial fibrillation (AF). One challenge in the catheter-based treatment of this arrhythmia is to develop an effective and safe ablation approach to achieve durable and consistent lesions around the PVs. The multipolar irrigated radiofrequency (RF) ablation catheter nMARQ™ was designed as a single-shot device with the aim to achieve these goals. This article reviews the current literature with respect to acute- and long- term success rates after PVI with this circular mapping and ablation device. Furthermore, since this device recently became discredited to potential lethal complications, we will also focus on the data available on safety issues with this ablation system.

Introduction

Pulmonary vein isolation (PVI) is an established method for the treatment of atrial fibrillation (AF). In 1998, Michel Haïssaguerre demonstrated that the pulmonary veins (PV) were an important anatomical structure harboring triggers for the initiation of AF.[1] Thus, the primary endpoint for interventional treatment of AF by ablation is circumferential electrical isolation of the PVs.[2] However, as this procedure is challenging and still time-consuming even for experienced operators, there is a need for workflow optimization, e.g. by novel ablation devices. In this context, so-called "single-shot' devices have been introduced in order to enable a quick and durable PV isolation, thereby increasing efficacy and safety of PVI procedures. Single-shot devices were developed as a tool aiming to provide circular transmural lesions by simultaneously mapping and ablating at multiple sites around the antra of the PVs via a single-transseptal access point.[3]

In 2011, a steerable multi-electrode catheter (8.4 F) with a deflectable tip (nMARQ™, Biosense Webster, Inc., Diamond Bar, Ca, USA) was introduced. The nMARQ™ catheter consists of ten irrigated electrodes, and is capable of full integration into the CARTO® electroanatomic mapping system[4] [Figure 1]. Energy delivery duration is set between 30 to 60 seconds, and radiofrequency (RF) ablation can be individually performed over each combination of the 10 electrodes in unipolar mode (maximum 25 W) or bipolar mode between two electrodes (maximum 15 W).[5]

Early studies suggested the nMARQ™ to be an effective and safe tool for PVI[4], [6]-[8] with one multicenter study confirming a high success rate after nMARQ™ procedures.[3] However, the device also presented with some safety concerns arising from some severe complications, questioning the safety of this novel device[9]-[11], and ultimately leading to the interim recall of the 2nd generation nMARQ™ catheter.[12] Therefore, we conducted this review of the current literature with respect to mid- and long-term efficacy as well as safety of the nMARQ™ ablation device.

Key Words

nMARQ, circular ablation catheter, atrial fibrillation, pulmonary vein isolation.

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Case Report

The electronic databases PubMed and Google Scholar were used to identify potential articles including prospective and retrospective studies, case reports, registries, editorials, and review articles. Search terms included "atrial fibrillation (AF)," "pulmonary vein isolation (PVI)," "circular ablation catheter," "multipolar ablation catheter," "single shot device," and "nMARQ™." Data from 81 identified articles were reviewed carefully for information regarding ablation with the nMARQ™ device. We summarized the data according to the available information on clinical outcome (n=11 studies), procedural parameters (n=14 studies) and safety outcome (n=16 studies).

Clinical outcome

Since the release of the first generation of this catheter in 2011, outcomes following nMARQ™ ablation from more than 1400 patients have been reported.[3], [4], [6], [7], [9], [13]-[18] Specifically, our search found 11 published studies, with follow-up (FU) data exceeding

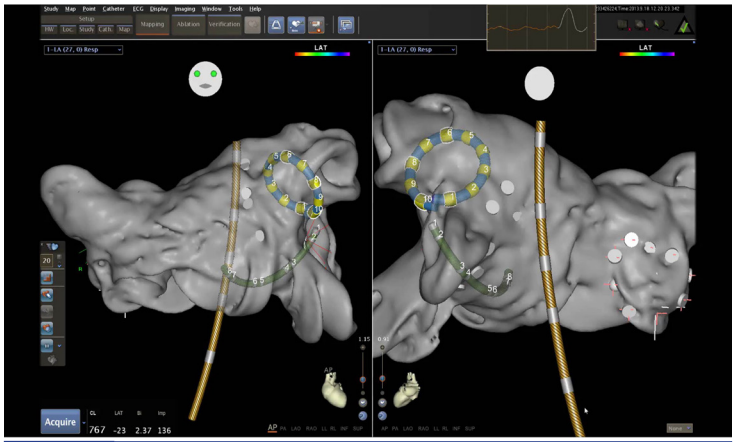

Figure 1: illustrates the position of the circular nMARQ™ catheter in the left atrium, recording the electroanatomical map in Carto® 3. Yellow-grey: temperature probe; green: RV catheter for phrenic nerve stimulation during ablation of right-sided PVs. Figure courtesy of Dr. Wakili

3 months post PVI. The outcome of interest in these studies was generally defined as recurrence of AF or the combination of AF with atrial flutter and atrial tachycardia following a 90-day blanking period after PVI. Results from one multicenter study, and 10 single-center studies reported overall mid-term success rates ranging from 52% to 80.9%. Success rates varied depending on AF type, FU duration, and the concomitant use of antiarrhythmic drugs (AAD) [Table 1].

For those patients that underwent ablation of paroxysmal AF, recurrence rates were between 22.8% and 35%[3],[16], and are comparable to those obtained by conventional RF, Cryoballoon, or different circumferential RF ablation catheters (PVAC) after one year (between 30.1 - 35.9%).[19]-[21] The very low recurrence rate of 22.8% reported by Rodriguez et al. may be in part attributable to the fact that all patients were administered AAD during the blanking period.[16] Burri et al. reported recurrence rates of 54% over 15 ± 4 months which were considerably higher than other published studies .[13] The authors suggested that in addition to the slightly longer FU duration compared to other studies, reduced power output (max. 15 watt unipolar), the restricted RF delivery, and the waiving on a circular mapping catheter to confirm PVI, could be causative for worse outcomes in their study[7], [18] (see chapter "acute efficacy").

Data on success rates after nMARQ™ ablation in persistent AF are scarce. The five published studies following patients with persistent AF reported recurrence rates ranging from 30% to 48%.[3], [9], [14], [15], [17] The clinical use of the nMARQ™ device has been limited so far in patients with persistent AF. Prior expert consensus documents from the HRS/EHRA/ECAS suggested that for patients with persistent AF "operators should consider more extensive ablation based on linear lesions or complex fractionated electrograms"[22], for which the nMARQ™ catheter is not intended. Notably, since Verma et al. reported that ablation strategies beyond conventional PVI did not translate into additional clinical benefit in persistent AF in the STAR-AF-II trial, the use of the single-shot devices, incl. the nMARQ™ catheter, re-gain attention for a PVI only treatment in patients with persistent AF.[23]

Acute efficacy of nMARQ™ guided ablation

Acute durable PVI (acute efficacy) with the nMARQ™ device ranged from 83% to 100% of treated patients, with acute efficacy in 95.7% to 100% of targeted veins[4], [18], [24] (see [Table 2]). Wakili et al. reported that 5 of 116 PVs (4.3%) could not successfully be isolated with the nMARQ™ catheter.[18] Zellerhoff et al. failed to acutely isolate three PVs (2x RSPV, 1x RIPV), Rodriguez-Entem, 2 PVs (1 RIPV and 1 LIPV), and Scaglione, 1 LSPV.[6], [7], [16] Indicated reasons for isolation failure comprised of difficulties in achieving a transmural lesion at the ridge, significant temperature rise in esophagus, catheter geometry, and limited device maneuverability.[7], [18] According to their single-center experience, Deneke et al. reported that through the routine use of a steerable sheath for catheter access into LA, when appropriate contact force in the LAA ridge region is achieved, all different anatomies of PVs should be treatable by the nMARQ™ device.[8], [14] Inconsistent with results from PVI with single-tip catheters and circular mapping catheters (CMC), most of the reported studies did not routinely perform exit block testing to confirm PVI. This was due to challenging intubation of small PVs with the nMARQ™ catheter.[18]

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With respect to acute success rates of PVI, these results are comparable to those obtained by conventional RF energy[25], PVAC [21],[26] and Cryoballoon ablations.[25],[27] However, most of these studies used the nMARQ™ as the intended "single-shot" device, without confirming the PV isolation with a standard CMC. Scaglione and Rosso et al. reported on an overall inconsistency between CMC and nMARQ™ signals in 22 of 102 PVs (22%) to 12 of 39 PVs (30%). Additionally, Rosso observed good consistency prior to PVI, but poor concordance after PVI. In all cases these variations led to further RF delivery.[7], [24] Wakili et al. reported on a discrepancy rate of 35% in their study[18] [Figure 2]. Scaglione et al. speculated that persistent PV potentials on the CMC after extinction on nMARQ™ suggest persistence of electrical conduction from the PV to the atrium. They suggested that the difference in inter-electrode spacing between CMC and nMARQ™, or the more proximal position of the nMARQ™ in the PVs, are causative for significant signal divergence.[7], [28], [29] In order to avoid false-positive PVI results which may impair the outcome of the procedure, Wakili et al. strongly recommended a dual transseptal approach with simultaneous PV potential recordings.[18]

Deneke et al. suggested that there may be procedure-related factors influencing the success rates following ablation with the nMARQ™

Table 1: Clinical outcomes of patients investigated in available literature. FU denotes follow-up; AAD antiarrhythmic drugs

Study	Patient number	Paroxysmal AF (n)	Paroxysmal AF (%)	FU (months)	Recurrence rate	AAD
Vurma, 2016	327	228	69.7	6±5	25% paroxysmal 48% persistent	OFF AAD
Wakili, 2016	29	29	100	12.4±9.3	28%	OFF AAD
Rodriguez-Entem, 2016	25	35	100	16.8±2.8	22.8%	ON AAD
Laish-Farkash, 2016	82	62	75.6	12	19.3%	ON AAD
Burri, 2016	50	50	100	15±4	54%	OFF AAD after blanking
Stabile, 2015	180	140	78	13.9±8.2	27% paroxysmal	OFF AAD
					30% persistent	at discretion of physician
Mahida, 2015	374	263	70.3	12	35% paroxysmal	20% ON AAD
					35% persistent	30% ON AAD
Deneke, 2015	145	77	53.1	12	31% paroxysmal	
					38% persistent	
Zellerhoff, 2014	39	39	100	4.7±2.5	34%	OFF AAD after blanking
Shin, 2014	25	25	100	4.1±1.6	19.1	OFF AAD
Scaglione, 2014	25	25	100	6	32	OFF AAD

device. In particular, Deneke et al. reported that overall success rates were positively associated with higher maximum energy delivery rates at the posterior wall (25 watt vs. 20 watt).[14] However, these higher energy delivery rates were likely associated with a higher risk for esophageal thermal damage.[5]

Procedural results

The development of the nMARQ™ as a single-shot device was driven by the intention to shorten and simplify PVI procedures, increase safety, and reduce radiation dose, all while producing equal (or better) success rates of other ablation devices. Pooled results for periprocedural data are depicted in [Table 2].

Total procedure times ranged from 72 ± 6.5 minutes[9] to 223 ± 53 minutes.[5] Total procedure time in the latter study is likely highest due to four cavotricuspid isthmus ablations, and one ablation of roof dependent LA tachycardia which was performed during the course of PVI. Summarized, total procedure times reported from the nMARQ™ device compared well with procedure times obtained from other PVI ablation modalities (Cryoballoon: 136 to 371 min [20], [30], [31]; PVAC: 121 to 137.1 min[32], [33]; RF 140.9 to 165 min[19], [25]). Multiple groups suggested after a learning period a mean reduction in overall procedure time of 19.1% to 62.1%.[4], [14], [24] However, Wakili et al. failed to show a significant nMARQ™ ablation learning curve with respect to overall procedure time.[18]

Mean fluoroscopy times varied over a broad range, from 1.8 minutes[7] to 35.5 minutes.[5] In the latter study, the prolonged fluoroscopy times may be explained by additional CMC use in order to confirm complete PVI. Ablation with the nMARQ™ reveals comparable fluoroscopy times as indicated in literature for other ablation devices (Cryoballoon: 21 to 40 min[19], [30], [31], [34]; PVAC 21

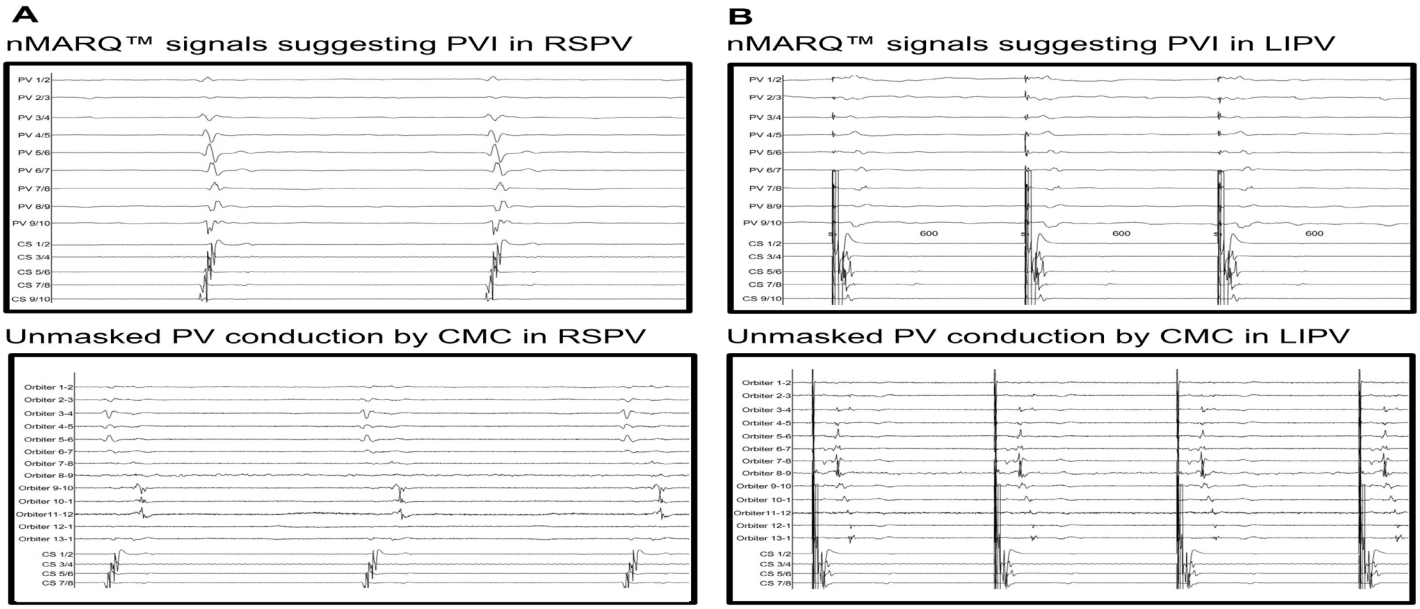

Figure 2: Insufficient signal accuracy of the nMARQ™ catheter.[18] The illustration shows intracardiac recordings of consecutive PV mappings by the nMARQ™ catheter and by a CMC of the same vein after ablation; (A) RSPV mapping with nMARQ™ suggests absence of PV conduction (upper panel) and subsequent CMC mapping shows persisting conduction in RSPV at electrodes 9–12 (lower panel); (B) Differential pacing: LIPV mapping with nMARQ™ (upper panel) suggests absence of PV conduction; subsequent CMC mapping unmasks persistent conduction in LIPV on CMC electrodes 3–13 (lower panel).

Table 2: summarizes acute success rates and procedural results with the nMARQTM ablation device. * highlights studies with PVI confirmation with additional circular mapping catheter

Study	no. of pts.	acute PVI success, n	isolated PVs	Targeted veins (%)	total procedure time (min)	Fluoroscopy time (min)	RF time (min)	Anesthesia Sedation
Vurma, 2016	327				69±22 paroxysmal	14.8±6.6 paroxysmal	18.9±6.4 paroxysmal	general anesthesia
					75±23 persistent	16.8±6.3 persistent	22.1±6.1 persistent	
Rodriguez-Entem, 2016	35	33 (94.3%)	138/140	98.6				mainly conscious sedation
Laish-Farkash, 2016	82	78 (95%)			81±18	30±8.5	11±4	conscious sedation
Burri, 2016	50	50 (100%)			100±25	22±8		conscious sedation
Stabile, 2015	180	176 (97.8%)		98	113±53	13.1±8.4	12.5±5.1	not specified
Mahida, 2015	374		1468/1474	99.6	114±42	24.4±14	13.5±6.4	not specified
Rillig, 2015	21	20 (95.2%)	87/88	98.9	223±53	35.5		conscious sedation
Deneke, 2015	145		556/559	99.5	115	17.25	18.5	not specified
Zellerhoff, 2014	39	37 (94.9%)	151/154	98.1	86±29	22.2±6.5	10±4.6	conscious sedation
Shin, 2014	25	25 (100%)	97/97	100	110±31	23±9	15±6	conscious sedation
Scaglione, 2014 *	25	24 (96%)	100/102	98	131±49	1.8±2	14.9±3.7	conscious sedation
Wakili, 2016*	29	24 (83%)	111/116	95.7	132.1±36.6	30.5±11.7	21±9	conscious sedation
Kiss, 2014	14	98%			108±25	21.1±7.8	7.7±3.4	conscious sedation
Rosso, 2014*	10	10 (100%)		100	109.3±38.4	31.3±11.2		both

to 33 min[21], [32]; single tip 16.6 to 24 min.[19], [25] A suggest learning curve shows a reduction of 51.5% to 64.5% of total fluoroscopy time .[4], [24]

With respect to total RF time, as the number of active electrodes during ablation can individually be varied, the comparison to different PVI modalities is challenging.[9] When reporting on RF duration, the majority of studies reported the total RF duration, without indication of the number of active electrodes. This hampers the direct comparison of RF times to other one shot devices or single-tip catheter approaches. However, total nMARQ™ RF times (7.7 to 18.5 min[9], [35]) are slightly longer compared to reported RF durations with conventional single tip catheters (33 min[25]; 21 min[18]). Only three studies used an additional CMC to confirm complete PVI. [7], [18], [24] Wakili et al. reported that the use of an additional CMC to confirm PVI was associated with longer RF durations, and with the identification of 19 of 29 PVs (65.5%) with persisting atrio-PV conduction after nMARQ™ ablation (21.0 ± 9.0 vs. 17.6 ± 6.5 min) .[18] Data on analyses of RF times per individual vein is scarce. The available literature provides evidence that RF times needed for PVI are significantly longer in the superior PV compared to RF times needed in the inferior PVs.[3], [7], [16] All but one study indicates that mean RF times with the nMARQ device are longest in the LSPV (191.6 ± 41.9 sec).

Safety

As the nMARQ™ catheter has shown to be associated with comparable outcomes to currently available ablation technologies, in respect to recurrence post ablation, a specific focus is placed on safety issues. In general, AF ablation is associated with a incidence of acute complications ranging from <1% to 6%.[36]

Esophageal thermal damage

Due to the specific design of circular ablation devices and therefore high energy delivery at the posterior wall, esophageal lesions are of major concern [Table 3]. Esophageal thermal damage (ETD) is considered a precursor of fistulas, even though the causal relation between fistulas and thermal esophageal lesions is largely unclear .[14] Following PVI with a single-tip, a high incidence of thermal lesions have been reported (thermal esophageal damage (11%) and gastroparesis (17%)).[37] Deneke et al. assessed 136 out of 145 patients with endoscopy after nMARQ™ ablation, and report on 7 ulcerous and 22 erythematous lesions after PVI with the nMARQ™.[14]

ETD resulting in fistulas can lead to fatal complications. The indicated mortality in literature after development of atrio-esophageal fistula (AEF) is 71%.[38] An overall incidence of 3 of 1417 patients (0.21%) that developed AEF has been derived from the published nMARQ™ studies. Of those reported cases of AEF, Vurma et al. reported fatal outcomes following development of AEF in 2 of 327 consecutive patients (0.6%) following ablation with the nMARQ™ device. This report led to an immediate recall of the nMARQ™ catheter in its 2nd generation.[9], [12] Deneke and Mahida et al. each reported cases of delayed occurrence of AEF, the latter reporting on a delay of 4.5 weeks between PVI procedure and occurrence of first symptoms.[3], [11]

Various safety precautions have therefore been suggested in order to avoid thermal esophageal damage. According to initial experience, the use of a thermal probe has been suggested in order to reduce the incidence of thermal damage during AF ablation at the posterior wall. [39], [40] Disagreement remains on the esophageal cut-off temperature during RF delivery, ranging from 39 degrees[41] to 41 degrees Celsius .[5], [42]

Considering the recent literature on nMARQ™ ablations, only one study[43] suggested a benefit of using a temperature probe during multipolar RF ablation.[14], [35], [41], [44] Consistent with other reports concerning RF ablation, Deneke et al. suggested an increased risk for ETD in patients with thermal probes during RF ablation (21% vs. 0%, p<0.001).[5], [8], [14], [18] They speculate a possible 'antenna' effect of the thermal probe intensifying local energy with heating at the esophageal region, or a stiffening of the esophagus itself avoiding the esophagus to sidestep during catheter pressure.[5], [14], [39], [45] However, in cases of large esophageal diameter, the probe is not able to cover the entire esophageal region (as shown by barium sulfate ingestion), and therefore may lead to an underestimation of the local temperature. This underestimation of temperature may result in a higher risk for esophageal thermal lesion.[41] According to those presented data, the use of thermal probes should therefore be avoided.

Other precautions suggested for ETD prevention comprise a reduction of the maximum power (20 watt [14]), and even lower temperatures when bipolar ablation is performed.[41] Limitation of RF time at the posterior wall is also recommend for ETD prevention .[5] The two cases of AEF reported by Vurma et al. occurred following ablation with a max. temp of 16 to 18 watts (30 sec max. duration for vast of energy deliveries).[9] It must be mentioned that the report of maximum delivered RF energy is often misleading. In order to avoid ETD, most operators only decrease RF power at the posterior wall.

Finally, the use of general anesthesia has been reported to serve as a risk factor for ETD.[46] Most of the patients undergoing ablation under general anesthesia also had esophageal temperature probes during the procedure. Therefore, the influence of general anesthesia as a risk factor for thermal lesions remains unclear, and needs to be critically questioned.

Thromboembolic complications

Thromboembolic complications are generally considered a major concern with the nMARQ™ device, which is based on former negative experience with the circular single-shot ablation PVAC device.[47], [48] Reviewing the current literature on nMARQ™ ablations, no stroke or transient ischemic attack (TIA) were reported. However, silent cerebral lesions (SCL), which likely represent small thromboembolic infarctions, have been reported in literature. Varying based on the ablation technology used, SCL were reported in up to 40% of patients after RF ablations.[14], [47], [49], [50] Since embolic-lowering maneuvers have been introduced into clinical practice, the use of the nMARQ™ device remains associated with the highest reported incidence of asymptomatic thromboembolic complications .[6], [8], [51] The clinical significance of these SCL is unclear. However, an association between SCL and neuropsychological changes, especially of verbal memory, has been suggested[52], yet other studies have failed to show an association.[53], [54]

Out of 16 reported studies on complication rates, six studies performed cerebral imaging (CT\MRI) after PVI to rule out SCL. [4], [6], [8], [14], [16], [53] Two groups found SCL following PVI with the nMARQ™ device, ranging from 1 in 19 patients (5%)[53] to 14 in 43 (33%).[55] However, none presented with any obvious neurological symptoms. The high percentage of 38% post-ablation SCL, as indicated by Deneke et al.[55], might overestimate the real percentage as Sugihara et al. found a high incidence of preexisting SCL before PVI.[53] This high prevalence of pre-existing lesions (12.3-92%) might represent a condition of inappropriate anticoagulation before PVI.[50], [51], [54]-[57] In this context, studies have indicated that the maintenance of preexisting anticoagulation, compared to discontinuation and bridging with heparin, contributed to a reduction of periprocedural

Table 3: An overview of published literature on procedure-related complications with the nMARQ™ system. PE denotes pericardial effusion/ tamponade; PNP phrenic nerve palsy; AEF atrio-esophageal fistula; SCE silent cerebral lesion; TP temperature probe; EGD esophago-gastro duodenoscopy; ETD esophageal thermal damage; LA left atrium; PVS pulmonary vein stenosis; PN phrenic nerve; RF radio-frequency; TIA transient ischemic attack

Study	Pt. No.	PE	Access site	ECG alteration	PNP	Stroke\ TIA	AEF	ETD	SCE	death	PVS	MRI\ CT LA	TP	EGD	PN test	RF
Vurma, 2016	327	0	13	2	0	0	2			2	0	No	no	no		16-18 W
Rodriguez-Entem, 2016	35	1			0	0	0			0	0	yes (n=19)		no	yes	20-25 W uni
Laish-Farkash, 2016	82	1	4	3		0	0			0		no		no		15-20 W uni
Burri, 2016	50	2		0	1	0	0			0		no	no	no	yes	15 W uni
Knecht, 2016	40	0	0	0		0	0			0		no	yes	no		15-20 W uni
Stabile, 2015	180	0		0	0	0	0			0		no	no	no	yes	20-25 W uni
Mahida, 2015	374	0		0	0	0	1			2	0	0	no	no		25 W uni- and bipolar
Rillig, 2015	21	0		0	1	0	0	4		0		0	yes	yes		10-20 W uni- and bipolar
Deneke, 2015	145	1	0	0	1	0	1	29/ 136	26/ 115	1	0	yes	103/ 145	yes	yes	20-25 W uni
Di Monaco, 2015	30	0	0	0	0	0	0	0		0		no	yes	yes	yes	15-18 W uni- and bipolar
Arroja, 2015	1	0	0	0	1	0	0	0	0	0	0				no	15 W
Zellerhoff, 2014	39	1								0	0	yes	no	no	no	25 W uni
Shin, 2014	25	0	0		0	0	0			0	0	yes	no	no	yes	20-25 W uni
Scaglione, 2014	25	0	3	0	0	0	0		0	0		0	no	no	yes	20-25 W uni
Kiss, 2014	14	0								0						20-25 W uni
Wakili, 2014	29	0	1	0	1	0	0	1		0	0	0	yes	yes	yes	18-20 W uni

cerebral events.[58], [59] In general, different anticoagulation regimens make the comparison of studies dealing with microbubbles during ablation difficult.[35] Kiss et al. demonstrated that nMARQ™ ablation was associated with a high incidence of microbubbles. This bubble formation seems to be higher than when compared to ablation with new-generation PVAC devices, or cryoballoon ablation.[35] The assessment of the intensity of micro emboli generation during ablation procedures is measured in the middle cerebral artery by transcranial Doppler.[35] However, this technique of measuring microbubbles by ultrasonic techniques has not been consistently validated with respect to the clinical significance. It remains completely unclear as to whether these microbubbles represent solid particles or gas and how they translate into a manifest clinical finding.

With respect to conditions predisposing to thrombi formation, the specific design of the circular nMARQ™ catheter with 10 irrigated electrodes is suspected to be causative for this phenomenon. Csanadi et al. speculated that the high volume flow of irrigation saline solution (6-7ml/ electrode, resulting in 60-70ml/min) can result in bubble formation and subsequent microembolism.[60] Further, charring on the electrodes is thought to be another major source of SCL, arising from former PVAC experience.[5] Shin reported the identification of charring on 3 of 15 cases (20%) with the nMARQ™ catheter.[4] Charring was found primarily between electrode 1 and 10. This location is where electrodes are delivering RF energy in close proximity, and is likely the source of a bipolar short circuit resulting in tissue and blood heating.[51] Therefore, Shin et al. recommend RF delivery only with sufficient distance between electrode 1 and 10 on fluoroscopy, 3D visualization, without indication of proximity by artifacts on the corresponding EGMs.[4]

Despite existing data from animal studies investigating the PVAC device, there is still discrepancy as to whether the use of unipolar over bipolar RF energy per se could reduce the incidence of microembolism.[61] Nevertheless, in order to reduce the incidence of SCL, abandonment of a bipolar RF energy use is recommended in general now. As catheter manipulations are thought to be a source of microbubble formation, the following precautions should be considered[54], [59]: at least half the calculated bolus dosage of heparin should be given before transseptal passage, continuous flushing of the long LA sheath, and whenever possible, retraction of the sheaths in RA. Additionally, a catheter change over the long LA sheath should be avoided.[35] This however questions the intention of these "single-shot" devices, because in addition to the PVI, an additional CMC may be required.[7], [18], [24] Further, the administration of a proton pump inhibitor should be considered for at least 6 weeks following ablation in order to prevent progression of esophageal thermal damage to ulceration.[5], [8]

Other severe complications

Other severe complications including pericardial effusion/tamponade and phrenic nerve palsy (PNP) were reported in 7 out of 16 cited studies.[5], [6], [10], [13]-[16], [18] Pericardial effusion/tamponade was reported in 6 out of 1417 (0.4%) patients, and PNP in 4 of 1417 patients (0.3%). However, the prevalence of PNP following nMARQ™ ablation is lower than in the literature for overall PVI procedures, with PNP rates ranging from 0.48% to 11%.[62]-[64] Although injury of the phrenic nerve is reported following various ablation techniques, it has been suggested to be more likely with the Cryoballoon.[20], [65] The exact mechanism of the high rate of PNP after circular PV ablation with the Cryoballoon remains unclear, especially with regard to the lower percentage of PNP after nMARQ™ of overall 0.3%.[10], [13], [66] This may be explained in part by a more antral ablation with nMARQ™ catheter compared to Cryoballoon (diameter 20 to 35mm vs. 23 or 28mm).[6] With respect to the underlying mechanism, experimental data suggested a Wallerian degeneration (axonal damage by coagulation), or an injury of the right pericardiophrenic artery, both with the potential for recovery.[62], [67], [68]

In order to avoid PNP during nMARQ™ ablation, Arroja et al. suggested a further power limitation of 12 to 15 watts, phrenic nerve stimulation on each electrode of the nMARQ™ catheter, and continuous phrenic nerve stimulation during RF application.[10] Additionally, Roka et al. reported on a novel technique to prevent PNP, by identifying the overlapping region between right and left atrium. RF applications proximal to this line are suggested to be safe with respect to PNP.[62] In order to rule out pulmonary vein stenosis following PVI, imaging modalities were reported on in five studies [Table 3], and no significant stenosis was mentioned.

Conclusions

The nMARQ™ catheter was developed in order to enable fast, durable, and safe PVI by using a single-transseptal approach. As presented, the literature reveals comparable acute and long-term clinical outcomes after AF ablation to single-tip and different other circular ablation catheters. With respect to procedural parameters, current studies failed to provide an evidence for reduction of total RF with the nMARQ™ device (see [Table 2]). However, these studies comprised initial experience, scientific evaluation with a learning curve and small patient cohorts in a majority of studies.

Although intended to function as a single-shot device, some issues were presented concerning the catheter's procedural performance. For example, when using the device via the intended single-transseptal approach without CMC confirmation, this results in insufficient PVI, and may be impairing ablation success rates. In order to perform this additional CMC assessment of complete PVI, it must be advanced in to LA by catheter change, or dual-transseptal approach. These approaches increase complexity and prolong procedure and fluoroscopy times. Further, catheter change in the LA is suggested to be associated with microembolism. Therefore, the intended single-shot character of this device requires investigation in larger prospective trials with strict intention-to-treat designs.

Still despite establishing safety precautions, a high rate of esophageal thermal damage and atrio-esophageal fistulas were reported with the nMARQ™ device, especially with the 2nd generation device. This is of major concern as these injuries often result in fatal outcomes. Following the re-launch of a new nMARQ™ generation, further investigation into the safety of this device with respect to esophageal thermal damage is absolutely essential prior evaluating the clinical efficacy. In general, based on the early and limited experience with few severe complications associated with the nMARQ™ device, a close FU of patients after PVI with all circular mapping devices should be aimed for.

In sum, following the idea of an easy-to-use and efficient ablation tool enabling fast and complete PVI, the nMARQ™ catheter has proven feasibility, but still needs further evaluation in order to establish a reliable safety profile before aiming for superiority with respect to procedural and clinical variables in larger trials.

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Conflict Of Interests

None.

Disclosures

None.

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Hypothetical "Anatomy" Of Brugada Phenomenon: "Long Qt Sine Long Qt" Syndrome Implicating Morphologically Undefined Specific "Brugada's Myocells"

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Abstract

The Brugada syndrome (BrS) is associated with increased risk of ventricular arrhythmias and sudden cardiac death. It generates genetically mediated arrhythmias posing a true pathophysiological challenge. In search of the similarities between BrS and long QT syndrome some novel insights are suggested. In patients with BrS the duration of QT interval is usually normal. Some investigators have found prolonged QT interval in the syndrome's natural course or the duration of QT segment have been extended by provocative tests unmasking BrS. Thus, BrS might be characterized as "long QT sine long QT" syndrome. The existence of two functional types of myocytes is suspected. Regarding structure and function the majority of ventricular myocardium is probably mostly healthy. The rest of myocardium (preferably the subepicardium of right ventricular outflow tract) due to its genotypic peculiarities demonstrates no negative influence on ventricular performance until early adulthood is reached and/or other unstable preconditions are fulfilled (nocturnal time, fever, specific drugs, etc.). Based on published findings of positive outcomes, following the epicardial ablation of the right ventricular outflow tract region, a new hypothetical concept suggesting the presence of specific, genetically affected "Brugada's myocells" is proposed. These cells as a suitable arrhythmogenic substrate reside intramurally within the subepicardial region of the outflow tract of right ventricle. In the daytime these cells likely are dormant but at rest their nocturnal proarrhythmic behavior is activated occasionally. Presumptions regarding the pathophysiology of BrS might be the focus of further discussion.

Introduction

The Brugada syndrome (BrS) was first described in 1992[1] as a unique set of electrocardiographic signs associated with sudden death in otherwise healthy adults without structural heart disease. It is an inherited arrhythmogenic disorder characterized by a typical Brugada-type ECG pattern of ST-segment and is associated with malignant ventricular arrhythmias.[1], [2] Increased ventricular vulnerability typically occurs at rest and during night time.[2], [3] Up to 20% of patients with BrS may suffer from supraventricular arrhythmias.[3]-[5]

A heated debate is ongoing about the underlying mechanisms of the genesis of VF.[6] Some authors[7] state, that BrS is always associated with a considerable prolongation of right ventricular repolarization. The electrical disorder is primary, that is, without concomitant underlying heart disease.[8] In early 2009 it was declared that BrS is a disease mainly of the right ventricle.[8] There is a consensus related to the right ventricular outflow tract (RVOT) which is the most likely substrate site regardless of the underlying mechanism.[6], [9]-[12] The purpose of this review is to develop refined understanding based on the findings of some similarities associated with BrS and long QT syndrome (LQTS). The abnormalities of repolarization and depolarization may be tracked in both syndromes. The existence of some specific/defected but morphologically still undefined "Brugada's myocells" is suspected; such a substrate most likely is responsible for VF/VT attacks.

Key Words

Brugada syndrome, arrhythmogenic substrate, ventricular arrhythmias, Brugada's myocells, "long QT sine long QT" syndrome.

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Various aspects of BrS as a baseline for new assumptions

BrS is attributed to the genetically determined entity i.e., a channelopathy that causes dysfunction of a cardiac channel participating in the action potential[8]; an electrical dysfunction favors the development of arrhythmias. The cardiac sodium channel gene, SCN_5A, is involved in two of such arrhythmogenic diseases, the BrS and one form of the long QT syndrome (LQT_3).[13] The mutation in the SCN_5A cardiac-voltage-gated sodium channel gene actually leads to a reduction in the fast sodium channel current and a premature termination of the ventricular epicardial action potential .[14], [15] Some reports have shown that different causes may mimic BrS. [16], [17] The Brugada signs are also known to be produced by drugs such as class IA and IC anti-arrhythmic agents, cocaine, tricyclic antidepressants.[14]

It is well-known that long QT interval is associated with an increased

propensity to ventricular arrhythmias.[18] The conditions comprising long QT syndrome and the BrS account for a substantial proportion of sudden cardiac deaths when no anatomic abnormalities are found.[19] However the precise mechanism of ventricular fibrillation/tachycardia (VF/VT) and ECG pattern in patients with BrS remains unresolved.[20] There are theories based on repolarization and depolarization abnormalities.[20]-[22] Excellent insights of Wilde and colleagues[21] have shown have shown support for the repolarization hypothesis as the predominant mechanism underlying BrS. This hypothesis relies on transmural dispersion of repolarization between the right ventricular (outflow tract) endocardium and epicardium.[21] In some prediction models[23] both repolarization and depolarization-related parameters seems to contribute to VF risk. A third hypothesis based on electrotonic current posits that current-to-load mismatch in the right ventricle and RVOT subepicardium is responsible for ST segment elevation.[24] Intermittent functional shift, interference or partial superimposition of repolarization/depolarization processes covering different myocardial regions may be assumed. Transmural inhomogeneity in repolarization is also indicated.[25] Hoogendijk and collegues[11] hypothesize that electrophysiological mechanism of the BrS could cause structural derangements. A comprehensive overview of BrS by Tse et al.[26] provides more insights into elctrophysiological mechanisms of arrhythmogenesis.

BrS seems to occur in individuals with structurally and functionally normal hearts.[8], [27] However, mild structural abnormalities are suspected.[28] Study by Nademanee et al.[29] suggests that microscopic fibrosis plays a role in the pathophysiology of BrS. Regardless of whether it is a late-stage by-product, or the original primary cause of BrS, this can lead to conduction impairment.[22] Whether structural alterations in BrS are primary or secondary is still unknown.[30]

A growing body of evidence suggests that a structural arrhythmogenic substrate underlying BrS may be located in RVOT.[20] Some clinical cases have demonstrated that a component of BrS substrate is functional rather than fixed structural replacement with fibrosis.[20] This viewpoint is favorably supported by the fact that BrS-type ECG pattern or VT/VF episodes may be provoked by fever.[12], [31], [32] Prompt and aggressive control of fever by antipyretics is helpful.[12], [31] There are reports related to the fever-induced QT interval prolongation and VF episodes while sleeping in healthy individuals.[34]

Three types of repolarization abnormalities have been described but only the coved-type ST-segment elevation (type-1 ECG pattern) renders the diagnostic value.[8], [31] Interestingly, the ECG typically fluctuates over time in Brugada patients, and then can change from type-1 to type-2 or type-3, or even be transiently normal.[8] Fragmented or prolonged QRS complexes in the same leads are also observed.[35], [36]

Brief characteristics of QT interval duration

Cyclic electrical processes in the ventricles consist of two alternating phases – depolarization and repolarization. The QT interval extends from the beginning of the QRS complex up to the end of the T wave. This interval represents the algebraic sum of the individual action potential of the ventricular myocytes, including both depolarization (the QRS complex or QJ interval) and repolarization (the T wave or JT interval).[37] Conventional ECG reflects the repolarization of all ventricular myocells.[37]

Commonly the QT intervals in BrS patients fall in the normal range.[38] Pitzalis and colleagues[7] however have stressed that typical ECG pattern of BrS is characterized by a considerable prolongation of QTc interval in right precordial leads. On the other hand, there is a wide range of QT interval duration that is considered abnormal, without a significant increase in risk.[39]

The sleep is accompanied by increased parasympathetic tone or by withdrawal of the sympathetic one[40], [41] and prolongs the QT interval independently of the slowing heart rate.[42], [43] This information is fundamental in understanding the potential mechanism(s) or VF/VT at rest or in night time in BrS patients. It is also well-known that marked lengthening of the QT interval is almost inevitably associated with the risk of sudden death and with increased temporal dispersion of repolarization which in turn, increases the duration of vulnerable period as well as decreases the threshold for VF.[19], [37] Temporal dispersal of the repolarization process may occur as a result of premature repolarization of some myocardial cells or as abnormally delayed repolarization of other cells.[37] An appeal to "other cells" by Kenny and Sutton[37] might be interpreted as a hint on the potentially existence of conglomerate of specific myocells. The putative accumulation of cells within the circumscribed region of right ventricle might be named as "Brugada's myocells". Likely the mass of "Brugada's myocells" is measurable and powerful enough to induce the dispersion/abnormality of repolarization reflecting on precordial ECGs. Reportedly, the abnormally delayed dispersion of premature ventricular repolarization poses a risk for VF/VT.[39], [44], [45]

Disclosure of arrhythmogenic region by modern treatment and epiloque

Recent studies have demonstrated beneficial clinical effects achieved by subepicardial substrate ablation over the RVOT.[20], [46] Normalization of the ECG and decreased recurrence of VT/VF episodes after ablation suggest that the anterior aspect of the RVOT epicardium is the primary site for the arrhythmogenic substrate in patients with BrS[20]; electroanatomic substrate is identified by endocardial and epicardial mapping system. According to Veerakul and Nademanee[6] we should have more confidence in treating BrS patient subset with catheter ablation alone without implantable cardioverter-defibrillator. Recently, Patocskai, Yoon and Antzelevitch[16] have declared that epicardial radiofrequency ablation exerts its beneficial effects by destroying the cells with the most prominent action potential notch, thus eliminating sites of abnormal repolarization and the substrate VT/VF. That is why the genetically altered myocardium eponymously might be entitled as "Brugada's myocells" which potentially represent fundamental arrhythmogenic substrate in genotype-positive patients. In the broad sense the Brugada's myocells might be characterized as containing robust morphological structure, diseased function and unpredictable behavior. The role of specific Brugada's myocells presumably increases due to decreased sympathetic cardiac tone occurring in the night time. Paradoxically – during a night's sleep the "Brugada's myocells" - as VF/VT triggers - demonstrate their activity (fortunately only occasionally) and vice versa - proarrhythmic cells are dormant in the daytime, while patients are awake.

Likely the volumetric parameters of healthy myocardium outweigh en mass the genetically involved one. The latter, i.e the minor part of myocytes potentially is responsible for the inadequacies or dynamic shift/overlap of depolarization/repolarization processes resulting in life-threatening VF/VT. According to some reports[14], [15] the

ECG changes may be transient over time. Subsequently, a vicious interrelationship of repolarization and depolarization processes is dynamic, unstable and unpredictable.

For many years or even throughout the patient's life time the intact myocells as the largest postion of myocardium with considerable heft considerable functional heft contribute to the maintenance of stable heart rhythm. Let's say the duration of QT interval is normal or close to it. Ventricular myocardium is compromised occasionally due to provoked/triggered activity of Brugada's myocells representing quite a small part of ventricular mass. Nocturnal incidental VF/VT episodes could be explained by occasional prolongation of QT interval which reflects the repolarization and depolarization abnormality. Prolongation of QT interval is probably provoked by the state of rest or sleep (due to vagal imbalance), especially in young or in middle aged patients. Such a consideration allows to construe new characteristics of BrS – "long QT sine long QT" syndrome. In general, any shift in duration of QT interval potentially is proarrhythmic.

Temporary or intermittent hyperpolarization facilitating the release of arrhythmia might not be ruled out.

Conclusions

The presence of specific, genetically implicated, and morphologically undefined ventricular myocells residing subepicardially are yet to be proven. Nocturnal cardiac events in patients with Brugada syndrome most likely manifest due to the triggered activity of putative "Brugada's myocells". These processes are highly influenced by circadian activity of parasympathetic tone. The changes of QT interval are provocative in regards to life-threatening ventricular tachyarrhythmias. Alterations of QT interval, however are not causal per se; they simply reflect mutual interrelationship between the healthy myocardium and relatively small portion of myocells. Taking into account the repolarization and depolarization abnormality in terms of QT duration fluctuation and electrocardiographic dynamicity the Brugada syndrome might be depicted as "long QT sine long QT" syndrome. Meanwhile such a speculative approach to a new explanation of Brugada syndrome remains a topic of discussion.

Conflict Of Interests

None.

Disclosures

None.

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Comparison of the Efficacy of PVAC® and nMARQ™ for paroxysmal Atrial Fibrillation

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Abstract

Pulmonary vein isolation (PVI) has become the mainstay of therapy for atrial fibrillation (AF) and one of the most frequently performed procedures in the cardiac electrophysiology laboratory. PVI by a single-tip radiofrequency (RF) ablation catheter remains a complex and time-consuming procedure, especially in centers with limited experience. In order to simplify the PVI procedure, to shorten it and reduce the complication rate, circular multi-electrode catheters were introduced for simultaneous mapping and ablation. The common concept of these "single-shot" AF ablation technologies is the creation of circular lesions for PVI by placing the ablation device at the antrum of the pulmonary veins without the need for continuous repositioning. In this review we describe the main features of two circular non-balloon ablation catheters– PVAC®, which is based on the phased RF, duty-cycled ablation technology, and nMARQ™, the irrigated multi-electrode electro-anatomically guided catheter - and compare the clinical outcomes of these technologies, mainly for paroxysmal AF patients, based on current available data.

Introduction

Pulmonary vein isolation (PVI) by a single-tip radiofrequency (RF) ablation catheter, the cornerstone of catheter ablation for atrial fibrillation (AF), remains a complex and time-consuming procedure. This point-by-point ablation technique requires extensive operator experience for efficiency and safety, and is usually associated with long procedure times, especially in centers with limited experience.

Novel AF ablation techniques ('single shot devices') have emerged in recent years with the intention to simplify PVI procedures, to shorten them, to reduce exposure to radiation and to reduce complication rates, with at least equally efficiency to conventional ablation approaches. The common concept of these "single-shot" AF ablation technologies is the creation of circular lesions for PVI by placing the ablation device at the antrum/ostium of the pulmonary veins (PVs) without the need for continuous repositioning.

Non-balloon alternatives for PVI are two circular multi-electrode catheters: the pulmonary vein ablation catheter (PVAC®; Medtronic Ablation Frontiers, Carlsbad, CA), which is based on the phased RF, duty-cycled ablation technology[1]-[4]; and the irrigated multi-electrode electroanatomically guided nMARQ™ catheter (Biosense Webster, Inc., Diamond Bar, CA, USA).[5]-[6] The two non-balloon multielectrode technologies, PVAC® and nMARQ™ catheters, are different in their cooling technology, the integration with electro-anatomical mapping (EAM) system, the ability of recording PV signals during ablation, the diameter of the spiral array at the distal end (25 vs. 35 mm), and the flexibility and structure of the catheter over the wire.

This review is not intended to compare the efficacy of the circular ablation catheters to conventional PVI with single tip catheters, neither to elaborate on the complication rates and the safety concerns of the circular ablation techniques; The aim of the review is to evaluate efficacy of PVAC® and nMARQ™ catheters and suggest an optional patient selection algorithm.

Key Words

nMARQ, PVAC, atrial fibrillation, circular ablation catheters.

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Technical differences and ablation strategy

PVAC® - Phased RF ablation technique

The PVAC® is one member of the phased RF AF ablation catheters family. The phased RF system utilizes anatomically designed, multi-electrode catheters with tissue temperature monitoring and a closed-loop power control generator to create contiguous, transmural lesions [Figure 1]. All three catheters monitor electrode-tissue temperature through thermocouples bonded directly to each electrode on the side of the electrode in contact with the tissue.

Power regulation is achieved through duty-cycling of the RF energy, rather than voltage control: in contrast to conventional RF ablation that delivers continuous RF energy, "on" and "off" periods alternate during duty-cycled ablation. The length of the "on" time is regulated to reach and maintain the target temperature. The time period with no RF delivery allows accurate temperature monitoring and provides time for the electrode to cool between RF applications.

The concept of unipolar and bipolar energy delivery (phasing) means, that the multi-electrode catheter design and the generator

enable simultaneous bipolar (between electrodes) as well as unipolar (from electrode to ground pad) delivery of RF energy. There is no voltage difference, thus no current flow, between neighboring electrodes while "in phase", so only unipolar energy is delivered between each electrode and the ground pad. When the voltages for the two adjacent electrodes are "out of phase", inter-electrode voltage difference results in bipolar RF delivery. The depth of the lesions was found to be proportional to the energy mode selected, with unipolar delivery causing the deepest lesions.[7] The generator is able to deliver a mixture of unipolar and bipolar ablations. This feature is used to titrate lesion depth during PVI: in circumstances where 4:1 RF energy delivered cannot isolate the PVs (as on the ridge of the left-sided veins) – then a ratio with a higher unipolar component should be considered (e.g. 2:1). In contrast, when ablating at the posterior wall of LA and in areas with close proximity to the esophagus and other critical structures, a higher ratio of bipolar component is preferred (e.g.4:1).

PVAC® consists of a 9F, 10-platinum electrode, over-the-wire deflectable catheter, 25 mm diameter spiral array at the distal end, with the capability of straightening the circular end over the wire into the vein. The over-the-wire design provides stability of the catheter in various anatomies. It is a non-irrigated duty-cycled phased RF catheter that is able to deliver RF energy with varying mixtures of unipolar and bipolar ablations not integrated into an EAM system. PVAC® is used to isolate and then validate the electrical isolation of all PVs. PV angiography through the guiding sheath can be used to assess the catheter position in relation to the ostium so as to avoid any RF application inside the PVs. Electrograms cannot be assessed during the delivery of phased RF current because of the electrical noise; however, electrical conduction of the PVs can be assessed between the applications. Duytschaever reported a 93% diagnostic accuracy for the verification of PVI when a conventional mapping catheter was used as a gold standard.[8] Pacing maneuvers or a conventional mapping catheter can be considered whenever doubt remains regarding gaps in PV isolation[9], particularly during the learning curve.

The GENius™ Multi-Channel RF Ablation Generator (Medtronic, Minneapolis MN, USA) contains 12 independently controlled RF generators for each electrode in the catheter. It monitors the temperature on each electrode and adapts the power to achieve and maintain the target temperature (nominally 60 °C). The GENius™ monitors the power and the temperature on each electrode and displays to the operator when the power and temperature are sufficient to create a good lesion (Contact IQ).[10]

Most of the data in the literature refer to this type of catheter. Recently, PVAC Gold catheter was introduced to the market. It contains 9 gold electrodes. Gold has more than 4 times better thermal conductivity than that of platinum. Thus it allows more uniform heating and faster cooling than platinum, providing the potential for precise temperature control across the electrode.[11] Because of gold's ability to deliver energy more efficiently and consistently, it provides the potential for generating equivalently deep lesions to platinum .[12] The number of electrodes was reduced from 10 to 9 in order to eliminate the potential bipolar short circuit between electrodes 1

Table 1: Acute and longer-term results of multi-electrode circular duty-cycled RF ablation (PVAC®)

Study	No.patients	Age	Paroxysml AF(%)	Mean LA diameter(mm)	Procedure time(min)	Fluoro time(min)	Efficacy-acute success(%)	Efficacy-long term success(%)	F/U duration(mo)	Major complications(%)	Year
Boersma et al.[1]	98	59±9	100	NA	84±29	18±8	100	83	6	0	2008
Fredesrdorf et al.[38]	21	59±12	81	NA	81±13	30±11	99	86	6	0	2009
Beukema et al.[39]	102	57.9±9.6	90	41.2±6.5	139.3±37.72	32.1±11.3	100	60.8	12.2±3.9	0	2010
Duytschaever et al.[8]	27	60±8	100	41±4	176±25	NA	93	74	3	0	2010
Wieczorek et al.[3]	73	56±12	100	44±3	122±27	20±11	99	85	6	0	2010
Bulava et al.[40]	51	56.5±9.9	100	41.2±5.4	107±31	16±5	98	77	6.6±0.4	0	2010
Choo et al.[41]	38	56.9±10.2	79	42±7.5	168±41	39±14	97(100 PAF)	68(73 PAF)	6	3.9	2011
Bittner et al.[42]	40	57±11	53	43±5	171±40	26±8	99	72	8.5±3.3	0	2011
Khaykin et al.[43]	31	63±10	100	39±6	125±25	36±14	100	67	6	0	2012
Tivig et al.[44]	143	61±10	100	40±6	128±38	29±13	100	76* 74*	7.1±5 7.1±5 15.9±2.8	2.6	2012
Beukema et al.[45]	89	56±10.4	100	42.5±3.4	138±35	31±13	100	84	12	0	2012
Mulder et al.[46]	120	59 (34-76)	100	40±5	86±26	NA	100	55 49	12 24	3	2012
Nardi et al.[47]	429	60±12	68	43±4	62±15	21±4	NA	75.1 PAF 54.7 CAF	22±5	1.8	2013
Malmborg et al.[48]	56	62±7	66	42±5	167±40	47±17	93	34	12	1.8	2013
Looi et al.[49]	75	60±10.1	100	48±4.2	135±54	46±29	NA	65.3	25.6±5.9	2.6	2013
Spitzer et al.[50]	388	61.7±9.7	80	42±6	67±18	15.6±5.7	>99	64.2	24	0.5	2014
De Greef et al.[51]	79	60±10	66	41±7	121±41	33±11	100	65	36	1.26	2014
Gal et al.[52]	230	56.6±10.3	83.9	41.7±4.7	133.9±38.8	31.9±12.3	99.8	47.7	43	1.3	2014
McReady et al.[4]	94	58±12	100	38±7	140±43	35±16	98	60	12	2	2014
Laish-Farkash et al.[19]	93	61.4±9.8	87	38.8±5.4	94±27	33±13	97	79	12	0	2015

and 10 and to reduce microembolism.[13]-[15] In addition, a 20-degree forward tilt was added to the distal circular segment of PVAC Gold catheter for a more uniform tissue contact with the PV antrum.

Other members of the phased RF family used for substrate modification are the multiarray septal catheter (MASC™), a three-arm pull-back electrode which is designed to map and ablate the interatrial septal wall. This catheter is introduced through the transseptal puncture site, and the electrodes are positioned against the septum by pulling back on the catheter. The four-arm multiarray ablation catheter (MAAC™) is designed to map and ablate arrhythmogenic drivers in the left atrial (LA) body, such as complex fractionated atrial electrograms (CFAEs) [Figure 1].

nMARQ™ - Multielectrode irrigated RF ablation technique

nMARQ™ is an irrigated circular RF catheter visible and intended for integration into the CARTO system (Biosense Webster, Inc. Diamond Bar, CA, USA), which allows 3D anatomical mapping of the left atrium (LA) and PVs [Figure 2]. It consists of ten separate, openly irrigated electrodes arranged on an 8.4F decapolar catheter with an adjustable circular array of 20–35 mm diameter. An irrigation line is connected to the catheter's central hub and perfused using a commercially available pump (during energy application 60 mL/min 0.9% saline via CoolFlow, Biosense Webster).

The corresponding generator (nMARQ™ Generator, BiosenseWebster)is capable of delivering RF energy over 10 separate channels independently. Up to 25 watts (W) of RF energy per electrode are delivered in unipolar mode with the temperature limited to 45 °C; (The RF energy is delivered in either unipolar or bipolar mode, but only unipolar RF is usually used for up to 60 s per application). Power delivery during ablation of the posterior wall varies between 20 and 25W in unipolar mode. In our practice and according to reports from other groups[16]-[19], unipolar RF energy is delivered with power settings of 20 W for the non-posterior zones and 15 W for the posterior areas with maximum impulse duration of 40 s. In bipolar mode, the maximum power delivery is 15W per electrode, also with temperature limited to 45°C. Each application lasts until the PV signals disappear, between 15 and 60 s each. In case of lack of atrial signals on some of the multi-electrodes, those displaying no signal are shut off during subsequent application.

With nMARQ™, atrial and PV signals can be recorded during ablation. During RF delivery, ablation-related parameters (temperature, impedance and power delivered) are monitored continuously for each active channel.Intermittent fluoroscopy is also used to assess movement of the diaphragm to avoid injury to the right phrenic nerve. Pacing for phrenic nerve capture and esophageal temperature monitoring are not routinely performed in all centers.

Prior to ablation, the individual LA anatomy is reconstructed with the CARTO system. Circular ablation can be guided by CT image integrated into fast anatomical map and by intra cardiac echo as well.[20] There is a visual display of the nMARQ™ System electrodes that are in close proximity to tissue, using the TissueConnect™ technology that measures constantly and collects phase differences between current and voltage. The position of the nMARQ™ catheter at the PV ostium is optimized using a combination of fluoroscopic imaging and the EAM. Our group has shown that addition of contrast injections to standard nMARQ™ procedure is feasible and safe. It has no benefit in routine use but may have a potential added value to EAM in catheter localization by newly trained operators and in selective cases of large/common PV anatomy.[21]

For evaluating isolation of PVs using nMARQ™ the entrance and exit block technique can be used for very large PVs, through which the whole catheter can be entered. In smaller veins, RF delivery is continued until no PV signals are observed at the antrum (along

Table 2: Acute and longer-term results of nMARQ circular irrigated multielectrode ablation catheter

Study	No.patients	Age	Paroxysml AF(%)	Mean LA diameter(mm)	Procedure time(min)	Fluoro time(min)	Efficacy-acute success(%)	Efficacy-long term success(%)	F/U duration(mo)	Major complications(%)	Year
Scaglione et al.[28]	25	57±13	100	44±8	131±49	1.8±2	96	68	6	0	2014
Zellerhoff et al.[6]	39	60±10	100	NA(area 19±5 cm2)	86±29	22.2±6.5	98	66	140±75	2.5	2014
Laish-Farkash et al.[19]	82	63±10.6	76	39.4±6	81±18	30±8.5	95	80.7	12	1.2	2015
Deneke et al.[53]	145	64±10	53	NA	115±36	17±7	99	66	12	2.1	2015
Mahida et al.[27]	374	60±10	70.3	NA	114±42	24±14	99.6**	65	12	0.5	2015
Stabile et al.[54]	180	58±10	78	46±10	113±53	13.1±8.4	98	PAF 73% Persistent 70%	13.9±8.2	0.5	2015
Vurma et al.[23]	327	PAF 63±10 Pers 64.8±8.2	69.7	39±5 44±5	69±22 75±23	14.8±6.6 16.8±6.3	NA	75(PAF)* 52(Persistent)*	6±5	0.6	2016
Rodriguez-Entem et al.[55]	35	57.3±8.6	100	41.2±3.1	79.5±39.3	31.6±8.2	98.6	77.2	16.8±2.8	2.8	2016
Burri et al.[18]	50	58±10	100	23±5	100±25	22±8	100	46(low power settings)	15±4	6	2016
Marai et al.[20]	31	55±13	87	45% nornal 42% mild 13% mod	130±21	22±3	97***	87	15.9±3.6	3.2	2016
Wakili et al.[16]	29	67.1±8.6	100	40.5±6.1	132±37(86.5±24.6 nMARQ only)	31±12	83	72	12.4±9.3	0*	2016
Rosso et al.[17]	36	58.7±10	64	NA	101±26.4	25.9±9.5	100##	78(PAF 82 Persistent 69)	19±2.6	0	2016

* One procedure off AAD**non-PV additional ablation: 13%PAF;27%persistent***13% touch-up ablations# one case of phrenic nerve palsy despite prophylactic stimulation and immediate abortion of ablation, one patient with esophageal lesion in the post-procedure endoscopic examination.## 2.7% touch-ups

the inner aspect of the circumferential ablation line) and atrial loss of capture can be proved (the pace-and-ablate technique)[22] or dissociated PV activity can be shown. Administration of adenosine or pacing of the ablation line is performed at the operator's discretion. Some centers use a different method[16]-[17], where the entire ablation is conducted while the recording circular lasso mapping catheter is positioned distal to the nMARQ™ catheter inside the corresponding PV. Repeated RF applications are delivered through the nMARQ™ poles facing the precise lasso electrodes showing persistent PV potentials until all the local PV electrograms recorded by the lasso catheter are disappeared. Isolation of the left-sided PVs is conducted during atrial pacing from the distal CS catheter whereas isolation of the right PVs are conducted during sinus rhythm or coronary sinus pacing. The endpoint of the procedure is the isolation of all PVs, attested by disappearance of all PV potentials in the lasso catheter within the vein and confirmed by pacing maneuvers.

The nMARQ™ catheter was first used in humans in May 2013, and the first series of patients were reported in 2014. The nMARQ™ catheter was recalled from clinical use in June 2015 due to issues with the thermocouple and reporting of three deaths,of which two were confirmed to be due to esophageal-atrial fistula.[23] The catheter was re-designed and the next prototype is under current evaluation.

Comparison of the efficacy of PVAC® and nMARQ™ for paroxysmal atrial fibrillation (PAF)

PVAC®

Acute Success and Procedural Parameters

Procedural parameters and acute outcomes from single- and multi-center studies are presented in Table 1. Acute procedural success by patient is defined as complete isolation of all targeted PVs. Acute success by vein is defined as the successful electrical disconnection of a targeted PV in which PV potentials are previously demonstrated.

A systematic review by Andrade et al.[24] has summarized 42 publications. Overall, 1162 patients had PVAC® based ablation for PAF and 347 for persistent AF. The average age was 58.5 ± 2.6 years, and 71.7% of patients were male. Average left ventricular ejection fraction was 60.5% ± 4.0%, and the left atrial dimension was 41.4 ± 1.9 mm. For PAF, the average procedure time was 116.9 ± 33.4 minutes, fluoroscopy time was 26.5 ± 9.6 minutes, and the number of PVAC® applications per patient was 25.1 ± 3.4. For persistent AF, the average procedure time was 137.1 ± 29.3 minutes with a fluoroscopy time of 31.6 ±12.4 minutes. Significantly more PVAC® applications were required to isolate common ostia when compared with individual PVs. The data on 1147 patients from 20 studies showed that acute PVI was achieved with the PVAC® alone, without concomitant use of a focal RF ablation catheter "touch-ups", in 98.57% of the patients and in 99.38% of the targeted PVs. Six studies reported the concomitant use of irrigated RF catheter ablation to complete PVI in a median of 5.7% of patients. There was no difference in acute procedural success between patients treated for PAF vs persistent AF. Predictors of failed acute PVI with PVAC® included larger PV size (>25 mm) and increased LA size (>58 mm). Compared to early procedures, centers with extensive experience reported a progressive decrease in procedural time (95 ± 26 vs 74 ± 21 minutes for PAF; 151 ± 50 vs 100 ± 17 minutes for persistent AF), fluoroscopy time (19 ± 9 vs 15 ± 7 minutes for PAF; 30 ± 15 vs 19 ± 6 minutes for persistent AF), and mean number of PVAC® applications per patient (29 ± 7 vs 25 ± 7 applications for PAF; 29 ± 8 vs 23 ± 5 for persistent AF). It should be noted that mean procedure times below 85 min have been reported from several experienced centers for cohorts of mainly PAF patients [Table 1].

The European survey on the efficacy and safety of PVAC®[25] included twenty centers from seven European countries, 2748 patients (77% with PAF). The mean procedure time was 122 min for paroxysmal and 145 min for persistent AF (P = 0.08). Fluoroscopy times (29.4 vs. 38.6 min, P = 0.13) and RF duration (28.3 vs.42.6 min, P <0.001) were shorter in paroxysmal AF. In patients with paroxysmal AF, the pulmonary veins were isolated using the PVAC® in all centers.

Longer-Term Outcome

Long-term success rates for different follow-up times from single- and multi- center studies are presented in [Table 1]. Long-term procedural success was defined as freedom from recurrent AF.

In the meta-analysis by Andrade et al.[24] summary analyses were limited to six studies (283 patients) for 6-month outcomes and 5 studies (272 Patients) for 12-month outcomes. For PAF, six-month freedom from recurrent AF ranged from 77.8% to 84.4%, yielding a pooled estimate of 81.36%. At one year, the pooled estimate for freedom from recurrent AF was limited by significant heterogeneity. For persistent AF, six-month freedom from recurrent AF ranged from 39.1% to 64.0%, yielding a pooled estimate of 54.1%.

In the European survey on the efficacy and safety of PVAC®[25] (2128 patients with PAF, 620 persistent AF) 81% had a structured follow-up defined as routine Holter-ECG after a mean of 11.2 months. The survey found in PAF patients an overall success rate of 82% [median 80%, interquartile range (IQR) 74–90%], with a first procedure success rate of 72% [median 74% (IQR 59–83%)]. In persistent AF, overall success rates were significantly lower with 70% [median 74% (IQR 60–92%)]; P = 0.05) as well as the first procedure success rate of 58% [median 55% (IQR 47–81%)]; (P = 0.001). The overall and first procedure success rates were similar among higher (79.1% and 68.8%) and lower volume centers (79.4% and 72.3%). However, a poorer success rate was reported off antiarrhythmic drugs (AAD) in the lower- volume centers (49.7%) than in the higher-volume centers (60.8%) centers. Further, the success rates were neither dependent on the duration of experience with duty-cycled RFA, which ranged from 1 to 4.7 years, nor with the number of procedures with duty-cycled RFA. There was a correlation between average LA diameter and success rate.

Mulder et al.[26] found that PV anatomy did not have a significant effect on the long-term results; only a tendency to a poorer outcome

Table 3: Phased RF ablation outcomes in comparison with nMARQ

Study	No.patients	Age	Paroxysml AF(%)	Mean LA diameter(mm)	Procedure time(min)	Fluoro time(min)	Additional ablation	Efficacy-acute success(%)	Efficacy-longterm success(%))	F/U duration(mo)
Laish-Farkash et al. [19]	PVAC:93 nMARQ:82	61±10 63±10.6	87 76	38.8±5.4 39.4±6	94±27 81±18	33±13 30±8.5	2 pts in each group were switched to the alternate technique	97 95	79 80.7	12 12

was seen for PVs with diameters>24 mm.

In patients with recurrent AF who underwent a second procedure after PVI by PVAC®, the reconnection rate was 73% of all previously isolated PVs.[40] Balt et al.[56] reported that in almost all patients (98%) with recurrent AF after previous PVAC® ablation at least one PV was reconnected, and all PVs were equally likely to show reconnection. Few studies demonstrated that superior veins were more often affected as compared with the inferior ones.[57] In other studies[58], [59], the highest rate of reconnection was observed for the inferior quadrant of the right lower PV (as opposed to the superior quadrant of the right upper PV with single tip catheters), most likely due to difficulties in appropriately engaging this vein with the PVAC® and early branching of this vein. As suggested by Rademakers et al.[59], optimal electrode-tissue contact with all electrode pairs may be more difficult to achieve due to the circular design of the PVAC® catheter.

Evaluation of the new PVAC Gold catheter is currently in progress. The post-market GOLD AF registry (ClinicalTrials.gov ID: NCT02433613) is a prospective, multi-center, single-arm, non-interventional and open-label registry, designed to evaluate the performance and describe the day-to-day clinical use of PVAC Gold phased RF PV ablation catheter. This study is intended to track minimum of 1000 patients in approximately 50 sites in Western, Central Europe, Israel and South Korea between April 2015 and February 2019. The primary endpoint is to estimate phased RF ablation mid-term success rates at 12 month follow-up. Success rates will be estimated as time to first AF recurrence and/or left atrial flutter.

nMARQ™

Acute Success and Procedural Parameters

Procedural parameters and acute outcomes from single- and multi-center studies are presented in Table 2.

For PAF, the average procedure time range from 69±22 to 114±42 minutes in large series of nMARQ™ patients[23], [27]; Fluoroscopy time range from 14.8±6.6 to 24±14 minutes.

Acute success rates in isolating the PVs using nMARQ™ catheter alone range from 83 to 100%. Some centers report the need for additional ablations using a single tip ablation catheter in order to achieve complete PV isolation[16]-[17], [20], [28], especially after confirmatory mapping with an additional diagnostic mapping catheter reveals persistent PV conduction.

Wakili et al.[16] described this problem in 19 out of 29 nMARQ™ patients. These patients underwent further ablation, which still failed to achieve PVI in 5 of the 29 (17%) nMARQ™ patients, mainly due to significant temperature rise in the esophagus (mainly in the posterior wall in the area of the left inferior PV) and technical limitations in reaching the right inferior PV. This need of an additional mapping catheter for confirmation caused a significant prolongation of the procedure duration compared with a conventional point-by-point PVI.

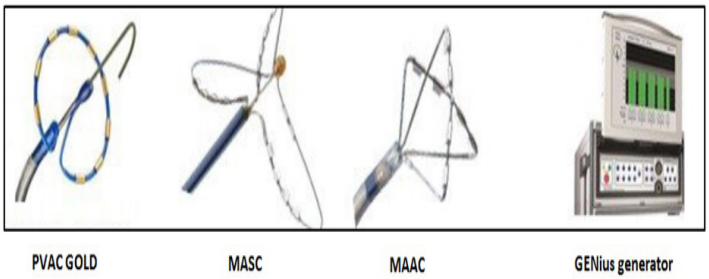

Figure 1: The phased RF catheter family (The circular multipolar pulmomary vein ablation catheter - PVAC GOLD; The multiarray septal catheter – MASC™; The multiarray ablation catheter - MACC™; and the The GENius™ Multi-Channel RF Ablation Generator). Image courtesy of Medtronic Inc.

Similarly, Rosso et al.[17] showed that procedure times were shorter for patients with paroxysmal AF ablated with circular catheters but 11% of patients assigned to nMARQ™ ablation procedure required point-by-point ablation to close gaps left within the antral circular ablation lines done with the circular ablation catheter. This group[29] and the group of Scaglione et al.[28] have shown that a lack of correlation between a diagnosis of PVI based on the local nMARQ™ electrograms and those recorded from a more distal Lasso catheter may be seen in up to one-third of PVs, a finding that could conceivably influence the long term results.

Mahida et al.[27] reported in a large multicenter study that RF times were longer for the superior veins as compared to the inferior veins. Ablation at non-PV sites was performed at the operating physician's discretion. Among patients with paroxysmal AF, 87% had PV isolation only while 13% had ablation at non-PV sites. Among persistent AF patients, 73% patients had PV isolation only while 27% had ablation at non-PV sites. Of these patients who had ablation at non-PV sites, 74% patients had ablation with nMARQ™ only. Of the 17% patients who had ablation with nMARQ™ and conventional catheters, 82% required ablation in the coronary sinus.

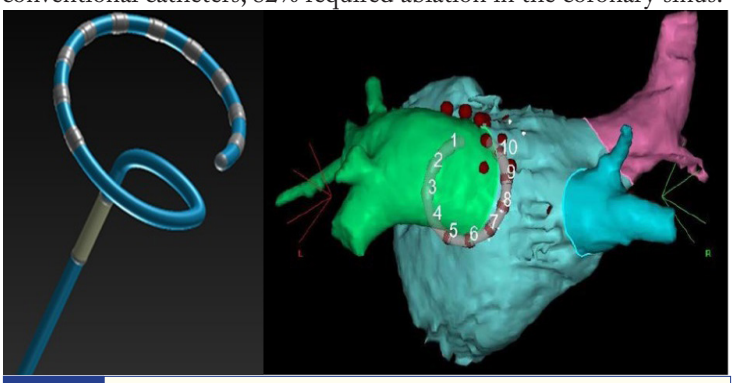

Figure 2: The nMARQ catheter – first generation

Longer-Term Outcome

Long-term success rates for different follow-up times from single- and multi- center studies are presented in [Table 2]. Long-term procedural success was defined as freedom from recurrent AF.

In PAF patients 66-87% of patients are free of recurrent AF after a follow-up duration of at least 1 year with single procedure and no AADs [Table 2]. Longer follow-up of 19±2.6 months in a recent study that included 36 patients after nMARQ™ ablation showed 82% success rate for PAF and 69% success rate for persistent AF ablation using nMARQ™ catheter with 2.7% touch-ups.[17]

Reports of esophageal injury in up to 50% of the patients[30]-[31] and cases of esophago-pericardial fistula[27],[32], have recently prompted caution to titrate energy from 20–25 W unipolar RF down to a maximum of 15 W unipolar RF.[33] Burri et al.[18] evaluated long-term outcomes of 50 AF patients after PVI using nMARQ™ with these low power settings. Follow-up was 15 ± 4 months (range 7–23 months). There were no cases of esophageal fistula or stroke during follow-up. AF recurred in 27 (54%) of patients. Of these, 63% underwent a redo procedure. Reconnections of at least two

PVs were documented in all patients (2 PVs in 2 patients, 3 PVs in 6 patients and 4 PVs in 9 patients). Reconnections were found in the left superior PV in 16 patients (94%), in the left inferior PV in 14 patients (82%), the right superior PV in 13 patients (76%) and the right inferior PV in 15 patients (88%). Isolation was achieved in all cases by point-by point RF application. There were no cases of atypical flutter or atrial tachycardia. Our group also used these low-power settings and reported the following long-term results:[19] 80.7% of nMARQ™ patients were free of AF after 1 year from index procedure, although 28% were on AADs. 4.8% patients underwent a second PVI, with an overall one-year success rate of 87.7% (26% on AADs).

Head to head comparison

Acute Success and Procedural Parameters

Our group has compared the efficacy of PVAC® vs. nMARQ™ in 175 consecutive symptomatic AF patients with a follow-up duration of at least 5 months [Table 3]. 93 patients underwent PVI using PVAC® (age 61.4±9.8 years; 60% male, 13% persistent AF) and 82 patients underwent PVI using nMARQ™ catheter (age 63.2+10.6 years; 67% male, 24% persistent AF).[19]

Procedure and radiation times were 94±27 and 33±13 min for PVAC® and 81±18 and 30±8.5 for nMARQ™ (P = 0.0008 and P = 0.18), respectively. The number of applications and the total burning times were 20±7 and 19±6.7 minutes for PVAC® and 16+5.6 and 11+4 minutes for nMARQ™ (P <0.0001 for both), respectively. Thus, the fluoroscopy time was comparable for both procedures, but the mean procedure time was longer for PVAC®. This could be explained by several causes: (1) the learning curve of PVAC® (which entered the market before nMARQ™ and required a transformation from point-by-point to circular ablation skills) was longer. We showed in our study that there were longer procedure and fluoroscopy times in the first 10 PVAC® patients but not in the first 10 nMARQ™ patients; (2) PVAC® patients had longer total burning time; and (3) the lack of 3D mapping using PVAC®, as opposed to nMARQ™.

The number of applications and the total burning time were shorter for nMARQ™ vs. PVAC®. This probably stems from the difference in technology: while the signals can be seen during ablation with nMARQ™ and ablation can be stopped at any time after PV signals are gone, with PVAC® the signals cannot be seen during ablation and an application of one minute each is the rule. It might be as well that the need to switch off pair 1 or 5 in PVAC® patients is a potential reason for more RF lesion applications that are needed for full circumferential line of ablation.

Because of the different size of the PVAC® and nMARQ™ catheters, their different flexibility, and the built-in ability of the PVAC® catheter to be straightened over the wire and enter the PVs, as opposed to nMARQ™, PV isolation was assessed by different methods for these catheters: In PVAC® patients we proved isolation by pacing and recording from inside and outside the vein and the coronary sinus, respectively, to prove entrance and exit block. The acute success rate was 97%. In nMARQ™ patients, the entrance and exit block technique was used in patients with very large PVs that the whole catheter could be entered into, as in Lasso catheter (17% of nMARQ™ patients). In smaller veins, RF delivery was continued until no PV signals were observed at the antrum (along the inner aspect of the circumferential ablation line) and atrial loss of capture could be proved (the pace-and-ablate technique) [22], [34] or dissociated PV activity could be shown (83% of nMARQ™ patients). The success rate was 95%.

In two nMARQ™ patients with small atria and small PVs and in two PVAC® patients with large PVs, the procedure failed with no ability to isolate the PVs; switching to the alternative technology was successful with 100% acute success rate. Three observations were noticed during the ablation procedures that were different when using these two ablation techniques and comparing them head to head: 1) we observed more arrhythmogenic activity at PV ostia during ablation in sinus rhythm when using the PVAC® vs. nMARQ™ system (95% of PVAC® patients vs. 36.5% of nMARQ™ patients) (P = 0.0001). We used a different definition for 'triggers'/'arrhythmogenic veins' than the one used in previous studies[35], and the long-term significance of this observation still needs to be resolved—perhaps with some similarity to the junctional response during slow pathway ablation in AV-node re-entrant tachycardia.[36] This difference in arrhythmogenic activity during ablation could stem from the presence of a guidewire in the PVAC® system or the different energy used: unipolar in nMARQ™ vs. the addition of bipolar application in PVAC®.

2) Another observation was RF application-induced coughing, probably when the PVAC® catheter was located unintentionally a few mm inside the PV, enforcing immediate cessation of the application. Using nMARQ™, the catheter was almost always out of the vein due to its larger diameter and the ability to inspect minor catheter movements by CARTO 3D mapping system; thus, we hardly ever observed this phenomenon with nMARQ™.

3) In another study comparing these two AF ablation techniques we found that there is no influence of catheter type on pain location during ablation using either PVAC® or nMARQ™.[37] The location of pain during PVI is not catheter dependent but rather a reflection of autonomic nerves physiology.

Longer-Term Outcome

In our study[19] one-year freedom from AF using PVAC® vs. nMARQ™, was 79% and 80.7%, respectively, after one procedure, and 88% vs. 87.7%, respectively, after redo procedures. Thus, we found no difference in 1-year freedom from AF results between the two techniques (despite different acute endpoints). This similar outcome was shown even though the diameter of the spiral array at the distal end of nMARQ™ is larger than PVAC®, indicating ablation on a more antral area. The larger PV isolation should intuitively relate to better clinical outcome, however, this was not shown, although the reduced number of applications and shorter total burning time with nMARQTM vs. PVAC® could be the direct implication of the size difference. Notably, the similar outcome was shown even though the

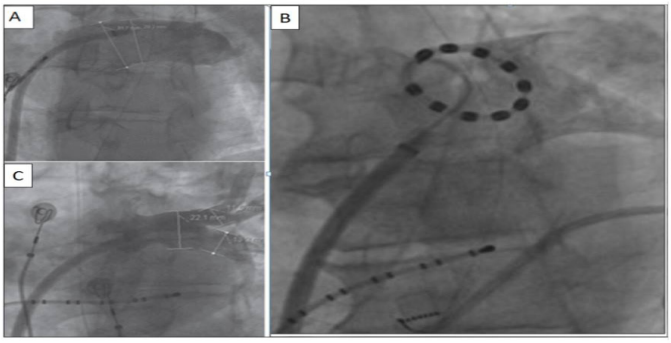

Figure 3: (A) Angiogram of a large left common pulmonary vein; (B) Same vein with an nMARQ catheter in its antrum; as opposed to (C) a normal size left common pulmonary vein.

nMARQ™ group included more patients with persistent AF. This result may suggest a better clinical outcome with the nMARQ™ since persistent AF patients usually have lower rate of freedom from AF after PVI vs. paroxysmal AF patients. [2]

Optional Target Population for Each Catheter

Despite this supposed clinical effectiveness of the nMARQ™ system, the issue of the occurrence of life-threatening esophageal fistulas related to this system is of major concern and requires further investigation.[23], [27], [30]-[32]

Similar to other studies[16], in our study[19] there were two nMARQ™ patients with too small atria and PVs that caused inability to deploy the catheter properly, especially in the right-sided veins. The nMARQ™ procedure was switched to PVAC® and the patients had successful PV isolation. In two failed PVAC® patients due to large PVs and inability to deploy the catheter properly, a redo procedure with nMARQ™ was successful with a better catheter–LA contact and more efficient burnings. Thus, a patient-based pre-ablation anatomy definition is probably warranted for appropriate selection of technology type. Pre-procedure imaging of LA and PVs may guide the operators in choosing the proper circular multi-electrode system: to use PVAC® catheter for smaller LA and PVs and nMARQ™ system for larger LA and larger/common-ostium PVs [Figure 3]. However, it is possible that a more anterior trans-septal puncture may solve that issue of small atria and PVs regarding the nMARQ™ catheter, as well as the introduction of the new nMARQ™ catheter prototype, which is more flexible and with the ability to reach a smaller minimal diameter vs. the first generation catheter. This catheter is under clinical evaluation nowadays.

nMARQ™ should also be considered as the preferred first step approach in cases of combined AF and left atrial flutter and in cases of redo procedures, because of the integrated 3D mapping and the capability of observing the signals during ablation. An important potential benefit of nMARQ™ over PVAC® is the 3D mapping option, which has an advantage in visualization of catheter location in relation to PV ostia, an advantage in voltage mapping of the atrium, an advantage in adding location points of the phrenic nerve route, a potential advantage in reducing fluoroscopy time when using CARTO-MERGE technology, and an advantage in adding lines of ablations outside PV ostium. Thus, nMARQ™ system can also be considered for patients who need additional lines of ablation on top of PVI, in order to save costs by using one catheter only. This suggested approach needs to be proved in future studies.

Conclusions

First generation nMARQ™ may not be suitable for very small atria, but for the rest of the patients undergoing PVI only, it appears faster, and is at least as effective as PVAC®, especially in patients that need electro-anatomical mapping for different indications. A patient-based pre-ablation anatomy definition is probably warranted for appropriate selection of technology type.

The recently introduced PVAC-GOLD catheter and the new prototype of nMARQ™, which is under current clinical evaluation, should be re-evaluated and compared for future patient selection algorithm.

Conflict Of Interests

None.

Disclosures

None.

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The Significance of Troponin Elevation in Atrial Fibrillation

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Abstract

Cardiac troponin assays have provided a significant contribution for the early diagnosis of cardiovascular events. There is significant evidence about the association between the absolute value of elevated cardiac troponin levels with the prognosis of patients with chest pain. However, it is well-known that elevated cardiac troponin levels may occur in situations other than acute coronary syndromes, as it happens with atrial fibrillation. The significance and prognosis of this elevation are not entirely clear.

We review the evidence about the meaning of such elevation in the setting of atrial fibrillation.

Introduction

Atrial fibrillation (AF) is the most common arrhythmia in the population and confers a higher risk of morbidity and mortality.[1] Atrial fibrillation increases the risk of mortality, stroke, heart failure and hospitalizations for cardiovascular causes. Its prevalence increases with patients' age, the presence of coronary artery disease, structural heart disease and elevated cardiac filling pressures, among other phenomena.[2]

Troponin is a protein that plays a role in myocyte contractile function and determination of its exclusively cardiac-specific form that has provided a significant progress for the early diagnosis of coronary events.[3] There is significant evidence about the association between elevated cardiac troponin levels and its absolute value with the prognosis of patients with chest pain.[4],[5] However, it is well-known that elevated cardiac troponin levels may occur in situations other than acute coronary syndromes, as it happens with supraventricular tachyarrhythmias.[6]–[8] The situations previously described, which predispose to the development of AF, could also elevate troponin levels. We shall review the evidence about the meaning of such elevation in the setting of atrial fibrillation.

Biology of cardiac troponins and diagnostic assays

Troponin consists of three subunits (troponin I, T, and C), which, together with tropomyosin, regulate the interaction between myosin and actin filaments of muscle contraction. This complex structure is organized in units called sarcomeres. Troponins are also found as a small free pool that exists in the cytosol, which is about 6% for cardiac troponin T (cTnT) and 3% for cardiac troponin I (cTnI). Troponins within the sarcomere exchange with the cytoplasmic pool.[3],[9]

Key Words

cardiac troponin, acute coronary syndrome, atrial fibrillation.

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All the methods for the quantification of cardiac troponins measure troponin plasma levels. Up to now, all these tests use monoclonal antibodies as specific detection methods.[10],[11] Troponin C does not have cardiac specificity and thus no assays have been developed to measure it.[12] The cardiac isoform of troponin I (cTnI) has a unique post-translational tail of 32 amino acids on the N-terminus. This sequence has made possible the generation of highly specific antibodies without cross-reactivity with other non-cardiac forms.[10] Three genes control cardiac troponin T transcription, generating different mRNA and producing a series of troponin isoforms. Cardiac muscle contains 4 troponin T isoforms, but only one is characteristic of the normal adult heart. During fetal development, cardiac and skeletal TnT are identical. The skeletal isoforms present in the fetal heart are replaced by the adult isoform late during fetal development. Re-expression of fetal forms, which occurs in cardiac and skeletal tissues in response to damage, produced measuring errors with the first-generation troponin assays. This problem was detected and solved once this antibody was replaced by one with high specificity.[3]

All this progress that has been achieved means that every time a method detects elevation of Troponin T or I, we may assure that the cardiac isoform is elevated.

Troponin assays have improved over the past 10 years, and cTn high-sensitivity (hs) assays have been introduced in clinical practice since 2012. High-sensitivity cTn assays have two main differences with the other assays. Firstly, their ability to reliably detect very low troponin levels in plasma, enabling the early detection of troponin release and allowing an earlier diagnosis. Secondly, the absolute coefficient of variation is much lower, which enables the reliable detection of small variations over the time and differentiates chronic elevations from those acute.[4]

Mechanisms of troponin release

The mechanisms of elevated troponin levels in the bloodstream are multiple. Myocyte necrosis produces enzymatic degradation of the internal structures and sustained release of high amounts of troponin. However, as it has been previously mentioned, small amounts of Troponin T and Troponin I are free in the cytoplasm and exchange

with those in the sarcomere. It would be expected that if there is release from this pool that the troponin would be released quickly and that blood levels would fall with rapid washout. The half-life of cTnT and cTnI in the blood is about 2 h. Rapid rise and fall within 24 h may therefore be consistent with release of this pool and reversible myocyte damage rather than myocyte necrosis, where a time-dependent fall over a longer period (4 to 10 days) would be expected because of gradual degradation of myofibrils and release of the troponin complex.[13]

The release of this pool would take place in situations in which the permeability of the cell membrane has been altered. Inflammation could not only alter the permeability of the cell membrane, but also induce necrosis, as it happens in myocarditis. Transient ischemia could also produce the same phenomenon.[14]

Another potential cause of troponin release during ischemia could be associated with cellular release of proteolytic troponin degradation products. Thus, proteolysis to create small fragments could allow these fragments to pass through a cell membrane with normal membrane integrity. Only 15 min of mild ischemia has been shown to cause development of cTnI degradation products.[15] The same mechanism could justify troponin elevation in heart failure with or without myocardial ischemia, and only be associated with elevated filling pressures.[16]

A study by Turer et al. demonstrated that rapid atrial pacing increased troponin levels in patients with and without coronary artery disease, with or without induced ischemia, which could be explained by the release of troponin after excessive myocardial fiber stretching, altering the structure of certain integrins and allowing release of troponin from the cytosolic pool into the bloodstream.[17]

Another potential mechanism of troponin release is normal myocyte cell turnover. Study of the integration of carbon-14 into the DNA of myocardial cells, generated by nuclear bomb testing, has shown that cardiac myocytes regenerate.[18] There is a decrease from 1% annual turnover at the age of 25 to 0.45% at the age of 75 years with approximately 50% of cells exchanged during a normal life span. Whether such low-grade turnover results in release of troponin to the systemic circulation is unknown.

Active secretion of vesicles (blebs) or membrane expression with shedding has been hypothesized to be a mechanism to enable troponin to be released from cardiac cells. These may be released into the circulation without rupture of the plasma membrane. There are also likely to be unknown causes of troponin elevations. It is not known as to why sepsis causes the release of troponin from cardiac myocytes, although heat shock proteins and tumor necrosis factor have been implicated.[19] It is thought that increased troponin levels with renal failure are not related to decreased renal excretion[13], but rather to toxic products, and supply and demand issues probably also play a role. It is also possible that there are low-grade reparative processes compensating for myocyte loss due to various causes.

Prognostic value of elevated troponin levels

Cardiac troponin is a sensitive and specific marker of myocardial damage.[1],[2],[3] Patients with elevated levels of troponin are considered to have an increased risk for major cardiac events.Multiple studies have shown the prognostic significance of minor troponin elevations in multiple cardiac patient populations, such as acute coronary syndromes and heart failure.[20],[21] Furthermore, it appears that even troponin levels that are just above the detection limit significantly influence the risk for future cardiac events even in healthy patients.[22]

In the scenario of AF, van den Bos et al reported that circulating cTnI levels were associated with mortality and major adverse cardiac events in a cohort of hospitalized patients. After adjustment for all baseline variables, minor troponin I elevation as well as a positive troponin I were independently correlated with death (HR: 2.35, 95% CI: 1.17–4.73 for minor elevation and HR: 3.77, 95% CI: 1.42–10.02 for positive troponin I). There was an independent association between the combined endpoint of death/MI and both a minor elevation in troponin I and a positive troponin I (HR: 1.99, 95% CI: 1.05–3.80 for minor elevation and HR: 3.03, 95% CI: 1.24–7.37 for a positive troponin I). Cumulative 3-year survival rates were 78% in the non-detectable troponin I group, 62% in the minor elevation group, and 57% in the positive troponin I group (log-rank $P < 0.001$).[23]

A sub-study of the Randomized Evaluation of Long-Term Anticoagulant Therapy trial (RE-LY), performed in 6189 patients with AF and treated with either warfarin or dabigatran, found that cTnI was predictive of thromboembolic events and cardiovascular mortality, and even after adjustment by potential confounding factors, the risk of stroke or systemic embolism was doubled to fivefold higher for cardiovascular mortality, in patients with the highest quartiles. Hijazi et al. demonstrated that persistent elevation of troponin I was seen in nearly half of the patients in the RE-LY study cohort comprising of patients with anticoagulated AF with ≥1 risk factor for stroke. As compared with none or transient elevation, persistent elevation of this biomarker over 3 months conferred a greater risk of stroke and vascular death over a period of 2 years.[24] Similar results have been shown in the Apixaban for the Prevention of Stroke in Subjects with Atrial Fibrillation (ARISTOTLE) biomarker study .[8] The sub-study results verified that the troponin levels were related to the risk of stroke and death, in a continuous fashion, independent of baseline characteristics and other biomarkers. Consequently, an even larger proportion of patients, 73%, were identified to have detectable levels. During a median 1.9 year period, the annual rates of stroke or systemic embolism ranged from 0.87% in the lowest hs-cTnT quartile to 2.13% in the highest hs-cTnT quartile (adjusted hazard ratio [HR]: 1.94; 95% confidence interval [CI]: 1.35 to 2.78; $p = 0.0010$). Adding hs-cTnT levels to the CHA_2DS_2VASc score improved the C statistic from 0.620 to 0.635 for stroke or systemic embolism ($p = 0.0226$), from 0.592 to 0.711 for cardiac death ($p < 0.0001$), and from 0.591 to 0.629 for major bleeding ($p < 0.0001$)[7]. These results were confirmed in the study by Roldan et al[25], in a stable and chronic anticoagulated AF cohort, whereby increased plasma hs-cTnT levels were associated with an adverse prognosis in AF patients, with regard to cardiovascular events and mortality. Patients with levels above the 50th percentile of the troponin distribution in an AF population had an increased risk of stroke, other ischemic events, and a higher mortality regardless of their risk as estimated by the $CHADS_2$ and CHA_2DS_2-VASc scores.

Elevated levels in patients with AF is a relevant issue, and even more important in those who present with angina pectoris or dyspnea. There are few existing studies that discuss the significance and diagnostic value of cardiac troponins in these patients. The first study evaluating the role of cTnI in AF patients in the acute setting was performed by Parwani et al, who evaluated 354 consecutive patients with the primary diagnosis of AF and clinical symptoms suggestive of myocardial ischemia presenting to an emergency department.[26] Fifty-one patients (14.4%) showed an elevated cTnI with a mean

value of 0.37 μg/L (range, 0.09 – 3.14), 45% underwent coronary angiography, and 6 of these patients (26%) had a significant coronary artery stenosis necessitating coronary intervention. There was no difference in mean cTnI between those with or without coronary artery disease (CAD), p = 0.69. The rest of the patients with elevated cTnI did not undergo coronary angiography because of low pretest likelihood for CAD, and non-invasive testing in these patients was negative. Patients with elevated cTnI complained significantly more often of angina pectoris. The type of AF (paroxysmal vs. persistent) did not have an influence on cTnI level. Multivariable analysis revealed that patients with AF and elevated cTnI showed higher heart rate, lower left ejection fraction, elevated serum creatinine, lower hemoglobin and were more likely to present with angina pectoris. In this setting, cTnI has a low positive predictive value regarding relevant coronary stenosis.

A study by Conti sought to investigate the presence of coronary atherosclerosis and adverse outcomes in patients with AF.[27] Consecutive patients with recent onset AF and without severe comorbidities were enrolled between 2004 and 2013. Patients with a troponin rise or with adverse outcomes were considered for coronary angiography. A propensity score matching was performed to adjust for baseline characteristics. The primary end point was the composite of acute coronary syndrome, revascularization, and cardiac death at 1, 12 month and 10 year follow-up. Of the patients enrolled, 3541 completed the study; 202 (6%) showed troponin rise; and 91 (3%), an adverse outcome. The value > 0.50 ng/L was associated with 55% sensitivity and 75% specificity in detection of critical stenosis and revascularization. In the matching cohort, the OR of troponin rise was 10 (CI, 4-22; p < 0.001). Patients presenting with a recent-onset AF and a troponin rise were more likely to achieve adverse coronary events, both in the short (9%) and long terms (9%), when compared with patients without troponin rise (1% and 1%, respectively; p< 0.001). Overall, during the follow-up of 10 years, 49% of patients with troponin rise who were submitted to coronary angiography underwent revascularization compared with 31% of patients without troponin rise (P< .001).

In contrast, a recent publication by Alghamry et al, reported the results of a retrospective cohort, which included 231 patients who presented with symptomatic AF (chest pain, dyspnea or palpitations) and had serial troponin measurements.[28] Cardiac TnI elevation above standard cut off was not predictive of CAD after adjustment for other predictors (OR 1.62, 95% CI 0.79-3.32. p=0.19). A ROC curve analysis for classification of CAD from cTnI peak was performed, showing an area under the curve value of 0.67 (95% CI 0.58–0.76), that indicates that cTnI peak as a diagnostic test is inadequate in discriminating between those with CAD and those without CAD. However, the highest cTnI concentration value (cTnI peak) was predictive of CAD (OR 2.02, 95% CI 1.02-3.97, p=0.04). Dyspnea on presentation (OR 4.52, 95% CI 1.87-10.91, p=0.001), known coronary artery disease (OR 3.44, 95% CI 1.42-8.32, p=0.006), and ST depression on the initial electrocardiogram (OR 2.57, 95% CI 1.11-5.97, p=0.028) were also identified as predictors of CAD in their cohort.

Our group performed a prospective study where 100 patients were consecutive included with a primary diagnosis of tachyarrhytmia.[6] Mean age was 64 ± 12 years and 59.8% were men. The most common arrhythmia at admission was atrial fibrillation (68%), followed by atrial flutter (16%) and reentrant tachycardia (16%). The results of the first determination of hs-cTnT were positive (> 14 ng/l) in 44.2% of the patients and the second determination, separated by 3 hours, was positive in 50.7% of the cases. The variation between the first and the second troponin levels was 1 (0-5) ng/l, and was > 7 ng/l in 24.6% of the cases, with a clear trend toward higher troponin values in reentrant tachycardias. Four cardiovascular events were reported in 30 days. In all the cases the patients had presented AF and there were no significant differences in hs-cTnT values. We concluded that there is a significant number of patients with supraventricular tachyarrhythmias who present elevated hs-cTnT levels. The association of this elevation with cardiovascular events seems to be very low.

The relationship between troponin elevation and heart rate was also explored in the work by Ulimoen et al. who reported that cTnT levels were significantly reduced both by **β**-blockers and calcium channel blockers.[29] They demonstrated that lowering the heart rate is associated with lower release of cTnT even in patients with permanent AF and heart rates well below 100 bpm, and may potentially challenge the findings of the RACE II study.

All this data is not conclusive about the meaning of troponin elevation in the setting of atrial fibrillation. Perhaps troponin increase is due to AF per se, or is caused by coexistent cardiovascular risk factors or may simply reflect a 'sick heart'. Thus, there is no established explanation for the association between high troponin and stroke.

Conclusions

Cardiac troponins are elevated in a significant proportion of patients with atrial fibrillation that predicts a worse outcome and greater cardio-embolic risk independently of the other known risk factors. Such elevation does not necessarily represent the expression of an ongoing acute coronary event. Future prospective studies with a larger number of patients might clarify this matter.

Conflict Of Interests

None.

Disclosures

None.

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Incorporating Stroke and Bleeding Risk Stratification Tools Into Atrial Fibrillation Management Making Sense of the Alphabet Soup

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Introduction

Atrial fibrillation (AF) is a very common rhythm disturbance, which is increasing in both incidence and prevalence globally. Some estimates predict a doubling in the incidence of and mortality rates related to AF over the next thirty years.[1],[2] These demographic and outcome projections demonstrate the need for the medical community to continue developing effective treatments for AF and the need of clinicians and society to pursue policies that will minimize the negative clinical consequences associated with AF.

Patients with AF often have an impaired quality of life due to a number of associated problematic arrhythmic issues such as tachycardia, bradycardia, loss of AV synchrony and rate irregularity. AF patients are also at higher risk for more deleterious clinical outcomes such as a tachycardia-mediated cardiomyopathy, stroke and death.[3] Cardio-embolic and cryptogenic strokes, many of which are secondary to thrombogenic processes associated with AF, together account for almost 50% of observed strokes.[4] Furthermore, when strokes occur in the setting of AF, they are often more disabling and associated with a higher mortality rate than strokes deriving from other etiologies.[5] AF-related stokes also have significant economic implications. Patients sustaining a stroke in the setting of AF have higher overall index and longitudinal medical costs than do patients with strokes resulting from other causes.[6]

Accordingly, preventing stroke is one of the most important tasks with which the medical community rendering care to AF patients is charged. In this review the importance of performing a thromboembolic and bleeding risk stratification assessment among all AF patients to determine the therapeutic risk: benefit ratios for oral anticoagulant (OAC) therapy will be discussed. This analysis will be followed by a review about how this algorithmic thromboembolic and bleeding risk stratification information can be used directly to determine the proper pharmacologic approach designed to lower stroke rates and minimize bleeding complications among divergent AF patient populations. The manuscript will conclude with a review of the status of global initiatives to create well-developed oral anticoagulation programs.

Key Words
Atrial Fibrillation, Stroke, Risk Stratification.

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Early Oral Anticoagulant Development And Algorithmic Usage In Atrial Fibrillation Patients

Since the isolation of warfarin by Campbell and Paul in the first half of the twentieth century OAC therapy has evolved to become a cornerstone in the treatment of patients with AF to reduce the risk of thromboembolic events, especially stroke.[7] In a number of pivotal trials warfarin was shown to be substantially better than placebo in lowering both stroke rates and mortality rates. In a meta-analysis of these older landmark trials Hart demonstrated an overall 62% relative stroke risk reduction and a 26% relative all-cause mortality risk reduction.[8]

However, the risk for thromboembolic events is quite variable among AF patients. Accordingly, a number of algorithms have been developed in an attempt to clarify more effectively the stroke risk so that the clinical decision-making processes can be tailored to align with individual patient profiles. The two most commonly employed algorithms to define the thromboembolic risk are the $CHADS_2$ and CHA_2DS_2-VASc algorithms [Table 1].[9],[10] Although widely used and clinically valuable, each of these algorithms has a number of limitations. Both were developed among focused patient populations with limited information about subsequent anticoagulation usage, minimal information about the post-discharge methods employed to define clinical outcomes and no original independent external validation.

The $CHADS_2$ And CHA_2DS_2-Vasc Algorithms: Defining The Atrial Fibrillation Patient At Low Risk For A Thromboembolic Event

Although there is overlap in the ability of the two algorithms to define thromboembolic risk, the CHA_2DS_2-VASc algorithm includes more demographic and clinical components to characterize that risk. By including more risk factors into the scoring algorithm for the CHA_2DS_2-VASc score, its developers hoped that it would result in a more accurate risk stratification process by categorizing more effectively patients into low, medium or high risk sub-groups than was possible with the $CHADS_2$ algorithm.

The initial risk stratification requirement, with which clinicians are faced, is the need to correctly define those patients, who are at low risk for a stroke. By accurately characterizing this group one

can identify patients in whom it would be prudent clinically to withhold OAC therapy. To this end, the available data suggest that the overall ability of the $CHADS_2$ score to identify low stroke risk patients is very limited, based on a number of published studies in which a variable stroke rate, ranging from 0.9% to 2.8%, has been reported among patients with a $CHADS_2$ score of 0 [Figure 1].[11]-[15] The ability of the $CHADS_2$ and CHA_2DS_2-VASc scores to predict stroke rates among potentially low risk patients was compared in a study by Coppens.[16] Patients with a $CHADS_2$ score of 0 had an overall annual stroke rate of 1.59%. However, after reclassification of these patients with a $CHADS_2$ score of 0, the resulting CHA_2DS_2-VASc scores in these patients ranged from 0 to 3. Based upon the reclassified CHA_2DS_2-VASc scores, the patients in this study had increasing annual relative stroke risks ranging from 0.84 for a CHA_2DS_2-VASc score of 0, 1.75 for a CHA_2DS_2-VASc score of 1, 2.69 for a CHA_2DS_2-VASc score of 2 and 3.20 for a score of 3. In another study, 25% of the patients with a $CHADS_2$ score of 0 were reclassified as having a CHA_2DS_2-VASc score of 0 or 1 and 43% were reclassified as having a CHA_2DS_2-VASc score of 0 to 2. All of these patients with reclassified CHA_2DS_2-VASc scores of 0 to 2 had a lower thromboembolic event rate than did the patients in the original $CHADS_2$ paper with a $CHADS_2$ score of 0.[9],[10] A subsequent external validation analysis similarly compared the differential ability of the $CHADS_2$ and CHA_2DS_2-VASc algorithms to stratify AF patients at risk for a number of clinical outcomes. In this analysis the CHA_2DS_2-VASc algorithm was better than the $CHADS_2$-algorithm in predicting hospitalization due to thromboembolism, death due to thromboembolism and all cause mortality up to 10 years after the initial risk assessment.[11]

Table 1: Stroke Risk Stratification With the $CHADS_2$* and CHA_2DS_2-VASc# Scoring Algorithms

Risk Factor	$CHADS_2$ Score	Risk Factor	CHA_2DS_2-VASc Score
CHF (recent)	1	CHF, LV Dysfunction	1
Hypertension (history)	1	Hypertension	1
Age > 75 years	1	Diabetes	1
Diabetes	1	Vascular Disease (Prior MI, PVD, Aortic Plaque)	1
Stroke/TIA	2	Female Gender	1
MAXIMUM SCORE	6	Age 65-74 years	1
		Age > 75 years	2
		Stroke/TIA	2
		MAXIMUM SCORE	9

* Gage BF et al. JAMA. 2001;285:2864–70.# Lip GYH et al. Chest 2010; 137: 263-72.

Accordingly, the available data suggest that the CHA_2DS_2-VASc algorithm is a more robust risk stratification tool. Based upon these and other comparative studies, the CHA_2DS_2-VASc score appears significantly more effective than the $CHADS_2$ score in identifying truly low risk patients in whom oral anticoagulation can be avoided.

Oral Anticoagulation Guideline Recommendations For Atrial Fibrillation Patients

The true benefit of a clinically-based algorithm stems from its ability to predict accurately clinical outcomes and secondarily, as a result of its predicative capability, its ability to drive clinical decision-making. Based upon a Markov assessment addressing the potential benefit of anticoagulant therapy among AF patients, Eckman suggested that, when the annual CVA risk is < 0.9%, anticoagulant therapy is not indicated.[17] In this analysis he proposed that the tipping point in favor of recommending chronic oral anticoagulation was found somewhere between an annual CVA risk of 0.9 to 1.7% based upon clinical features, the overall bleeding risk and the selected oral anticoagulant. Accordingly, given the annual stroke rates reported in the original $CHADS_2$ paper, OAC would not be held in any patients. Based upon the annual event rates reported in the original CHA_2DS_2-VASc paper OAC would be held in all patients with a CHA_2DS_2-VASc score of 0; administered to all patients with a CHA_2DS_2-VASc score ≥ 2, assuming that there was no contraindication, and of indeterminate benefit in patients with a CHA_2DS_2-VASc score of 1.

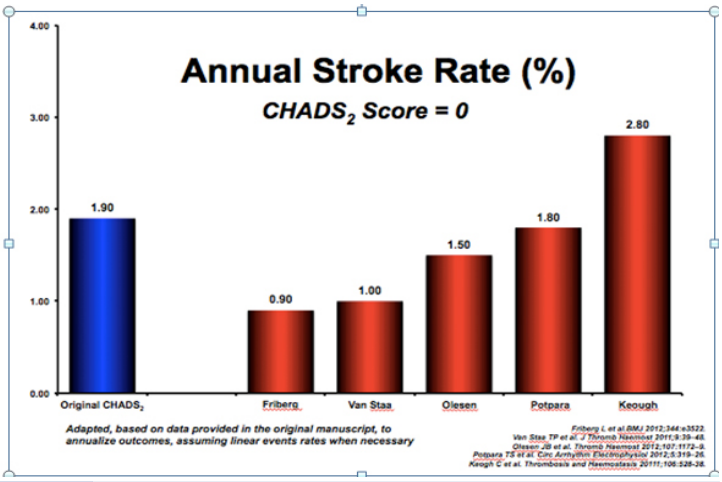

Figure 1: Differential Stroke Risk Factors

On the basis of data derived from studies, assessing the ability of the $CHADS_2$ and CHA_2DS_2-VASc scores to define thromboembolic risk, and statistical analyses, such as those performed by Eckberg, guidelines have been developed by the major cardiovascular and arrhythmia societies to assist clinicians in deciding when to use oral anticoagulant therapy in patients with AF.[18].[19] Accordingly, for patients with a CHA_2DS_2-VASc score of 0 the published ESC and AHA, ACC, HRS guidelines indicate that no anticoagulant therapy is warranted for patients with a CHA_2DS_2-VASc score of 0 while anticoagulation is recommended for patients with a CHA_2DS_2-VASc score ≥ 2 in whom there are no contraindication. Both of these are class I indication recommendations.[18],[19]

Anticoagulation Controversies: Decision-Making In Atrial Fibrillation Patients With A CHA_2DS_2-VASc Score Of 1

Significant controversy persists, however, upon what anticoagulant decisions constitute the best approach among patients with a CHA_2DS_2-VASc score of 1. This is a very important question as the data suggest that between 9.7% and 17.6% of AF patients have a CHA_2DS_2-VASc score of 1.[10],[12],[20],[21] Furthermore, the thromboembolic event rates across published studies with a CHA_2DS_2-VASc score of 1 are quite broad, ranging from 0.5% to 6.6%.[12],[22]-[27]

Based upon the variable thromboembolic event rates observed in patients with a CHA_2DS_2-VASc score of 1, the established guidelines differ slightly in their recommendations for anticoagulant usage in this patient population. The AHA/ACC/HRS guidelines, published in 2014, state that either no anticoagulant therapy or oral anticoagulation treatment "may be considered" for AF patients with a CHA_2DS_2-VASc score of 1.[18] The 2012 ESC guidelines suggest that

anticoagulant usage in this population "should be considered" for AF patients with a CHA_2DS_2-VASc score of 1.[19] This subtle variation in the published guidelines creates a therapeutic conundrum for clinicians when faced with making decisions about anticoagulation in these patients. Four possible options are presented below to help inform and assist clinicians when trying to make these difficult decisions.

The first suggested process focuses upon how the individual risk factors operative in the algorithms are used in clinical practice. Patients suffering from heart failure in the original $CHADS_2$ manuscript had to have a history of a "recent heart failure exacerbation", not just a history of heart failure, to have it included as a risk factor. Hypertension was defined in the original $CHADS_2$ paper to include patients with a "history of hypertension" rather than a specific BP value at the time of enrollment.[9] In the original CHA_2DS_2-VASc manuscript the definitions for hypertension and heart failure were not clearly provided. Additionally the vascular disease risk factor was defined to include patients with a prior myocardial infarction, peripheral artery disease or aortic plaque.[10]

Table 2: Stroke Risk Stratification with the ATRIA Scoring Algorithm

Risk Factor	No Prior CVA	Prior CVA
Age		
> 85 years	6	9
75 - 84	5	7
65 - 74	3	7
< 65	0	8
Female Gender	1	1
Diabetes	1	1
Heart Failure	1	1
Hypertension	1	1
Proteinuria eGFR < 45	1	1
mL/min/1.73m² or ESRD	1	1
MAXIMUM SCORE	12	15

Singer DE et al. J Am Heart Assoc 2013;2:e000250.

The recognized risk factors, which constitute the $CHADS_2$ and CHA_2DS_2-VASc scores are not always employed in clinical practice today in the manner in which they were developed and originally used.[9],[10] Decision-making in all clinical arenas frequently does morph over time as original criteria are often applied in a broader manner. Thus, advancements in diagnostic testing and 'indication creep' may lead to new ways in which these risk factors are defined and used that are very different from those observed in the original studies. Accordingly, the event rates observed among patients with particular risk factors might be very different today than they were when reported in those original studies because of an alteration in the employed definitions. For example, a patient with a positive calcium score, but no history of clinically active coronary disease, may have a very different stroke risk than a patient with a prior MI and significant peripheral vascular disease. Similarly a patient with recent heart failure secondary to a newly diagnosed tachycardia-mediated cardiomyopathy, which resolves with appropriate therapy, may not have the same thromboembolic risk as a patient with a long-standing cardiomyopathy associated with a chronically reduced ejection fraction but no recent heart failure.

This 'indication creep' places the decision-making processes into a more tenuous arena in which the scientific support in the literature is often lacking. Therefore, when clinicians are faced with recommending treatment approaches to patients, a strict application of the original definitions is more likely to yield results in line with those reported by the authors in the original research papers. Thus, an important first step for clinicians, contemplating anticoagulation decisions among AF patients with a borderline CHA_2DS_2-VASc score, is to ensure that the manner in which the point assignments are created is in alignment with the original definitions as presented in the published literature. Acknowledging the limitations of the risk stratification algorithms and the guidelines upon which they were built can sometimes inform the decision-making process in a borderline patient.

Table 3: Bleeding Risk Stratification with the HAS-BLED Algorithm

Risk Factor	Score
Labile INR's	1
Bleeding Predisposition	1
Age > 65 years or Frailty	1
Hypertension with SBP > 160 mm Hg	1
Prior CVA	1
Bleeding Risk Drugs or Alcohol Abuse	1,2
Abnormal Renal or Hepatic Function	1,2
MAXIMUM SCORE	9

Pisters R et al. Chest. 2010;138:1093–1100.

Secondly, it is important to realize that each of the risk factors, which comprise the $CHADS_2$ and the CHA_2DS_2-VASc scores, may not be equal in their predictive accuracy. For example, in the van Staa study, the thromboembolic risk associated with hypertension was proportional to the level of observed hypertension.[13] The annual stroke risk increased proportionally from a baseline relative risk of 1 for a systolic BP of 120 mm HG to a greater than 4-fold risk among patients with a systolic BP > 180 mm HG. Similarly in two other studies the thromboembolic risk among patients in whom female gender, heart failure, diabetes, vascular disease and hypertension constituted risk factors was similar.[11],[12] However, in both of these studies those patients with a prior CVA/TIA or advanced age had a substantially higher stroke risk during follow-up, indicating that these two risk factors were associated with a higher risk than other risk factors [Figure 2]. In the Olesen study patients with combinations of risk factors had different risk profiles. For example patients with a CHA_2DS_2-VASc score of 2 in whom the two risk factors were female gender and heart failure had a relatively low risk with a hazard ratio for thromboembolic complications of 1.32 while patients with hypertension and heart failure had a substantially higher hazard ratio for thromboembolic complications of 4.19.[11]

Accordingly, assessment of the particular risk factors present may result in allocating patients to higher or lower risk groups based upon the specific risk factors. For example, a 43-year-old male patient with mild, well-controlled diabetes may have a different thromboembolic risk than a 74 year old male patient without other risk factors even though they both have a CHA_2DS_2-VASc of 1. Similarly an asymptomatic 48-year-old patient with minimal CAD detected on a CT angiogram may have a different risk than a patient of the same age with advanced coronary, peripheral vascular and cerebrovascular disease despite having the same CHA_2DS_2-VASc score. Therefore, differential assessment of the risk factors and judicious application thereof may be beneficial in borderline patients.

A third consideration for clinicians, when trying to decide on whether to pursue oral anticoagulant therapy among AF patients with a CHA_2DS_2-VASc score of 1, is to assess for the presence or absence of other risk factors potentially associated with an enhanced thromboembolic risk. Although the $CHADS_2$ and CHA_2DS_2-VASc scores have become commonly used in the clinical sphere, based upon published guidelines, there is data suggesting that other clinical features, not included in these algorithms, can also help to clarify the thromboembolic risk. In some studies the presence of obstructive sleep apnea (OSA) in AF patients has been associated with a higher risk for an ischemic CVA.[28] In addition, effective treatment for OSA in a number of studies has resulted in a reduction in that risk.[29] Although the data to date are conflicting, a number of studies have suggested a relationship between the degree of renal dysfunction and the thromboembolic risk in AF patients.[30],[31] In the Loire Valley Atrial Fibrillation Project and the Tiawanese database PVD was associated with a higher thromboembolic risk among AF patients.[32],[33] Genetic and racial differences may also be associated with different thromboembolic risks. Several recent studies have noted a higher stroke risk among Asian and African-American patients with AF after adjusting for other risk factors.[33],[34] A number of anatomical considerations also may impact the stroke risk. For example, in one study, left atrial size correlated inversely with rates of stroke-free survival.[35] In the SAVE and SCD-HeFT studies higher rates of stroke and thromboembolic event rates correlated with greater degrees of left ventricular systolic dysfunction.[36],[37] Among patients with a borderline CHA_2DS_2-VASc score, assessing for the presence or absence of additional thromboembolic risk factors might prove advantageous.

Finally, although the $CHADS_2$ and CHA_2DS_2-VASc scores have become a standard by which oral anticoagulant decisions are made, they are not the only algorithms available to assess risk. The ATRIA stroke risk score was developed by analyzing a population of patients participating in the Kaiser Permanante patient database [Table 2].[38] This score dichotomized patients into groups with and without a prior stroke then further analyzed patients based upon additional age and limited renal function breakouts while continuing to assess for the other characteristics included in the $CHADS_2$ and CHA_2DS_2-VASc scoring algorithms. Patients assessed with the ATRIA score have a total maximal potential score of 15 points. By using a larger number of operative clinical characteristics it was hoped that there might be greater risk differentiation possibilities.

Table 4: Bleeding Risk Stratification with the $HEMORR_2HAGES$ Algorithm

Risk Factor	Score
Hepatic or Renal Disease	1
Alcohol Abuse	1
Malignancy	1
Age > 75 years	1
Decreased Platelet Count or Function	1
Rebleeding Risk	2
Hypertension w/o Adequate Control	1
Anemia	1
Genetic Risk Factors	1
Elevated Falling Risk	1
Prior CVA	1
MAXIMUM SCORE	12

Gage BF et al. Am Heart J. 2006;151:713–9.

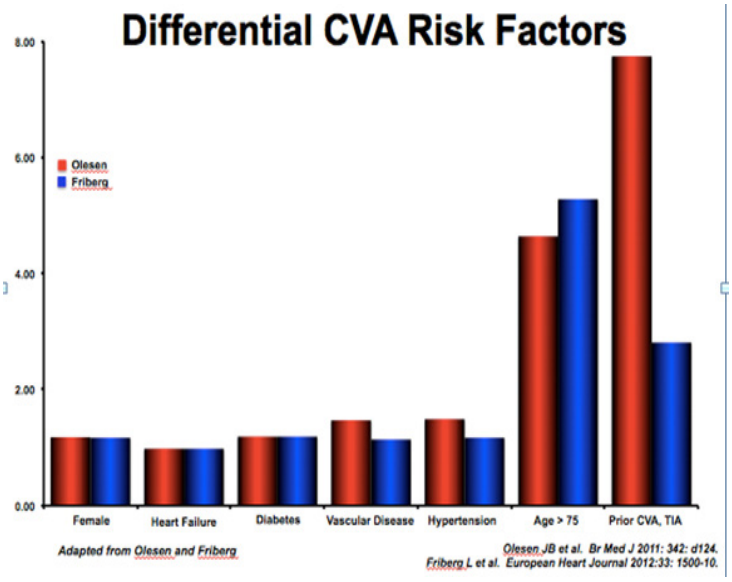

Figure 2: Variability of Stroke Risk among Patients with a $CHADS_2$ Score of 0

When one compares risk stratification schemas, based on data presented in the original papers, 46.7% of the patients in the ATRIA manuscript were defined as low risk using the ATRIA stroke risk score (score of 0-5 points) vs. 49.7% of the patients in the $CHADS_2$ manuscript in whom that risk was defined as low by the $CHADS_2$ score (score of 0-1 points) and only 7.6% of the patients in whom the risk was defined as low by the CHA_2DS_2-VASc score (score of 0 points).[9],[10],[38] In each of these publications the annual stroke rates for these low risk groups were respectively 0.63%, 0.88% and 0.04%. Although patients with a low CHA_2DS_2-VASc score, according to the original classification schema, have the lowest stroke event rate, unfortunately only 19.3% of the patients classified by the CHA_2DS_2-VASc algorithm are characterized as low risk.

Therefore it appears difficult to identify a truly moderate sized low risk CHA_2DS_2-VASc patient group in whom the use of an OAC may not be needed. Presumably the patients within the 'high' risk CHA_2DS_2-VASc group (80.7% of the patients) have a variable risk, which might be better differentiated into low and high risk groups by using the ATRIA stroke risk score. When these groups were classified in Singer's study into low risk patients with an annual thromboembolic event rate per 100 person-years <1% only 1.5% of these events were identified using the $CHADS_2$ score, 9.9% using the CHA_2DS_2-VASc score and 14.0% using the ATRIA stroke risk score.[38] In a similar study, in which the ATRIA stroke risk algorithm was employed, 46.2% of the patients were characterized as low risk based upon an annual thromboembolic risk rate of 0.4-1.31%.[39] The ATRIAL stroke risk score therefore may help to separate patients with a borderline CHA_2DS_2-VASc score into groups in whom OAC can be safely avoided and groups in whom treatment with an OAC would be clinically beneficial.

These findings beg the question about when and under what circumstances the ATRIA stroke risk score should be used. To this end the ATRIA stroke risk score appears most beneficial when applied to patients with a CHA_2DS_2-VASc score of 1 in whom there are concerns about serious bleeding to identify patients in whom the perceived thromboembolic risk seems to be very low so that one can avoid OAC therapy. Conversely, when the bleeding risk is felt to be

acceptably low, the CHA_2DS_2-VASc score alone should be sufficient to determine the thromboembolic risk and dictate therapy. Caution should be exercised in using the ATRIA stroke risk score in isolation to avoid oral anticoagulation under-treatment.

In summary, when faced with providing patients with a borderline CHA_2DS_2-VASc of 1 with a recommendation to maximize clinical benefit, using the definitions in a strict and cautious manner; realizing that the individual risk criteria are different in their predictive capacity; considering other less well recognized clinical risk factors and using an alternative scoring tool as a supplement may allow one to reach a better clinical decision endpoint.

The Role Of Bleeding Risk Assessment In Atrial Fibrillation Patients

Complete patient risk assessment also requires that one perform an analysis of the bleeding risk. A number of scoring tools (e.g. HAS BLED, ATRIA bleeding risk score, $HEMORR_2HAGES$, etc.) have been proposed to define the bleeding risk among AF patients [Table 3]-[Table 5].[40]-[42] The thromboembolic and bleeding risk factor algorithms overlap somewhat but to an incomplete degree. Unfortunately the predictive accuracy of all of these algorithms to identify patients at high risk for a major bleeding event is limited, as defined by the low c-statistic values.[43] In direct comparisons and meta analyses the HAS-BLED score has had a better predictive accuracy than either the ATRIA Bleeding Risk Score or the $HEMORR_2HAGES$ score.[44],[45] Accordingly HAS-BLED has become the standard algorithm to be used when attempting to define the bleeding risk in AF patients in whom oral anticoagulant therapy is being considered.

After determining the thromboembolic and bleeding risk rates one must then render a decision on whether to initiate or withhold anticoagulant therapy. Although bleeding is certainly a problematic clinical issue and major bleeding a serious clinical concern, ordinarily cerebral ischemic events, whether they are embolic, thrombotic or hemorrhagic, are frequently life-altering events with more negative clinical impact than most non-cerebral bleeding events. In one study among elderly AF patients at risk for both an embolic CVA and significant bleeding the quality adjusted life year benefit was significantly better among the patients treated with anticoagulation when compared to those in whom no anticoagulation was administered.[46] In the Swedish National Discharge Registry (HDR) Friberg demonstrated that the net clinical benefit favored oral anticoagulation in almost all AF patients except for those with a very low ischemic stroke risk (i.e. CHA_2DS_2-VASc score of 0) or a very high bleeding risk.[47]

Based upon the available information the default decision should be directed toward chronic anticoagulant therapy. Therefore, rather than precluding a decision to anticoagulate patients with an elevated CHA_2DS_2-VASc score, an elevated HAS-BLED score should lead to a focused approach directed at reducing the associated bleeding risk. Efforts to control blood pressure; limit alcohol use and provide for a stable environment in which the fall risk is minimized should be undertaken. A critical assessment of the potential benefit associated with concomitant usage of antiplatelet agents and non-steroidal anti-inflammatory agents should be performed. The existence of consistently elevated or labile INRs might lead one to recommend that a NOAC be used in place of warfarin. Accordingly, the bleeding risk scores, when elevated, should not be used to avoid anticoagulation, but alternatively, should be used to inform the management decision-making process toward a focus upon the modification of associated bleeding risk factors.

Table 5: Bleeding Risk Stratification with the ATRIA Bleeding Algorithm

Risk Factor	Score
Hypertension	1
Prior Hemorrhage	1
Age > 75 years	2
Anemia	3
Significant Renal Disease (eGFR < 30 mL/min or Dialysis	3
MAXIMUM SCORE	10

Fang MC et al. J Am Coll Cardiol 2011;58:395–401.

The Global Atrial Fibrillation Oral Antricoagulation Reportcard

Given the overall benefit of chronic oral anticoagulant therapy among AF patients in preventing thromboembolic events, especially stroke, OAC should be standard practice in the clinical arena for patients with an appropriately defined risk in whom there are no contra-indications. Similarly the use of oral anticoagulants among patients with a low thromboembolic risk should not be undertaken in most clinical scenarios. Unfortunately the available data on oral anticoagulation usage rates and patterns among AF patients suggests that practice patterns do not align with these recommendations.

In a study performed among patients with a $CHADS_2$ score >1, selected from the National Cardiovascular Data Registry PINNACLE program between July 2008 and December 2009, Chan observed an overall rate of anticoagulant usage of only 55% with a range from approximately 25% to ~ 80%.48 In another study, evaluating patients in the UK with a history of AF, 39.7% of patients with a CHA_2DS_2-VASc score > 2 and 39.5% of patients with a $CHADS_2$ score > 1 were not receiving appropriate OAC therapy. During a 12-month follow-up, anticoagulated patients had statistically lower CVA (OR: 0.60, CI: 0.45-0.81) and death (OR: 0.54, CI: 0.38-0.75) rates, $p < 0.001$.[49]

Among patients enrolled in the large international "Global Anticoagulant Registry in the FIELD (GARFIELD)" registry, guideline-driven oral anticoagulation decisions did not appear to be commonplace.[50] In patients with $CHADS_2$ and CHA_2DS_2-VASc scores > 2 only 62.0% and 59.3% of patients respectively received oral anticoagulant therapy. Unfortunately many low risk patients (i.e. 42.5% of patients with a $CHADS_2$ score of 0 and 38.7% of patients with a CHA_2DS_2-VASc score of 0) were administered oral anticoagulant therapy, exposing them to a bleeding risk not in general justified by the presently available data. KAKKA

Inappropriate oral anticoagulation therapy in AF patients, when not indicated because of a low thromboembolic risk, and the failure to initiate anticoagulant therapy in at risk AF patients, when indicated by established guidelines, both constitute a failure to deliver care according to defined quality directives. Clinicians individually and organizations systemically should work together to put into place processes, which ensure the initiation and maintenance of therapeutic approaches that align with established standards of care. By doing such we will improve the likelihood of advancing better clinical outcomes.

Summary

Atrial fibrillation is a common medical problem, which is expected

to increase globally both in incidence and prevalence, given an aging population that has a higher prevalence of clinical problems associated with its development. Stroke is an unfortunate and perhaps the most devastating complication observed among patients with AF. Effective thromboembolic risk stratification and the employment of therapeutic interventions to minimize that risk in patients at risk can result in substantial health and socio-economic benefits.

For most patients the CHA_2DS_2-VASc score permits clinicians to define effectively the thromboembolic risk. The available data suggests that it is better than the $CHADS_2$ score, especially when trying to identify low risk patients. For patients on either side of the risk-benefit spectrum with either a CHA_2DS_2-VASc score of 0 or > 2 the therapeutic decision-making process is usually rather simple in the absence of anticoagulation contraindications.

However, therapeutic controversies concerning long-term oral anticoagulation therapy exist. For borderline patients with a CHA_2DS_2-VASc score of 1 additional considerations (e.g. analyzing the particular components of the individual risk factors, weighing the individual thromboembolic event rates associated with each of the defined risk factors, including additional risk factors in the assessment equation or using a supplemental risk sore algorithm [e.g. the ATRIA stroke risk score]) may result in a more informed and hopefully better clinical decision.

Similarly, for patients with a high bleeding risk the performance of a bleeding assessment enhances the decision-making process. For most AF patients, with a CHA_2DS_2-VASc score for whom oral anticoagulation is recommended, the risk: benefit analysis will favor the employment of oral anticoagulation. For many if not most of those patients with an augmented thromboembolic and bleeding risk, careful consideration and modification of an associated lifestyle activity and/or alternative pharmacological anticoagulation options is a requisite part of the patient engagement process. In a small number of at risk patients the risk: benefit analysis will result in a clinical decision to avoid oral anticoagulation.

Perhaps the most important component necessary to facilitate addressing effectively this issue at the individual and societal level is the realization that existing scenarios in place to render clinical decisions have failed to establish a high degree of adherence to established practice guidelines. When practicing in situations without established and effective processes, clinicians often fail to provide best-in-breed thromboembolic risk decisions to their patients. In some cases the decisions create unnecessary bleeding risk when oral anticoagulants are inappropriately recommended. In other scenarios they fail to mitigate the thromboembolic risk when oral anticoagulants are not given to patients in whom the guidelines recommend that they be administered. Accordingly, clinicians and healthcare organizations should hold themselves individually and collectively responsible to ensure better clinical outcomes. They should work together to establish, within their institutions, systemic processes, which will augment the likelihood that excellent clinical outcomes will manifest. By addressing these issues at the individual and societal level we adhere to the ethical tenets of our profession; improve the quality of life as experienced by our patients and advance the overall health of our regional and global communities.

Conflict Of Interests

None.

Disclosures

None.

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Stroke Prevention For Patients With Atrial Fibrillation: Beyond The Guidelines

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Abstract

Atrial fibrillation (AF) is the most common serious heart rhythm disorder and is associated with an increased risk of ischemic stroke. This risk can be moderated with oral anticoagulation therapy, but the decision to do so must be balanced against the risks of bleeding. Herein, we discuss three emerging areas where more high-quality evidence is required to guide risk stratification: 1) the relationships between the pattern and burden of AF and stroke 2) the risk conferred by short episodes of device-detected "sub-clinical" atrial fibrillation (SCAF) and 3) the significance of AF that occurs transiently with stress (AFOTS), as is often detected during medical illness or after surgery.

Introduction

Atrial fibrillation (AF) is the most common serious heart rhythm disorder, with a lifetime incidence of 1 in 4 for patients >40 years of age.[1] AF is a major cause of death and disability, as it is associated with a 4-5 fold increase in the risk of ischemic stroke.[2] In patients with AF, oral anticoagulation (OAC) therapy can reduce the risk of stroke by about two-thirds and the risk of all-cause mortality by approximately one-quarter, but is associated with an increased risk of bleeding.[3], [4] Risk stratification is important to identify patients with AF who can benefit from OAC therapy. There are, however, several common clinical scenarios where guidelines do not yet provide direction for stroke prevention; or do so based on limited high-quality evidence.

AF Burden and the Risk of Stroke

Current AF guidelines recommend risk stratification, to estimate the risks of stroke and bleeding and offering OAC to patients who have a favorable risk-benefit profile.[5]-[7] The risk of stroke and bleeding are estimated based on the patient's age and comorbidities; typically using the CHA_2DS_2-VASc score for stroke[8]-[12], and the HAS-BLED score for major bleeding.[13]-[15] Current guidelines do not consider the pattern of AF (paroxysmal, persistent and permanent), nor the burden of time that a patient spends in AF when estimating the risk of stroke and whether or not to offer patients OAC .[5]-[7]

Emerging evidence suggests that the pattern, frequency and duration of episodes of AF (also known as arrhythmia burden) may influence stroke risk. A large analysis of more than 6500 aspirin-treated patients from the ACTIVE-A and AVERROES trials suggested a clear gradient of increasing risk of stroke/systemic embolism (SE) from paroxysmal to persistent to permanent AF. In this study, which included rigorously adjudicated outcomes, annualized ischemic rates of stroke/SE rates were 2.1, 3.0, and 4.2% respectively, with an adjusted hazard ratio (HR) of 1.83 (95% CI 1.43-2.35; P < 0.001) for permanent vs. paroxysmal AF and 1.44 (95% CI 1.05-1.98 P = 0.02) for persistent vs. paroxysmal AF.[16] The concept of differing risk according to AF pattern is further supported by a report from the Fushimi AF registry that demonstrated that sustained (permanent or persistent) AF was independently associated with a higher incidence of stroke/SE as compared to paroxysmal AF (non-OAC users: HR 2.2, 95% CI 1.3–3.7; P<0.01 and OAC users: HR 1.7, 95% CI 1.1-2.9; P=0.03).[17] Owing to observations of increasing risk of stroke/SE with increasing AF burden, some authors have proposed that embolic risk be estimated on the basis of refined algorithms that consider both the burden of AF and patient characteristics.[18], [19] Such schemata represent an emerging area of research, but require further prospective validation before they can be used clinically.

In the meantime, it should be stressed that the presence of paroxysmal AF does NOT obviate the need for OAC in patients with additional stroke risk factors. In the pooled ACTIVE-A and AVERROES analysis, the 5 year rate of stroke among patients with paroxysmal AF was approximately 10% - this is well above our current threshold to consider treatment with OAC.[16] Another group of patients of interest are young patients without additional stroke risk factors who have persistent or permanent AF, which may place them at increased risk of stroke and other adverse neurological outcomes.[20], [21] Approximately 10-15% of patients with AF may not have any additional stroke risk factors, but still have some risk of stroke.[22] Such patients are currently being randomized to receive aspirin or 15 mg of rivaroxaban once daily in the BRAIN-AF trial (NCT02387229) to determine if stroke (clinical and covert) as well as cognitive decline can be prevented through the use of OAC.

Key Words

Atrial fibrillation, subclinical, stress, stroke.

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Subclinical Atrial Fibrillation (SCAF)

Given the current widespread use of continuous long-term cardiac monitoring, it is now recognized that many patients have evidence of short-lasting AF, without recognizable symptoms. This phenomenon has been termed subclinical atrial fibrillation (SCAF), and was first described in studies of pacemaker patients, such as ASSERT, TRENDS and MOST, where it was initially given the more descriptive term "atrial high-rate episodes (AHRE)".[23]-[25] SCAF does not simply mean asymptomatic AF, which could encompass AF that is permanent. Arrhythmias referred to as SCAF must also be short-lasting, be detected only with long-term continuous monitoring, and not captured on routine surface ECG.[23], [26]-[29] The concept is that short-lasting AF detected after many weeks of monitoring represents a low overall burden of AF, which appears to convey an increased risk of stroke/SE, albeit lower than would be expected in otherwise similar patients with clinical AF.[23], [25]

The management of patients with SCAF is much less clear. High quality evidence for treatment benefit is lacking. The Relationship Between Daily Atrial Tachyarrhythmia Burden From Implantable Device Diagnostics and Stroke Risk (TRENDS) study was among the first to suggest that SCAF was associated with an increased thromboembolic risk, although these were prospective observational study included some patients with clinical AF.[24], [25] The increased stroke risk associated with SCAF was confirmed in The Asymptomatic Atrial Fibrillation and Stroke Evaluation in Pacemaker Patients and the Atrial Fibrillation Reduction Atrial Pacing Trial (ASSERT), which reported exclusively on patients without a known history of clinical AF.[23] In this study, SCAF was associated with an increased risk of new clinical AF (HR 5.56, 95%CI 3.78-8.17; P<0.001) and of ischemic stroke/SE (HR 2.49, 95%CI 1.28-4.85; P=0.007). However, among patients with an average CHADS2 score of 2, the annual risk of stroke was only 1.3%; far lower than would be expected in similar patients with clinical AF [Table 1].[9]

Where it is generally accepted that SCAF is associated with an increased risk of stroke, the decision to anti-coagulate patients with SCAF is not straightforward. Despite the assertion of some experts that patients with SCAF and additional risk factors for stroke are high risk and merit OAC, clinical practice varies.[23], [30]-[36]

There are several reasons why patients with SCAF might not derive the same risk-benefit from OAC as similar patients with clinical AF. First, the reported thromboembolic rates in patients with SCAF are low compared with patients with clinical AF who have otherwise similar risk profiles (Table 1).[9], [23], [25] Second, the Randomized trial of atrial arrhythmia monitoring to guide anticoagulation in patients with implanted defibrillator and cardiac resynchronization devices (IMPACT) was stopped for futility.[37]This study was designed to test the hypothesis that initiation and withdrawal of OAC guided by continuous ambulatory monitoring of the atrial electrogram would improve clinical outcomes by reducing the combined rate of stroke, systemic embolism, and major bleeding as compared with conventional clinical management.[33] Third, it is important to recognize that observational data have failed to show a temporal relationship between SCAF and stroke in the majority of patients.[25], [29], [38], [39] For example, in an analysis of the ASSERT trial, only 8% of patients had SCAF detected in the 30 days prior to their stroke/SE. Furthermore, 16% of patients with SCAF and ischemic stroke/SE did not have any SCAF detected prior to their stroke/SE.[29] Similarly, in the TRENDS study, 73% of patients who experienced a stroke/SE had zero AF burden in the 30 days prior to their event.[40] These findings, in particular, raise the possibility that stroke/SE in patients with AF may occur secondary to pathophysiologic mechanisms other than the classically hypothesized construct of a minimum of 24 to 48 hours AF leading to atrial stasis, clot formation and subsequent SE.[41] Fourth, the trials that established the benefit of OAC for stroke prevention in AF were comprised predominantly of patients with sustained AF or high burdens of paroxysmal AF [3], [4], and data suggest that patients with paroxysmal AF may be at lower (albeit still significant) risk of stroke, as discussed in the previous section. The burden of SCAF has also been identified as a possible risk factor for stroke. In the TRENDS study, as compared to patients without AF, patients with <5.5 hours of SCAF were not at increased risk of stroke/TIA/SE (HR 0.98, 95% CI 0.34-2.82; p =0.97, but there was a trend towards increased risk in patients with >5.5 hours of SCAF (HR 2.2, 95% CI 0.96-5.05; p=0.06).[25] In an analysis of data from the ASSERT study, the risk of ischemic stroke/SE was found to be increased with episodes of SCAF as short as 6 minutes in duration (RR 1.77, 95% CI 1.01-3.10; p=0.047) and the relative risk reached as high as 4.96 (95% CI 2.39-10.3; p<0.01) with episodes >24 hours in duration.[23] It is conceivable that on a spectrum of risk, SCAF could fall lower than paroxysmal AF and below a threshold at which the benefits of stroke prevention from OAC are outweighed by the risks of bleeding. Even assuming that OAC confers the same relative risk reduction for stroke in patients with SCAF as compared to those clinical AF, the lower absolute risk of stroke may have an important impact on the risk-benefit ratio and cost-effectiveness of OAC. As a result, clinical practice remains divided regarding the treatment of SCAF. At least two randomized clinical trials are underway to address the use of OAC for patients with SCAF, including Apixaban for the Reduction of Thrombo-Embolism in Patients With Device-Detected Sub-Clinical Atrial Fibrillation (ARTESiA, NCT01938248) and Non-vitamin K Antagonist Oral Anticoagulants in Patients With Atrial High Rate Episodes (NOAH, NCT02618577).

Table 1: Comparison of annualized event rates in patients with clinical AF, according to Gage et al., and SCAF, according to Healey et al.[9], [23]

	Rate of Ischemic Stroke/ Systemic Embolism (%/year)	
$CHADS_2$ Score	Clinical AF	SCAF
1	1.9	0.56
2	2.8	1.29
>2	4.0-12.5	3.78

Atrial Fibrillation Occurring Transiently with Stress (AFOTS)

Uncertainly surrounds the approach to stroke prevention for patients who experience AF occurring transiently with stress (AFOTS). In patients without a history of the arrhythmia, AF is often observed for the first time in the setting of an acute stressor, such as medical illness or surgery, typically while the patient is undergoing continuous surface ECG monitoring. Physicians frequently do not prescribe OAC therapy when it is judged that AF may have occurred due to a potentially reversible precipitant.[6], [42]-[45]

It is not known whether a presentation of AFOTS occurs secondary to a reversible cause and is ultimately benign, or is simply

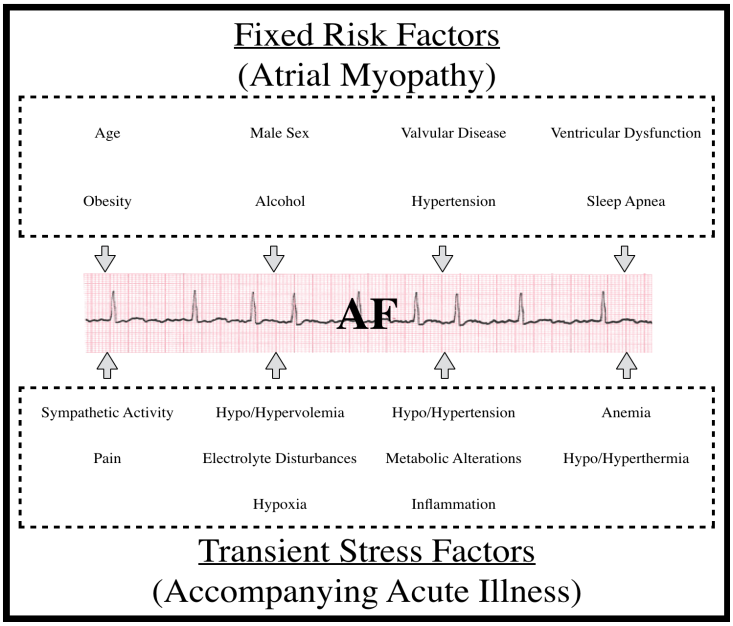

Figure 1: **Pathophysiological Factors implicated in Atrial Fibrillation Occurring Transiently with Stress (AFOTS).**

the first documentation of paroxysmal AF and is therefore associated with an increased risk of stroke.[46] Major guidelines do not currently make recommendations for OAC or for post-discharge screening for recurrent AF in patients who experience AFOTS.[5]-[7] Moreover, more recent guidelines have acknowledged that we are lacking in data to direct the long-term management of patients with AFOTS.[6]

It can be conceptualized that during an episode of AFOTS, there is interplay between fixed and transient arrhythmogenic factors [Figure 1].[44],[47]-[57] Traditional risk factors for AF are present in many acutely ill patients, and may have led to the development of AF-promoting electro-anatomical alterations in atrial tissue.[48],[50] This substrate has been termed atrial myopathy.[57],[58] In the setting of acute stress, such as accompanies acute medical illness or surgery, multiple additional and potentially provoking acute factors come into play.[51]-[56] What remains unknown is to what degree an episode of AFOTS represents a predisposition for recurrence of AF (and therefore a risk of stroke, heart failure and death).

AFOTS occurs frequently (incidence 4-44%) in the setting of acute illness.[56],[59]-[83] AFOTS has been shown to occur with many medical illnesses, including local and systemic infections, myocardial infarction, hyperthyroidism, lung disease and venous thromboembolic disease. In patients admitted to general medical wards and intensive care units, AFOTS is common across a wide variety of conditions. The incidence of AFOTS has been reported to range from 5-44% in sepsis[60], [66]-[74], 4-18% in acute pulmonary syndromes (e.g. pneumonia, exacerbation of chronic obstructive pulmonary disease and pulmonary embolism)[75]-[80] and 10-25% in hyperthyroidism.[81],[82] AFOTS is also common in post-surgical patients. Here, the incidence of AFOTS is approximately 1% for all surgery, 8-10% in vascular surgery, 9-14% in colorectal surgery, 10-35% in thoracic surgery and 18-50% in cardiac surgery.[84]-[96] Across the literature, the incidence of AFOTS tends to be higher in prospective studies. This likely originates from the fact that detection of AFOTS usually requires continuous monitoring and active surveillance facilitates recognition of this intermittent arrhythmia. The incidence also tends to be higher in critically ill patients. This could be a reflection of an increased propensity for AFOTS with more severe illness or simply a reflection of more intensive rhythm monitoring.

Some data exist on the recurrence of AF following AFOTS, but these are limited to retrospective study designs and rely on opportunistic diagnosis of AF through non-systematic follow-up methods. A recent publication from the Framingham Heart Study investigated long-term AF outcomes after diagnosis during a secondary precipitant (i.e. AFOTS). AFOTS precipitants included surgery, acute myocardial infarction, acute infection, acute alcohol consumption, thyrotoxicosis, acute pericardial disease and acute pulmonary syndromes. In this study, patients with AFOTS had an AF recurrence rate of 42% at 5 years. This was similar to the 59% recurrence rate of AF for patients in the cohort whose first presentation of AF was not in the setting of AFOTS (i.e. incident paroxysmal AF). Stroke risk (HR 1.13, 95%CI; 0.82-1.57; P=0.45) and mortality (HR 1.00, 95%CI 0.87-1.1.5; P=0.95) did not differ between those with AFOTS and those with incident paroxysmal AF.[97] A retrospective study using a United States Medicare 5% sample investigated long-term outcomes following development of AFOTS during sepsis. Recurrence of AF after discharge was ascertained through health care claims using International Classification of Diseases (ICD-9) codes. In this study, incidence of AF recurrence at one-year following sepsis hospitalizations was 44% in AFOTS patients. This was significantly higher than patients who did not have AFOTS during sepsis (7.7%, p<0.001). Compared with patients with no AF during sepsis, those with AFOTS during sepsis had greater 5-year risks of ischemic stroke (5.3% vs. 4.7%, HR 1.22, 95%CI 1.10-1.36), and death (74.8% vs. 72.1%, HR 1.04; 95%CI 1.01-1.07).[98] Gialdini et al. reported on a 1,729,360-person retrospective cohort study of surgical patients who experienced AFOTS. Recurrence of AF after discharge was ascertained through health care claims using ICD-9 codes. Even though ICD-9 coding may lack sensitivity for AF detection, the investigators found the one-year rate of recurrent AF after an episode of AFOTS associated with non-cardiac surgery to be 37%. This was higher than the rate of new AF diagnosis in patients without AFOTS (1.5%). At 1 year after hospitalization for non-cardiac surgery, cumulative rates of stroke were 1.47% in those with perioperative AF and 0.36% in those without AF (HR for all stroke = 2.0, 95%CI 1.7-2.3; HR for embolic stroke = 4.9, 95%CI 3.5-6.7).[84]

Where the three above studies provide a strong signal that AFOTS is associated with a risk of recurrent AF and stroke, they have important limitations that greatly impair their sensitivity for ascertaining recurrent AF. Thus, they have likely underestimated the rate of AF recurrence after AFOTS. First, none of these studies systematically investigated AF recurrence. Not all participants in these studies would have been subject to the same post-AFOTS monitoring strategy and it is likely that many were not subject to any monitoring at all. Therefore, study populations are heterogeneous and subject to bias towards lower rates of AF recurrence. Second, by relying on opportunistic diagnosis of AF, these studies are more likely to miss a substantial proportion of asymptomatic or unrecognized AF. Consequently, where the specificity for the diagnosis of recurrent AF is reasonably high, the ability to rule out AF is much more limited. Third, the most sensitive technology that would have been employed in either study would have been a 48-hour Holter monitor – a tool that is less sensitive as compared to the best technologies that are available currently, which includes patch ECG monitors that can be

worn for 14 or more days and the implantable loop recorder.[99],[100] It is also important to note that because these studies did not employ a prospective and systematic strategy for monitoring for recurrent AF, they are therefore unable to offer clinicians any guidance on post-discharge rhythm monitoring for patients who manifest AFOTS. Prospective studies with systematic and sensitive screening are required to better define the recurrence rate of AF after AFOTS.

Take home messages

• Clinical guidelines for stroke prevention in patients with atrial fibrillation do not currently take pattern and duration of arrhythmia into account as part of risk stratification. More recent studies show that these factors may be important and further research is required to develop risk stratification schemata that incorporate clinical characteristics and arrhythmia burden.

• Where subclinical atrial fibrillation (SCAF) is associated with a risk of stroke and systemic embolism, the benefit of oral anti-coagulation in this patient group is not established and the results of ongoing clinical trials are awaited to help direct their management.

• Atrial fibrillation is often detected transiently in the setting of an acute, reversible stressor, such as a medical illness or surgery (AFOTS). AF recurs by 5 years in about half of these patients. However; the true rate may be under-estimated, as most studies used relatively insensitive methods to detect recurrent AF. Further studies employing prospective screening strategies that are both systematic and sensitive are required to better define recurrence rates and to guide management with respect to strategies for detection of recurrent AF and/or provision of prophylaxis against stroke.

Conflict Of Interests

None.

Disclosures

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Use of Barbed Suture for Wound Closure in Electrophysiology Device Procedures

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Introduction

Electrophysiology devices include pacemakers, implantable cardioverter defibrillators and loop recorders (CIED). These devices are usually implanted surgically into the subcutaneous space. The surgical wound is then closed by primary intention in multiple layers using various suture materials. A good approximation of the incision is needed to reduce the risk of wound dehiscence, infection or hematoma. The QuillTM Device (Quill Surgical Specialties Corporation, Reading, PA) is a barbed suture often used to close surgical incisions after gynecologic and orthopedic procedures [Figure 1]. Barbed suture use in these surgical fields is reportedly associated with faster wound closure, increased cost-effectiveness and uniform distribution of tension across the suture line.[1],[2] The latter being less likely to lead to complications of dehiscence and hematoma.[2]

The use of barbed suture in EP device procedures has not been reported. We investigated the effectiveness of this suture on wound closure in patients after CIED procedure to ascertain whether these sutures may have an advantage in device implant procedures.

Methods

To assess the usefulness of this suture material during CIED we retrospectively compared the closure success and complications in patients undergoing CIED at SUNY Downstate from January 2006 – May 2011 (without Quill sutures) and June 2011 - July 2014 (with Quill sutures). A single operator was involved in all implants. In addition to oral antibiotics for 5 days all the patients received IV antibiotics peri-procedurally, which were either cefazolin 1-2 gm or clindamycin 600 mg. The breakdown by the type of the procedure is shown in [Table 1].

We have identified charts of 413 patients who underwent CIED (de-novo, upgrades and replacements) in our institution. Data was collected based on demographics (age, gender) and presence of infection in the 3-month post operative period. The primary outcome was closure success and pocket infection/dehiscence within 3 months of CIED.

Key Words
CIED, barbed suture, device implantation.

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Results

After the procedure, 413 patients were followed up in 3 months. Barbed sutures (Quill Surgical Specialties Corporation, Reading, PA) were used in 229 patients, and non-barbed sutures were used in 184 patients. In both groups pocket closure was successful. There was a non-significant trend toward a lower infection rate with barbed versus non-barbed suture 1.31%, vs 1.63% p= 0.78 [Figure 2].

Subgroup analysis demonstrated that out of the 3 infected barbed sutured wounds, all infections occurred in women and no barbed sutured wound infection was found in men. Out of the 3 infected non barbed sutured wounds, 2 infections occurred in men and 1 in a woman. But, additionally, out of the 3 infected barbed sutured wounds, 2 infections occurred in individuals younger than 65 while 1 occurred in an individual older than 65. Likewise, for the 3 non barbed sutured infected wounds, 2 infections occurred in patients younger than 65 while 1 occurred in a patient older than 65. Hence, patients under 65 years of age had higher infection rates.

Discussion

Our study shows similar rates of infection in barbed and non-barbed sutures. Varied results have been reported in prior studies. Some suggested that the use of barbed sutures is associated with decreased rates of infection compared to traditional sutures. Others found no difference in the infection rate, cosmesis and dehiscence relative to conventional suture.[5],[7],[8] Barbed sutures allow for a uniform distribution of tension across the suture line, [Figure 1] which is posed to decrease wound dehiscence and hematoma.[2] This may particularly be useful for CIED procedures since the bulk of the implanted device may cause tension during wound closure. In our casual experience these sutures do extremely well in closing wounds in patients following device extractions in which significant skin necrosis and infection require wide margin resection. Barbed suture eliminates the need for knot tying, which allows for faster and lesser wearisome wound closure, and may decrease the risk of glove perforation for the operator during knot tying. Finally, our infection rates 1.63% were similar to previously published ones. The national average (1.61%),[4] confirmed the safety and usefulness of this suture material for wound closure during CIED procedures.

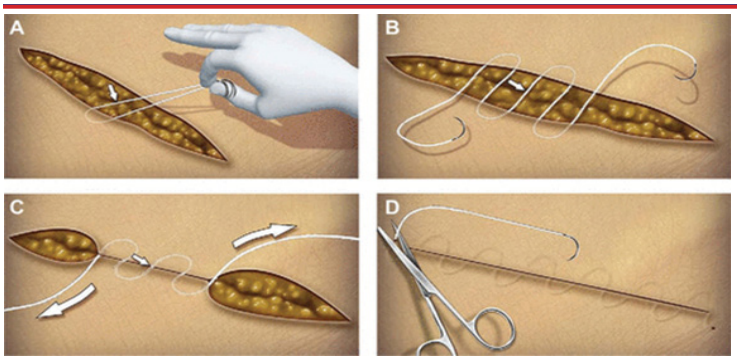

Figure 1: Displays how barbed suture is used to close surgical wounds[3]

Table 1: Breakdown of CIED procedures.

Procedure Type	Barbed suture	Non-Barbed suture	P
ICD	35.3 %	39.8 %	NS
PM	28.2 %	27.0 %	NS
CRT	17.9 %	17.3 %	NS
Upgrade	11.9 %	12.8 %	NS
Generator change	5.8 %	2.6 %	NS
ILR	.2 %	.51 %	NS

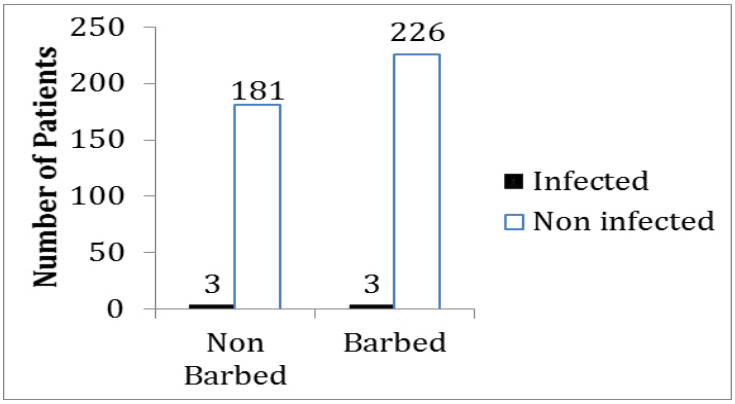

Figure 2: The infection rates.

Conflict Of interests

None.

Disclosures

None.

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Letters to Editor

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Rhythm Control for Post-Operative Atrial Fibrillation. Still A Promising Future?

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Abstract

Gillinov et al., (N Eng J Med. 2016; 374:20,1911-21) investigated the outcome of two strategies for managing post-operative atrial fibrillation (POAF) rate versus rhythm control. The trial was multicenter trial conducted in 23 centers in the US and Canada. The intervention for patients in the rate-control group was medications with a goal of HR <100b/m, where the rhythm-control group was treated with amiodarone ± rate slowing agent, and electrical cardioversion was given if AF persisted for 24-48 hours after randomization. The trial end point was hospital length of stay (LOSHOSP) within 60 days after randomization. POAF occurred in 33% of patients. The LOSHOSP was similar in both groups (median, 5.1 for rate control days and 5.0 days for rhythm control group, respectively; P=0.76). The rates of death (P=0.64) or overall serious adverse events (24.8 per 100 patient-months in the rate-control group and 26.4 per 100 patient-months in the rhythm-control group, P=0.61), including thromboembolic and bleeding events did not show statistical significant differences. The authors concluded that both treatment strategies did not offer a clinical advantage over the other. We discussed how these results changed the working guidelines for managing POAF as the methodological limitations that underline the need for further investigations.

Summary

In the recently published guidelines for the management of atrial fibrillation (AF) rate control strategy for post-operative atrial fibrillation (POAF) plus anticoagulation was given level of evidence B, class II a.[1] Moreover the Canadian Cardiovascular Society (CCS) Atrial Fibrillation (AF) Guidelines Committee recommended that POAF could be managed equally with rate or rhythm control strategies.[2] Both guidelines changed in reference to a recently published randomized controlled trial by Gillinov et al., where the authors did not find significant difference in their primary and secondary end points, the former end point was the length of hospitalization within 60 days after randomization,[3] the potential side effects of antiarrythmicss and cardioversion were beyond favoring this strategy over rhythm control. According to Mann et al., 2007 when AF causes life-threatening deterioration in hemodynamics, emergency cardioversion should be done, irrespective of the AF duration. Electrical cardioversion should also be considered also with hemodynamic instability that is not life threatening.[4]

The guidlines mentioned that asymptomatic POAF would be managed with rate control as a first choice, however Gillinov, put similar preferences for rate and rhythm control, the authors ignored the results of hemodynamically unstable patients and did not define a protocol to exclude them, we noted that the authors of the mentioned trial did not mention anything about the symptoms.[1],[2]

Gillinov, did not subdivide the patients according to post-operative cardiac dimensions and functions which could greatly influence the outcome, they also did not consider prior structural heart disease. There is recent data suggests that rhythm control would provide better outcomes in selected subgroups of heart failure patients.[5] Moreover the atrium account for for 25% of end diastolic volume in, a minimum effect will be noted when AF develop, but marked reduction in the cardiac output observed in case of impairment of diastolic filling by mitral stenosis.[6] The latter effects are more pronounced with tachycardia. Cessation of cardiac output in POAF referred to loss of atrial systole, augmentation of pulmonary capillary wedge pressure and increased valvular regurge.[7]

Finally, Giilinov did not report any complication for electrical cardioversion and side effects of antiarrhythmic were not great as claimed in their hypothesis to support favoring rate control.

The trial recruited total of 2109 patients from 24 centers in the US and Canada, on average only 88 patients per center, with POAF incidence 33%. We believe that a larger extended trial that incorporate the cardiac output and functions parameters, excluding hemodynamically unstable patients, longer term follow up with subgroup analysis could come with some interesting results.

Key Words

POAF, rate control, rhythm control.

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Conflict Of interests

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Disclosures

None.

Acknowledgment

To all remembers of CT surgery, Heart hospital, Hamad medical corporation.

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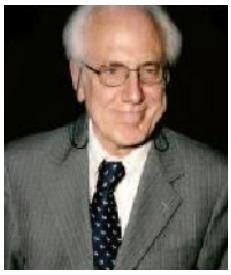

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