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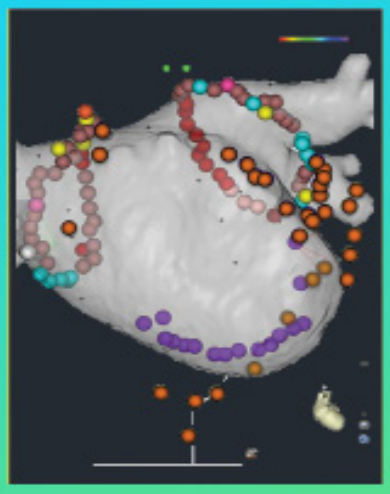

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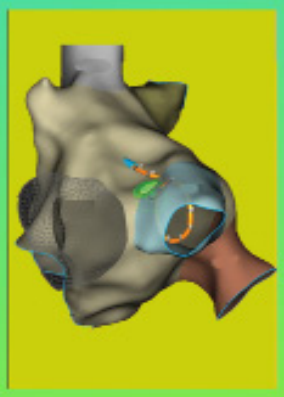

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JAFIB® Journal of Atrial Fibrillation

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Editorial

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Wading through the dangers of COVID-19...

Journal of Atrial Fibrillation (JAFIB)

Apr - May 2020

Issue 6

Volume 12

Dhanunjaya (DJ)Lakkireddy
MD, FACC, FHRS
Editor-in-Chief, JAFIB

Dear Colleagues

Welcome to the Volume12/Issue-6 of the Journal of Atrial Fibrillation. The Journal extends its heartfelt sympathies to many unsung healthcare heroes who lost their lives while saving the lives of many others who were affected by COVID-19. As the world slowly tries to unlock itself from the COVID-19 isolation and tries to establish a reasonable sense of normalcy, the second wave looms at our doorstep as a cruel reminder. We learnt so many things from this unprecedented global pandemic. The entire humanity had to relearn how it conducted business on many fronts. Online meeting platforms have become integral part of our professional and personal lives. On a personal level this hiatus in my life gave a better perspective to the things that used to miss on the personal front. Evening dinners and the weekend togethers with family which typically got shorted by many meetings and travel, were back on the calendar giving me more family time. I am sure it was the same for all of you.

Electrophysiology services rebooting has been a slow but definite process. The Tri-society document on EP reboot has been timely in navigating this process. Building patient confidence while maintaining highest level of safety through aggressive testing and appropriate isolation of positive cases should continue for this process to be successful. Many continued medical education programs have been cancelled and many more are in the process. Our reliance on online learning tools has significantly increased and will continue so.

We lost three important people in electrophysiology this past few weeks – Hein JJ Wellens, Jiang Ming Li and Eduardo Sosa. Hein JJ Wellens, the pioneer in Cardiac Electrophysiology lost his battle to cancer in the Netherlands. Many building blocks of knowledge that helped EP evolve to be the most robust sub-specialty of cardiology were laid down by him. A person who touched many lives with kindness, friendship and played the role of a true global ambassador for Heart Rhythm Society was Jiang Ming Li who lost his life to sudden cardiac arrest. Eduardo Sosa in San Paulo quietly explored the fifth chamber of the heart, the pericardial space in his pursuit of solving the Chagasic Ventricular Arrhythmia. He taught the world how to enter and explore the pericardial space when there is no fluid. Subsequently this work inspired us to use a long micropuncture needle to minimize access related complications. Their contributions to the EP world were different and yet impactful in so many ways. I personally crossed paths with all of these three amazing individuals on several occasions and they will be remembered fondly. We should pause for a moment and appreciate our colleagues who are shaping the field in many ways. If you have not done it already, in the next four weeks take time to thank ten colleagues of yours for what they do everyday to keep our work move forwards.

In the current issue of the journal we have many excellent papers ranging from the role of yoga in heart failure patients through the use of high definition mapping in atrial fibrillation ablation. I once again thank all the editorial team members and the reviewers for their contributions to the continued success of JAFIB. I also dedicate this issue to all the health care workers around the world who are working in the frontlines of our continued battle against COVID-19.

JAFIB Memoriam

Journal of Atrial Fibrillation

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IN MEMORIAM

Hein J.J. Wellens, MD, Ph.D.
13-Nov-1935
to
9-June-2020

Henrick Joan Joost Wellens, Emeritus Professor of Cardiology, was born November 13, 1935 in The Hague, and passed away on June 9, 2020 in Mastricht, His cardiology training was under the tutelage of Professor Dirk Durrer at the Cardiology Department of the University of Amsterdam. Durrer had begun epicardial mapping studies in humans with Wolff Parkinson White syndrome in this period. Wellens completed doctoral thesis there on the subject of " Electrical stimulation of the Heart in the study and treatment of tachycardias' in 1971 This work started his journey to seminal contributions in clinical electrophysiology of both supraventricular and ventricular tachycardias. He described his methods of programmed electrical stimulation for initiation of ventricular tachycardia and its termination by electrical stimulation in landmark articles in the seventies and they are still in routine clinical use today.

Wellens became Professor and Head of Cardiology at the University of Maastricht, The Netherlands and completed his career there remaining as Emeritus Professor of Cardiology till his death. He was known as a remarkable and accessible teacher, training electrophysiologists from all over the world, many of whom are eminent leaders of our field today. He was awarded the Pioneer in Cardiac Pacing and Electrophysiology Award of the North American Society of Pacing and Electrophysiology in 1995 and the Distinguished Teacher Award in 2000. He was later knighted for his contributions by the Queen in The Netherlands. His scientific interests focused on the physiology of tachycardias and antiarrhythmictherapies. He was widely published author of original articles, book monographs and remained a globally travelled lecturer and teacher till his passing. He leaves behind his wife Inez and four children Floor, Willimijn, Maarten and Jooske.

Sanjeev Saksena
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Professor of Medicine & Past President, North American Society of Pacing and Electrophysiology, Warren, New Jersey (USA)

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Confirmation of Pulmonary Vein Isolation with High-Density Mapping: Comparison to Traditional Workflows

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Abstract

Pulmonary vein isolation (PVI) is the cornerstone of atrial fibrillation (AF) ablation. Yet tools and techniques used for confirmation of PVI vary greatly, and it is unclear whether the use of any particular combination of tools and techniques provides greater sensitivity for identifying gaps periprocedurally. It has been suggested that the use of a high-density mapping catheter, which enables simultaneous recording of adjacent bipolar EGMs in two directions, may provide improved sensitivity for gap identification. Anonymized, acute procedural data was prospectively collected in AF ablation cases utilizing various workflows for confirmation of PVI. Post-hoc analysis was performed to evaluate the incidence of gaps detected by different diagnostic catheter technologies, including a high-density mapping catheter and circular mapping catheters (CMCs), and common techniques such as pacing the ablation lines. A total of 139 cases were included across three subgroup analyses: 99 cases were included in an indirect comparison of three mapping catheter technologies, revealing gaps in 36.7%, 38.9%, and 81.8% of cases utilizing a 10-pole CMC, 20-pole CMC, and a high-density mapping catheter, respectively; a direct comparison of diagnostic catheter technologies in 18 cryoballoon ablation cases revealed residual gaps in 22.2% of patients identified by high-density mapping which were missed previously with the use of a 3.3F CMC; in 22 cases utilizing a technique of pacing the ablation lines, high-density mapping identified residual gaps in 68.2% of patients. This proof of concept analysis demonstrated that the use of a high-density catheter which records orthogonal bipoles simultaneously, appears to improve acute detection of gaps in PVI lines relative to other commonly utilized techniques and technologies. The long-term impact of ablating these concealed gaps remains unclear. Further study, including direct comparison of diagnostic catheter technologies in a randomized setting with long-term followup, is warranted.

Key Words

Atrial Fibrillation, Pulmonary vein isolation (PVI), High density mapping.

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Introduction

Pulmonary vein isolation (PVI) is the cornerstone of atrial fibrillation (AF) ablation, but the precise methodology used for confirming this endpoint varies greatly across operators. Circular mapping catheters are the most commonly used tool for confirming PVI, and bidirectional block is widely regarded as the optimal

endpoint. Assessment of entrance block is relatively simple, but confirmation of exit block presents technical challenges, requiring confirmation of local capture within the pulmonary vein while avoiding locations which result in far-field superior vena cava or left atrial appendage capture[1-3]. These technical challenges may make it difficult to obtain objective confirmation of bidirectional block in all patients.

In an effort to augment the assessment of durable PVI, some have advocated for protocols incorporating waiting periods, adenosine, and/or isoproterenol. While dormant conduction can be unmasked using these techniques, randomized trials have provided conflicting results in terms of long-term efficacy[4-6]. Additional techniques have been proposed, including pacing the ablation lines around the pulmonary veins to confirm loss of pace capture. Results of these studies appear promising, but procedural efficiency may be sacrificed[7, 8]. Cryoballoon ablation was later introduced as a simplified method for creating continuous lesions. This methodology has its own limitations however, such as the uniform delivery cryoablation therapy around segments of the pulmonary veins which have varying myocardial thickness. Confirmation of PVI in these cases is commonly achieved using a circular mapping catheter which is subject to the same limitations previously identified.

A limitation common to all bipolar electrogram recordings is directional sensitivity: larger amplitudes are recorded when the wavefront is propagating parallel to the electrode pair compared to when propagation is perpendicular to the electrode pair. This limitation of standard bipoles may be important when assessing pulmonary vein isolation, considering that previous study has demonstrated longitudinal, circumferential, and oblique myocardial fiber entry into the pulmonary veins[10]. Standard diagnostic catheters often incorporate bipoles arranged in a single plane, which could fail to identify activation entering the veins at an angle oblique or perpendicular to those bipoles. The Advisor™ HD Grid Mapping Catheter (HD Grid) (Abbott, Minneapolis, MN) is a high-density mapping catheter which uniquely enables sampling of bipolar electrograms in two directions, simultaneously (Figure 1). It has been suggested that this may enable detection of local electrograms which could be missed by other technologies[11]. We sought to collate multicenter data enabling a comparative assessment of sensitivity to PVI gap detection between this high-density mapping catheter and other diagnostic catheter technologies.

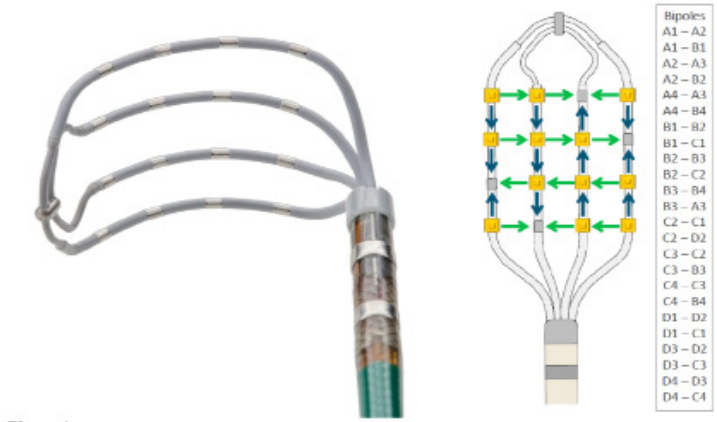

Figure 1: Advisor HD Grid Mapping Catheter, Sensor Enabled (left) and an example HD Wave Solution configuration which records bipolar electrograms in two directions, simultaneously (right).

Table 1: Waiting period utilization and duration distribution across the three groups included in the circular mapping catheter analysis. While 12 out of the 30 (40%) cases in the CMC10 group reported utilization of a 30 minute waiting period, 35 out of 36 (97.2%) cases in CMC 20 group and 29 out of 33 (87.9%) cases in the HD Grid group did not utilize a waiting period as part of the PVI confirmation method.

Waiting Period Duration (min)	CMC10 (n = 30)	CMC20 (n = 36)	HD Grid (n = 33)
0 (no waiting period)	3.3% (1/30)	97.2% (35/36)	87.9% (29/33)
5	26.7% (8/30)	0.0% (0/36)	3.0% (1/33)
15	16.7% (5/30)	0.0% (0/36)	6.1% (2/33)
20	6.7% (2/30)	2.8% (1/36)	0.0% (0/33)
30	40.0% (12/30)	0.0% (0/36)	3.0% (1/33)
NR	6.7% (2/30)	0.0% (0/36)	0.0% (0/33)

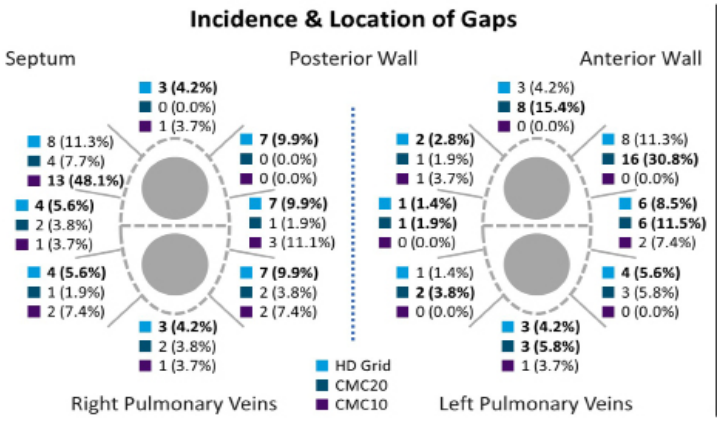

Figure 2: Incidence and location of gaps identified by three diagnostic catheter technologies (percentage of total gaps detected by each technology). HD Grid identified significantly more gaps than the other two technologies (p = 0.015), identifying an average of 49.0% and 139.1% more gaps per patient than CMC20 and CMC10, respectively (HD Grid: 2.15/patient; CMC20: 1.44/patient; CMC10: 0.9/patient).

Methods

Data Collection

Anonymized, acute procedural data were prospectively collected in atrial fibrillation ablation cases performed from May – October 2019, at 24 centers in the United States and Europe. All procedures were conducted per the operator's standard of care. Data was self-reported using a standardized case report form.

Analysis

The primary outcome of each post-hoc analysis was the incidence and location of gaps detected by various pulmonary vein isolation confirmation techniques and diagnostic catheter technologies. Criteria for confirming presence of a gap were left to the discresion of the operator. Included was an indirect comparison of HD Grid to

Table 2: Ablation catheter utilization across the three groups included in the circular mapping catheter analysis. Contact force-sensing catheters were used in all but 1 case.

Ablation Catheter	CMC10	CMC20	HD Grid
TactiCath SE	40.0% (12/30)	100.0% (36/36)	100.0% (33/33)
TactiCath Quartz	56.7% (17/30)	0.0% (0/36)	0.0% (0/33)
Other	3.3% (1/30)	0.0% (0/36)	0.0% (0/33)

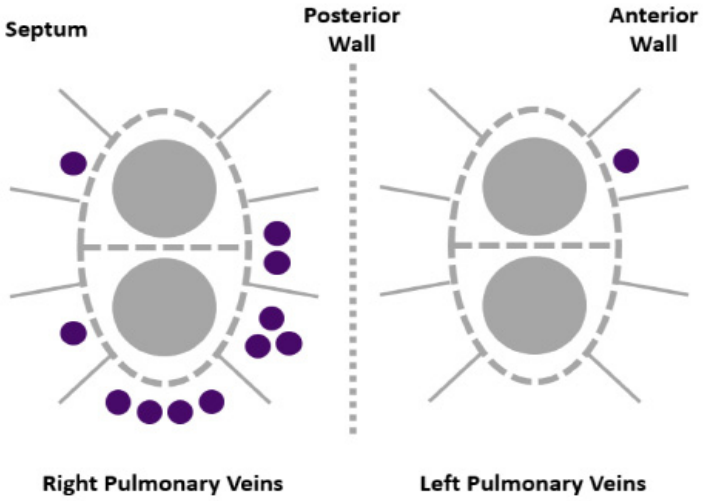

Figure 3: Incidence and location of residual gaps (across all cryoablation patients in which gaps were recorded) identified by Advisor HD Grid, which were not identified by the Achieve. The Achieve catheter was used to confirm isolation after cryoablation followed by the use of the HD Grid to reconfirm isolation. The HD Grid identified a total of 12 gaps in 4 (22.2%) patients, which were missed by the Achieve catheter. All except for one gap were in the right pulmonary veins. The majority of the gaps identified in the right pulmonary veins were located in the inferior regions.

circular mapping catheters (Circular Mapping Catheters), a direct comparison of HD Grid to the Achieve maping catheter (Medtronic, Minneapolis, MN) post-cryoballoon ablation (Cryoballoon Ablation), and a direct comparison of HD Grid to a technique of pacing the ablation lines (Loss of Pace Capture). The EnSite Precision Cardiac Mapping System (Abbott, Minneapolis, MN) was utilized in cases which included 3D mapping. Cases meeting the criteria for each group were selected for inclusion.

Circular Mapping Catheters

De novo atrial fibrillation radiofrequency (RF) ablation procedures utilizing a 10-pole circular mapping catheter (CMC10), 20-pole circular mapping catheter (CMC20), and HD Grid were selected for analysis. PVI confirmation techniques, along with the incidence and location of gaps, were recorded. The proportion of patients in which each technology identified a gap was quantified along with the average number of gaps identified per patient.

Cryoballoon Ablation

Atrial fibrillation cryoablation procedures in which isolation was confirmed with the Achieve mapping catheter followed by secondary confirmation with the HD Grid, were selected for analysis. The incidence and location of residual gaps identified by the HD Grid was quantified.

Table 3: Ablation power utilization across the three groups included in the circular mapping catheter analysis.

Ablation Power	CMC10	CMC20	HD Grid
Anterior/Roof Pulmonary Vein Segments			
30W	73.3% (22/30)	0.0% (0/36)	12.1% (4/33)
35W	10.0% (3/30)	11.1% (4/36)	21.2% (7/33)
40W	0.0% (0/30)	30.6% (11/36)	3.0% (1/33)
45W	0.0% (0/30)	16.7% (6/36)	54.5% (18/33)
50W	16.7% (5/30)	41.7% (15/36)	9.1% (3/33)
Posterior/Inferior Pulmonary Vein Segments			
25W	50.0% (15/30)	0.0% (0/36)	6.1% (2/33)
30W	33.3% (10/30)	11.1% (4/36)	27.3% (9/33)
35W	0.0% (0/30)	30.6% (11/36)	21.2% (7/33)
45W	0.0% (0/30)	16.7% (6/36)	36.4% (12/33)
50W	16.7% (5/30)	41.7% (15/36)	9.1% (3/33)

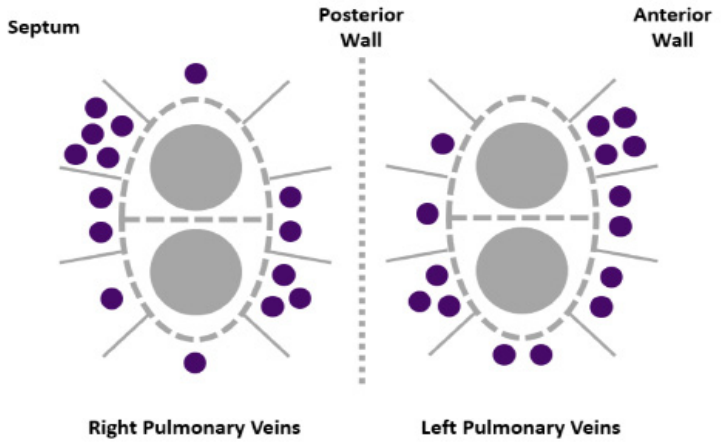

Figure 4: Incidence and location of residual gaps (across all pacing-cohort patients in which gaps were recorded) identified by Advisor HD Grid, which were not identified by pacing the ablation line. PVI was confirmed by pacing along the ablation line with subsequent PVI assessment using HD Grid and the HD Wave configuration. The HD Grid identified a total of 30 gaps in 15 (68.2%) patients, which were initially missed by pacing along the ablation lines.

Loss of Pace Capture

Atrial fibrillation RF ablation procedures in which isolation was confirmed using a technique of pacing the ablation lines followed by secondary confirmation with the HD Grid, were selected for analysis. The incidence and location of residual gaps identified by the HD Grid was quantified.

Statistical Analysis

Post-hoc statistical analysis was performed. Categorical variables are expressed as counts and percentages. Difference between the groups were tested for statistical significance by one-way ANOVA or two sample t-test. A two tailed p value less than 0.05 was considered statistically significant.

Results

Data was collected in a total of 198 atrial fibrillation ablation cases, 50.5% of which were contributed by operators in Europe. A total of 139 cases met the inclusion criteria for one of the three analyses.

Circular Mapping Catheters

A total of 99 cases met the inclusion criteria. PVI was confirmed via entrance and/or exit block in all cases. CMC10 was utilized in 30 cases (66.7% PAF; 33.3% PersAF), CMC20 in 36 (38.9% PAF; 61.1% PersAF), and HD Grid in 33 (69.7% PAF; 27.3% PersAF; 3.0% LsPersAF). Average age was 62.8 ± 12.1, 68.3 ± 10.9, and 65.1 ± 8.7 years in the CMC10, CMC20, and HD Grid groups, respectively. Use of adenosine varied across groups (CMC10: 6.7%; CMC20: 86.1%; HD Grid: 41.7%, $p<0.05$), as did application of a waiting period ranging from 5-30 minutes (CMC10: 96.7%; CMC20: 2.8%; HD Grid: 11.1%, $p<0.05$); Table 1 shows the distribution of waiting period duration across the three groups. The ablation catheters and power settings used in each group are identified in Tables 2 and 3. Gaps were identified in in 36.7%, 38.9%, and 81.8% of cases using CMC10, CMC20, and HD Grid, respectively. HD Grid identified significantly more gaps than the other two technologies ($p = 0.015$), identifying an average of 49.0% and 139.1% more gaps per patient than CMC20 and CMC10, respectively (Average number of gaps per patient - HD Grid: 2.15/patient; CMC20: 1.44/patient; CMC10: 0.9/patient). The location and incidence of gaps identified by each technology is shown in Figure 2.

Cryoballoon Ablation

A total of 18 cases met the inclusion criteria. De novo and repeat ablations represented 77.8% and 22.2% of cases, respectively. 3D mapping was employed in 94.4% of cases. A left common pulmonary vein was present and ablated in 11.1% (2/18). The 28mm cryoballoon was utilized in all cases, with a single case using both a 23mm and 28mm cryoballoon. The 3.3F CMC was used to confirm isolation in all cases using a variety of techniques: voltage mapping (72.2%), exit block (44.4%), entrance block (38.9%), propagation mapping (5.6%), and activation mapping (5.6%); note: total exceeds 100% as more than one technique may be employed in a single case. The HD Grid identified a total of 12 gaps in 4 (22.2%) patients, which were missed by the 3.3F CMC. All except for one gap were in the right pulmonary veins. The majority of the gaps identified in the right pulmonary veins were located in the inferior regions (Figure 3). No adenosine or isoproterenol use was documented in any case.

Loss of Pace Capture

A total of 22 cases met the inclusion criteria. De novo and repeat ablations represented 72.7% and 22.7% of cases, respectively (4.5% not reported). PVI was confirmed by pacing along the ablation line with an average output of 8.8 ± 1.9mA and pulse width of 2.2 ± 0.7ms (10mA at 2ms was utilized in 59.1%). Subsequent PVI assessment was performed with HD Grid. PVI confirmation techniques with HD Grid included exit block confirmation (90.9%), voltage mapping (59.1%), loss of pace capture along ablation lines (40.9%), entrance block confirmation (18.2%), and activation mapping (4.5%); note: total exceeds 100% as more than one technique may be employed in a single case. The HD Grid identified a total of 30 gaps in 15 (68.2%) patients, which were initially missed by pacing along the ablation lines. Gaps were quite evenly distributed around the left and right pulmonary veins (Figure 4). No adenosine or isoproterenol use was documented in any case.

Discussion

Acute procedural endpoints which provide objective and consistent assessment of durable pulmonary vein isolation have been elusive. This could be the result of insufficient sensitivity of commonly used diagnostic tools and techniques for the acute detection of gaps in these lesion sets. The results presented in this proof of concept analysis suggest that sensitivity for gap detection is indeed highly variable when comparing multiple common workflows for PVI confirmation.

One early study compared the resolution of PV potentials recorded by a 20-pole CMC (1mm bipole spacing) to those recorded by the same catheter with bipoles configured to mimic a 10-pole CMC (6mm bipole spacing)[12]. The 20-pole configuration recorded PV potentials with higher amplitude and greater detail as demonstrated by an increase in observed fractionation. Improved EGM resolution has also been identified in studies evaluating high-density mapping catheters[13-15]. Considering these previous findings, it is no surprise that more gaps were identified in cases utilizing catheters with increasing electrode number and decreasing bipole spacing. Interestingly, this trend existed despite scarce application of waiting periods in the CMC20 and HD Grid groups while waiting periods were applied quite uniformly in the CMC10 group, with 70.0% applying a waiting period of 15 minutes or more. Increasing waiting time should improve detection of gaps yet in this case, it appears the impact of diagnostic catheter technology outweighed the potential impact of waiting periods.

Perhaps less apparent is the cause of the difference in gap incidence observed with HD Grid and 20-pole CMCs, which have a similar number of electrodes and bipole spacing (Figure 2). One explanation could be the effect of wavefront direction on the amplitude of bipolar EGMs, with larger amplitudes recorded when the wavefront is propagating parallel to the electrode pair compared to when propagation is perpendicular to the electrode pair. This directional sensitivity has been well documented clinically[11, 13, 16-21]. By recording bipolar electrograms in two directions simultaneously, HD Grid could enable better discrimination of local electrograms suggesting the presence of a gap. Another possible explanation could be the relative location at which electrograms are sampled. Circular mapping catheters tend to be positioned more distally in the vein, potentially missing shorter fibers in the antral portion of the vein which may be identified when the HD Grid is used in a manner that samples closer to the ablation line. While the underlying mechanism is not completely understood, the indirect comparison presented here demonstrates a strong trend suggestive of improved gap detection with the HD Grid. Results from direct comparison of HD Grid to the Achieve mapping catheter post-cryoablation appear to validate the hypothesis that HD Grid improves gap detection. Residual gaps were identified in approximately 20% of patients with the HD Grid after isolation had been confirmed using the Achieve, with the majority of the gaps identified around the right inferior pulmonary veins (Figure 3).

A technique of pacing the ablation lines around the pulmonary veins, confirming loss of pace capture, has also been suggested to improve PVI durability. Previous trials have demonstrated PVI rates, as confirmed by electrograms on the circular mapping catheter, of 95-97% following loss of pace capture along the ablation lines[7, 8]. Further, randomized trials have demonstrated significantly improved long-term outcomes when this technique is used as an adjunct to bidirectional block confirmed by a circular mapping catheter[8, 22]. Our results build on this work by establishing a direct comparison to a contemporary, high-density mapping catheter. While the sample size is small, the rate of residual gaps detected by HD Grid after confirming isolation by pacing suggests that this technique, used in isolation, may not be sufficient for confirmation of PVI (Figure 4).

Limitations across all of these analyses include the relatively small sample sizes and observational nature of the data collection (i.e., ablation technique, PVI confirmation technique, etc. likely varied between operators and there was no minimum operator experience criteria for participation). Criteria for confirmation of gaps were not standardized, instead being left to the discretion of the operator. Considering specifically the indirect comparison (Circular Mapping Catheters), results could be impacted by factors such as the operator, ablation technique, PVI confirmation technique, patient demographics (e.g., left atrial diameter or CHA_2DS_2-VASc), etc. It must also be noted that direct comparisons consistently assessed PVI with the HD Grid after confirming isolation with other techniques.

Despite these limitations, the results suggest that as new diagnostic catheter technologies are introduced, it would be prudent to reassess even routine aspects of atrial fibrillation ablation, such as confirmation of PVI. Additional study is warranted, and randomized trials will be necessary to validate the clinical value provided by these technologies.

Conclusion

Diagnostic catheter technology continues to evolve rapidly, but studies investigating the impact that these technologies may have in assessing durable PVI remain scarce. Use of the HD Grid catheter appears to improve acute detection of gaps in PVI lines relative to other commonly utilized technologies. The impact that ablation of these concealed gaps may have on long-term clinical outcomes remains unknown. Further study, including direct comparison of diagnostic catheter technologies in a randomized setting, is warranted.

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Meditation for Improved Clinical Outcomes in Patients with Implantable Defibrillators for Heart Failure- Pilot Study

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Abstract

Background: Sympathetic activation is associated with congestive heart failure (CHF) and leads to adverse clinical events.We hypothesized that meditation by reducing emotional reactivity would have beneficial effect in reducing arrhythmias compared to control patients.

Methods: Patients known to have CHF and implantable cardioverter defibrillators (ICD) were randomized to Vipassana meditation or usual care control group. Meditation group underwent classes three times during the first week, thereafter once every two weeks. They were encouraged to practice meditation at least once everyday. The ICD was followed by clinic/ remote visits. Atrial (AA) and ventricular arrhythmias (VA) as well cardiac events were assessed in follow up. Chi square test was used to compare nominal variables and t test for continuous variables.

Results: Patients (n=25, 65% male, mean LVEF 25%, HTN 38%, Diabetes 12%, coronary artery disease 38%, NYHA class 2.2) were followed for 79 ± 36 months. Comparing meditation vs control, survival was higher (88%vs 67%); there was less cumulative sustained AF episodes (mean 0.9, IQR 0-1 vs 2.5, IQR 2-4, p=0.045), sustained VT occurred (25% vs 55%, amiodarone use (none vs 44%), and VT ablation in 6.6% vs 33% in the meditation group.

Conclusions: In this first pilot study of meditation in CHF patients with ICD, during long term follow up, there is a trend for improved survival and reduced arrhythmias in patients randomized to meditation.

Introduction

Congestive heart failure (CHF) is associated with significant mortality and a poor median survival.[1] Mortality correlates with functional class and is attributed to sudden cardiac death due to ventricular arrhythmias (VA) or pump failure. These patients are also at higher risk of atrial fibrillation (AF), leading increased morbidity including recurrent hospitalization and stroke.[2]

Sympathetic activation measured by nor-epinephrine levels is correlated with increased mortality, worsening symptoms and increased hospitalization in patients with CHF.[3, 4] Higher resting heart rate is indicative of higher sympathetic tone and a multitude of beta-blocker trials have shown reduction in mortality in patients with congestive heart failure suggesting that sympathetic activation has a significant role in the incidence of sudden cardiac death from ventricular arrhythmias.[5] Studies have shown that implantable cardioverter defibrillator (ICD) and cardiac resynchronization therapy defibrillator (CRTD) improve survival by treating ventricular arrhythmias and by resynchronization of the ventricles respectively.[6] However, unless the left ventricular ejection (LVEF) improves, these modalities do not reduce incident arrhythmias.

Meditation is a restful alert state of mind and has been associated with decreased sympathetic and heightened vagal tones.[7] Physiological markers of norepinephrine levels, vasomotor tone, heart rate and blood pressure have been shown to be lower in meditators.[8-10] These effects likely can counter the heightened sympathetic activation in heart failure patients.

We hypothesized that meditation reduces atrial and ventricular arrhythmias in patients with congestive heart failure during long term follow up.

Methods

Study subjects

After Institutional review board approval, patients were recruited from the Device clinic at our institution and consented for the study. Patients were randomized to two groups: Meditation group were taught Vipassana meditation by a dedicated professional, while the control group was offered usual care consistent with community

Key Words

Meditation, Heart Failure, Arrhythmias.

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standards and health education.

Patients were included if they were ≥ 18 yrs, had an implanted ICD or CRTD for CHF indication according to ACC/AHA/ HRS guidelines.[6] Patients were excluded if life expectancy was < than 6 months due to non-cardiac causes, pregnant, major psychiatry illness, end stage liver, renal or pulmonary diseases, active alcohol or drug abuse and those who were meditators at baseline. Their baseline demographics, co- morbidities, medications, New York Heart Association (NYHA) class, LVEF, 6-min walk duration, BNP levels were assessed. After randomization, the study group was enrolled in meditation classes, three times in the first week after enrollment. Thereafter they attended classes once every two weeks until six months. They were encouraged to meditate at home every day for as long as they can sustain. At the end of six months, BNP levels and 6- min walk test was repeated. All these patients underwent routine device follow up at 3- month intervals per recommendation by guidelines. Arrhythmia log were evaluated and documented during every clinic visit.

Meditation

Subjects were seated in a quiet room on a cushion on the floor or in a straight-backed chair. Those sitting on the floor cross their legs in a comfortable position and those sitting on a chair were requested to place their feet flat on the floor. All adopted the head-and-shoulders posture of meditation -- back straight, hands resting gently on the thighs, head and spine aligned and shoulders relaxed. The eyes were partially open with the gaze directed downward about four feet in front.

Subjects were given instructions by an experienced teacher on the basic technique of concentration-meditation focusing on the breath, leading to the entry stage of Vipassana mediation. While the subjects focus on their breath, they were asked to be aware and follow any random thoughts, feelings, sounds, sights, smells, that arise but knowingly bring the mind gently back to breath. Similarly if one felt a sense of discomfort anywhere in the body, they were asked to adjust their position mindfully, and return to the breath. However, once the subject mastered the breath alone concentration (one-pointedness) there is expected to be less interruptions by other sensations, thoughts, feelings etc. The subjects were then expected to eventually become capable of knowing the breath sensation while focusing on bodily sensations, feelings, thoughts and mental qualities. Concentration leading to Vipassana is a self-investigation process towards perfection which is achieved through practice. The point of this technique is not to stop thinking or achieve a state of bliss, but to become aware of mental activity.

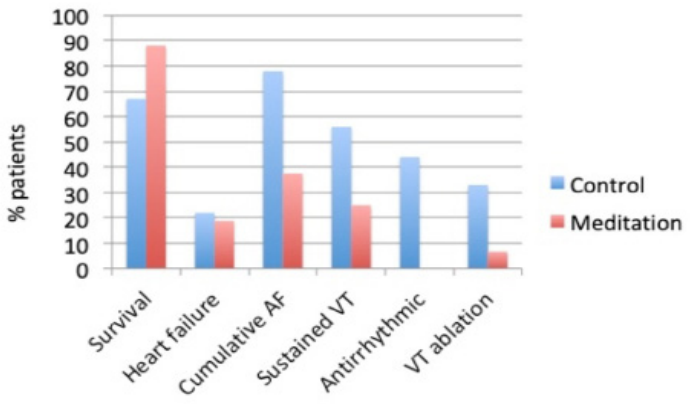

Figure 1: Comparison of clinical outcomes: Blue bars and red bars represent controls and meditators respectively. AF- atrial fibrillation; VT- ventricular tachycardia.

Table 1: Baseline characteristics.

	Control	Meditation	P value
Age	64 + 13	49.7 + 9	0.005
Gender	67	63	ns
NYHA class	2.2 + 8	2.3 + 4	ns
6 min walk	379 + 89	425 + 93	0.03
BNP (IQR)	299 (133-277)	117 (47-97)	ns
Baseline NSVT	11%	35%	ns
Baseline AF	22%	21%	ns
LVEF	24 + 5	26 + 7	ns
Beta blockers	100%	100%	ns
ACEI/ARB	89%	94%	ns
Antiarrhythmic therapy	22%	none	ns
Hypertension	44%	31%	ns
Diabetes	11%	13%	ns
Coronary artery disease	33%	44%	ns

NYHA- New York Heart Association; BNP- B- natriuretic peptide; IQR- interquartile range; NSVT- Non-sustained ventricular tachycardia; AF- Atrial fibrillation; LVEF- left ventricular ejection fraction; ACEI/ ARB- angiotensin converting enzyme inhibitor/

Primary clinical endpoint was cumulative occurrence of AF; secondary end points were mortality, heart failure hospitalization and ventricular arrhythmias. If patients had VA requiring therapy by the device, it was considered sustained VA. Any AF > 7 days duration was considered persistent AF; episodes of AF were tracked, if AF occurred during any visit, the mean episodes were considered cumulative AF. Antiarrhythmic therapy use, ablation, heart failure and survival were also tracked.

Statistics

STATA 13.1 was used for all statistical analyses. Continuous variables are expressed as mean + SD or IQR; categorical variables are presented as percentages, comparisons were performed with t-test and X^2 test respectively. Paired t-test was performed to compare baseline vs follow up BNP and 6- min walk distances among the groups. Adjustment of comorbidities for the clinical outcomes were performed using logistic regression; p-value < 0.05 was considered significant.

Results

Baseline characteristics

Twenty-five patients were enrolled (65% male, mean LVEF 25%, hypertension 38%, Diabetes 12%, coronary artery disease 38%, NYHAclass 2.2) were followed for 84±32 months. Majority of them were implanted for primary prevention (84%). Nine patients were in

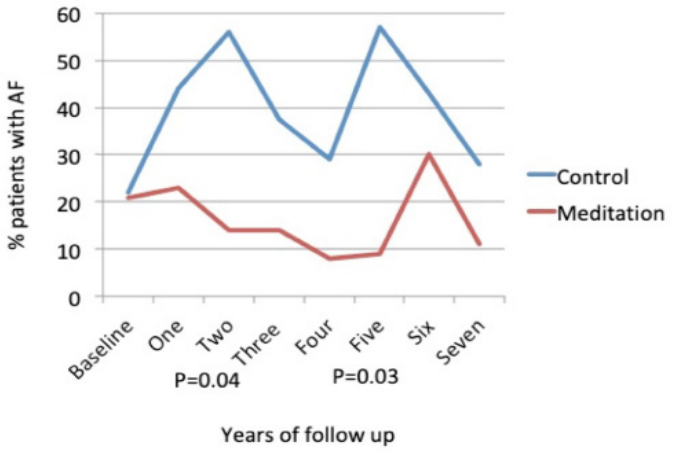

Figure 2: X axis represents years of follow up; Y axis- percent of patients with atrial fibrillation. Blue line and red lines represent control and meditators respectively.

the control arm and 16 in meditation arm. Patients attended 5.9±4.7 classes, with a mean attendance of 55±35 %. The average duration from device implant was 33.6±31.8 months. At baseline (table 1), the meditation group was younger and had longer 6-min walk duration. There was no difference in mean LVEF, beta-blocker or antiarrhythmic drug use.

Atrial fibrillation

During the initial interrogation at enrollment, three patients in control (mean 1.44 min, 0.48 min/month) and two patients in meditation (mean 0.67 min, 0.21 min/month) has documented episodes of paroxysmal AF.

One patient who had persistent AF in meditation group died after cardiac surgery before first three month follow up, therefore was not considered for outcome.

The cumulative AF episodes at six months increased to 127/month in control group vs 0.67 episodes/month in the meditation group. One patient in control group developed persistent AF at six months. Cumulative AF episodes at the end of follow up occurred in 78% of controls vs 37.5% among meditators with mean 0.9, (IQR 0-1) vs 2.5, (IQR 2-4), p=0.045 episodes per visit (fig 1).

The cumulative AF duration increased to 4311 (IQR0-4.3) min/month in controls and 2.7 (IQR 0-0.01) min in meditation group. The duration was driven by three patients in control (11%) who developed persistent AF vs none in mediation group. The patients who had documented AF episodes remained lower in meditation group compared to controls. (Fig 2).

Table 2: Results

(%)	Control (n=9)	Meditation (n=16)	
Survival	67	88	ns
HF hospitalization	22	19	ns
Cumulative AF	78	37.5	0.05
Persistent AF	11	none	ns
Sustained VT	56	25	ns
Ablation for VT	33	6.7	0.09
Antiarrhythmic use	44	none	0.004

Ventricular tachycardia

At baseline, one patient in the control group had 43 episodes of NSVT and five patients in meditation group had NSVT (mean episodes 2.8, IQR 0,1), at six months, 22% of control and 28% (ns) of meditation groups had VT; mean duration of VT increased from baseline to six months in both arms: 0.9 to 8.9 sec in controls (ns) and 3.1 to 8.7 sec (ns) in meditation groups respectively. In the control arm, the number of patients with VT increased from 11% to 22%, while in the meditation arm less patients had VT (38.4 % to 31%) after six months. At the end of long term follow up, although both groups had increase in VT burden, the increase was more significant in the control group-11% to 78%, p=0.003 vs 38% to 64%, p=0.04 in the meditation group. There was no sustained VA at baseline after implantation of the tachy arrhythmia device; during follow up, the control group had higher proportion of sustained VT (56% in control vs 25% in meditation, ns) (table 2, fig-3) as well as need for antiarrhythmic therapy and ablation.

Baseline BNP was non -significantly higher in control group (table 1); there was no significant change between baseline BNP to 6 -month BNP in either groups [mean (IQR)- control: 304 (136-166); meditation: 113 (33-88)]. Six- minute walk was longer in meditation group compared to control at baseline (table 1). Neither group had any significant change in 6- min walk at 6 months (control: 370±152 vs 454±101, ns).

At the end of follow up, 67% in control group vs 87.5% in meditation group were alive (ns) (table 2, fig-1). One patient in meditation group died at 1.4 months after enrollment in the perioperative period after cardiac surgery. Heart failure hospitalization occurred in 22% of control vs 18.8% of meditators.

Discussion

Our principal findings are improved cardiac end points of all parameters investigated in the meditation group. The survival,

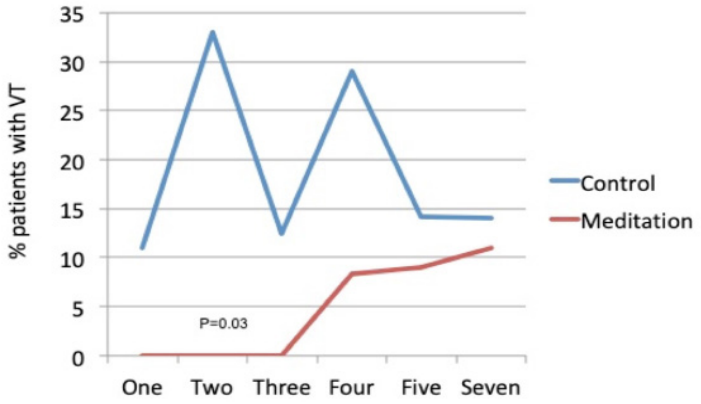

Figure 3: X-axis represents years of follow up; Y axis- percent of patients with sustained ventricular tachycardia requiring therapy. Blue line and red lines represent control and meditators respectively.

heart failure hospitalizations, AF and sustained VT were lower in meditation group. Cumulative AF episodes per visit and need for antiarrhythmic therapy were significantly lower in the meditation group. Though both groups had an increase in VT burden, the episodes were higher in the control group. Although the patients in the meditation group had lower BNP levels and longer 6-min walk distance, they had higher baseline NSVT. This difference could partially explain the difference in outcomes.

Atrial fibrillation is widely accepted as triggered by foci located in thoracic veins; the triggers have been linked to autonomic nervous system via cardiac ganglionic plexi [11] prompting an interest in modulation by ablation.[12] The well acknowledged paradigms of sympathetic stimulation induced ventricular arrhythmias are in congenital conditions including long QT syndrome and catecholaminergic polymorphic ventricular tachycardia. Beta-blockers have been the main stay of therapy in these conditions; refractory arrhythmias have been treated by sympathetic denervation. [13,14] In patients with recurrent shocks from ICD, cardiac sympathetic denervation of thoracic ganglia with or without renal denervation has been shown to reduce arrhythmic events.[15, 16] These efforts cumulatively reiterate the beneficial effects of reversing sympathetic effects on the electrical stimulation of myocardium.

Meditation in scientific terms refers to concentration of mind in order to bring about certain physiologic alterations. Meditation has been used to alleviate stress and anxiety including work place burn outs.[17-19] Since many of these emotions have physiological effects leading to adverse cardiac outcomes, these have been evaluated in clinical settings. Some physiological studies of meditation have shown reduced respiratory rates, decreased skin conductance, total peripheral resistance, cortisol and norepinephrine (NE) levels in healthy populations.[8, 20-22] Improved autonomic balance with reduced sympathetic and enhanced vagal effects have been noted with practice of meditation.[23] Improved Blood pressure in normal and hypertensive individuals have been demonstrated even with short-term meditation.[10, 24] In elderly patients with congestive heart failure, meditation has been shown to reduce NE levels and improve quality of life.[25]

Although different spiritual and non-spiritual techniques have been employed, the basic concept is to focus the mind on a repetitive thought, sound or image. Focusing on the breath has an advantage of something very accessible to everyone. Therefore, one becomes increasingly sensitive to the changes in the body and becomes psychologically tuned to the body rhythms. Concentration on breath as the object of meditation has been shown to improve well-being.[26]

Yoga is a form of meditation in association with structured physical exercises known as “asanas”. Yoga therapy has reduced symptomatic and asymptomatic episodes of AF during short term follow up in patients known to have AF.[27] Since yoga practice requires physical activity that may not be embraced by many of the older patients with heart failure, we chose simple Vipassana meditation to focus only on the mind body effects of meditation. In contrast to the Yoga My heart study where patients acted as their own control, we used a randomized control design in this pilot study. The average number of classes attended was 5.9±4.7 classes, with a mean attendance of 55± 35 %, though we had hoped for 100% attendance. The limitations were the distance for travel and majority of them chose to meditate at home. We had to trust that they were performing meditation based on their verbal report. Our goal was to have larger randomized study groups, however the enrollment was slow. Two patients from meditation group dropped out after the initial class, however we included them in the analysis. Due to limited funding, we could not extend the study for further enrollment. However, we followed these patients for longer period of time to assess their clinical outcomes. We did not identify any adverse effects from meditation.

After focusing two decades on the invasive management of AF by ablation, the electrophysiology world has refocused on lifestyle changes after the results of ARREST-AF and LEGACY studies, which have shown improved control of AF with risk factor modification.[28, 29] One of the key risk factors addressed was weight reduction; mindfulness based approach has been shown to improve eating behaviors and reduction in BMI. [30, 31] Similarly, revisiting arrhythmia control with the old world approach of mindfulness meditation may have positive clinical effects in conjunction with advanced technology.

The effect of meditation on physiological parameters is by reducing emotional reactivity. These have been associated with structural changes in the prefrontal cortex, cingulate cortex, insula and hippocampus in MRI studies.[32] Although these changes are seen even after short-term training, the inertness to negative images seem to require long term practice of meditation [33] as noted in the Buddhist monks.[34] In our investigation, our training period was short, however patients were expected to meditate long term. We did not find any change in heart failure parameters such as BNP or 6 min walk test, however the arrhythmic events were reduced. A larger sustained web or smart phone based meditation study acceptable by many would make it easier for patients and might provide more insight into the clinical benefits.

Limitations

We acknowledge that this is a small pilot study to investigate the effects of meditation in the high-risk heart failure patients with implantable tachyarrhythmia devices. The ability and willingness to attend regular meditation classes and follow through every day is an important factor to assess the clinical effects. Our strength is the study design of randomization and a long term follow up. To our best knowledge, ours is the first study to investigate the clinical effects of meditation in heart failure patients.

Conclusion

In our pilot randomized control trial, meditation seems to have positive effects on cardiac arrhythmia events; we need larger multicenter investigation to evaluate the beneficial effects.

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Association of the H_2FPEF Risk Score with Recurrence of Atrial Fibrillation Following Pulmonary Vein Isolation

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Abstract

Background: While atrial fibrillation (AF) and heart failure with preserved ejection fraction (HFpEF) commonly coexist, the efficacy of pulmonary vein isolation in the setting of HFpEF is unclear.

Methods: In a cohort of patients who underwent cryoballoon ablation (CBA) from 2011 to 2016, we calculated the H_2FPEF risk score, a novel 6-item score (scale: 0-9 points) that accurately predicts the probability of HFpEF. We compared characteristics of patients by H_2FPEF score and evaluated the association of H_2FPEF score with 12-month recurrence of AF post-procedure.

Results: Of patients with available data to calculate the H_2FPEF score (n=105), the median H2FPEF score was 5 (interquartile range: 4-6), corresponding to >80% probability of HFpEF. Compared to patients with H_2FPEF scores ≤4 (n=34), patients with H_2FPEF scores of 5 and 6 (n=46) and ≥7 (n=25) carried higher rates of hypertension (≤4: 21% vs. 5 and 6: 63% vs. ≥7: 88%, P<0.001) and diabetes (≤4: 0% vs. 5 and 6: 9% vs. ≥7: 32%, P=0.001). The overall 12-month recurrence rate of AF was 21%. There was no association between H_2FPEF score and recurrence of AF at 12 months (OR per SD increase in log-H_2FPEF score: 0.87, 95% CI: 0.54-1.40, P=0.57).

Conclusion: Among patients undergoing CBA for AF, median H_2FPEF scores are elevated, and screening for occult HFpEF may be warranted in this population. There was no association of the H_2FPEF score and AF recurrence at 12 months, suggesting efficacy of CBA even among patients with high H_2FPEF scores.

Introduction

Atrial fibrillation (AF) and heart failure (HF) with preserved ejection fraction (HFpEF) frequently coexist. Over 60% of patients with HFpEF may experience AF at some point during their lifetime, and AF is more closely associated with incident HFpEF than HF with reduced ejection fraction (HFrEF).[1] Indeed, both in-hospital and long-term outcomes among those burdened with both AF and HFpEF are worse compared to the presence of either syndrome in isolation.[2-4] Recently, AF was identified as the single strongest predictor of the diagnosis of HFpEF among dyspneic patients.[5] Notably, the vast majority of patients with persistent AF and unexplained dyspnea may have occult HFpEF after invasive hemodynamic investigation.[6] Given its predictive ability, AF has been incorporated into a novel risk score for HFpEF, termed the H_2FPEF risk score.[5] This risk score has demonstrated adequate prediction of HFpEF as confirmed by invasive hemodynamic testing.[5] Of the 6 clinical and echocardiographic variables that comprise the H_2FPEF risk score, AF represents the most heavily-weighted variable, accounting for 3 points of the 9-point composite.[5] Despite the close relationship between these 2 syndromes, management of AF in HFpEF remains unclear. While recent randomized clinical trial data have emerged that support the clinical utility of catheter ablation in the setting of HFrEF, parallel investigations in HFpEF are currently lacking.[7, 8] Although pulmonary vein isolation (PVI) is an effective treatment for AF,[9] its efficacy in the setting of HFpEF is unclear. Additionally, the association of the H_2FPEF score with natriuretic peptides, a biomarker frequently used to diagnose HFpEF, is not well-established in AF and could offer insight into the diagnostic utility of natriuretic peptides for HFpEF in the setting of AF. We thus evaluated 1) the distribution of H_2FPEF scores and natriuretic peptide levels among patients undergoing PVI using cryoballoon and 2) the association of the H_2FPEF risk score and recurrence of AF following cryoballoon catheter ablation. We hypothesized that

Key Words

Atrial Fibrillation; Heart Failure With Preserved Ejection Fraction; Ablation; Recurrence; Risk Score

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in patients undergoing PVI, H_2FPEF scores are: 1) relatively high; 2) associated with higher natriuretic peptide levels; and 3) associated with increased risk of AF recurrence.

Methods

Study Population

Consecutive AF patients who underwent cryoballoon ablation at a single academic center (Northwestern Memorial Hospital, Chicago, IL) between January 1, 2011 and December 31, 2016 were evaluated for study inclusion. Patients included in the analysis were required to have transthoracic echocardiograms of sufficient quality for calculation of the H_2FPEF score obtained within 1 year prior to ablation. Patients with a history of reduced left ventricular ejection fraction (LVEF), defined as <45%, were excluded. This study was approved by the institutional review board of Northwestern University.

Calculation of H_2FPEF Score

The H_2FPEF score was calculated for all patients with available echocardiographic and clinical data based on the components of the score: AF (3 points), age > 60 years (1 point), body mass index (BMI) >30 kg/m2 (2 points), ≥2 anti-hypertensive medications (1 point), pulmonary artery systolic pressure (PASP) >35 mmHg (1 point), and E/e' >9 (1 point). Age and BMI were obtained from the date of cryoballoon ablation. Anti-hypertensive medications were recorded from the most recent pre-procedure clinic visit. Comprehensive 2-dimensional echocardiograms with Doppler were performed at Northwestern Memorial Hospital according to American Society of Echocardiography standards.[10-12] PASP was calculated using the modified Bernoulli equation of peak tricuspid valve regurgitation velocity plus right atrial pressure. The average of septal and lateral E/e' measurements was obtained. Additional echocardiographic indices included left atrial (LA) volume (LAV) and LVEF. LAV was calculated by through the biplane method using apical 2- and 4- chamber views. B-type natriuretic peptide (BNP) levels were additionally recorded if they had been obtained prior to cryoablation.

Cryoballoon Ablation and Rhythm Surveillance Protocols

Cryoballoon ablation was performed as previously described.[13] Cryoballoon ablation was performed by one of six cardiac

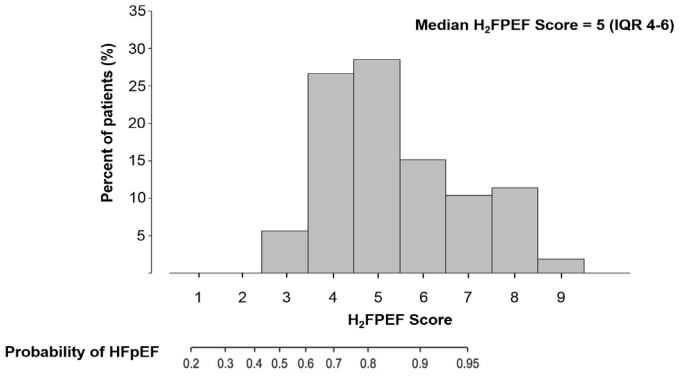

Figure 1: Distribution of H_2FPEF Scores. HFpEF = heart failure with preserved ejection fraction.

Table 1: Baseline Characteristics Stratified by H_2FPEF Score.

	H_2FPEF Score			
Characteristic	**≤4 (n=34)**	**5 and 6(n=46)**	**≥7 (n=25)**	**P value**
Age (years), mean±SD	59.0±13.0	64.7±9.3	66.7±4.2	0.007
Female sex, n (%)	8 (24)	21 (46)	11 (44)	0.10
Asian, n (%)	1 (3)	3 (7)	1 (4)	0.05
Black, n (%)	0 (0)	1 (2)	4 (17)	
White, n (%)	33 (97)	41 (89)	17 (74)	
Persistent atrial fibrillation, n (%)	14 (41)	24 (52)	11 (44)	0.59
Hypertension, n (%)	7 (21)	29 (63)	22 (88)	<0.001
Diabetes mellitus, n (%)	0 (0)	4 (9)	8 (32)	0.001
Coronary artery disease, n (%)	5 (15)	7 (15)	3 (12)	0.93
Obstructive sleep apnea, n (%)	1 (3)	8 (17)	6 (24)	0.05
Stroke or transient ischemic attack, n (%)	2 (6)	2 (4)	1 (4)	0.93
Body mass index (kg/m^2), median (IQR)	25.9 (23.4-27.0)	27.3 (24.6-30.4)	33.4 (31.5-36.5)	<0.001
Glomerular filtration rate (mL/min/1.73m^2) mean±SD	83.1±19.7	74.9±18.6	73.7±17.4	0.09
Medications				
β blocker, n (%)	14 (41)	27 (59)	17 (68)	0.10
Calcium channel blocker, n (%)	5 (15)	9 (20)	6 (24)	0.66
Angiotensin-converting enzyme inhibitor/Angiotensin receptor blocker, n (%)	11 (32)	13 (28)	13 (52)	0.12
Mineralocorticoid antagonist, n (%)	2 (6)	0 (0)	2 (8)	0.19
Statin, n (%)	12 (35)	18 (39)	8 (32)	0.83
Anticoagulation, n (%)	23 (68)	38 (83)	22 (88)	0.12
Echocardiography				
Left ventricular ejection fraction (%,) median (IQR)	60 (55-62)	60 (55-65)	60 (55-64)	0.47
Left atrial volume (mL), median (IQR)	64.9 (51.7-89.2)	67.1 (57.9-86.5)	80.8 (67.1-93.5)	0.14
E/e', median (IQR)	7.6 (6.8-9.4)	9.0 (7.5-11.5)	10.4 (9.3-13.5)	<0.001
Pulmonary artery systolic pressure (mmHg), median (IQR)	26.5 (21.0-31.5)	29.0 (26.0-33.2)	33.0 (28.8-38.0)	<0.001

IQR = interquartile range

electrophysiologists. A Baylis RF needle (Baylis, Burlington, MA) and an SL1 (Abbott, Chicago, IL) or Preface (Biosense Webster, New Brunswick, NJ) sheath were used for trans-septal puncture across the interatrial septum. Intravenous heparin was given with an activated clotting time goal of > 300 s. The Arctic Front Advance cryoballoon (Medtronic Inc., Minneapolis, MN) and lasso catheters were introduced into the LA using the Cryosheath (Medtronic Inc., Minneapolis, MN). Pulmonary vein venograms were performed to confirm balloon occlusion of each pulmonary vein ostium. Target temperatures were -30 to -55°C. Lesion duration evolved over time from two 4-min freezes per vein to two 3-min freezes per vein, with some operators limiting veins to a single 3-min application if time to effect was < 30 s. Entry and exit block were confirmed following

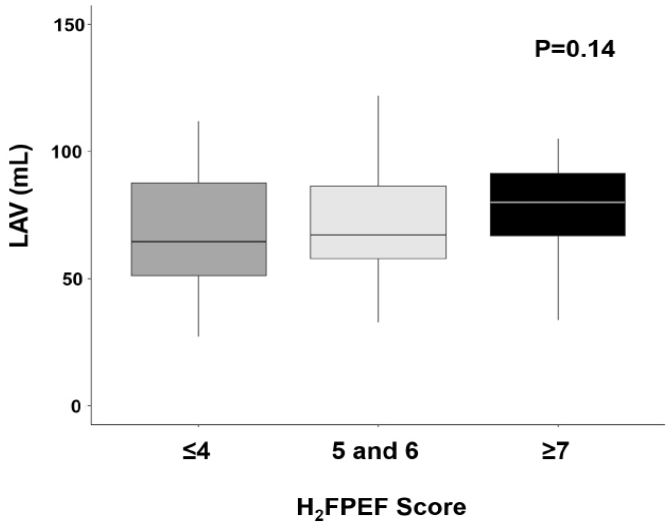

Figure 2: Left Atrial Volumes By H_2FPEF Score. LAV = left atrial volume.

cryoballoon ablation. Cardioversion to sinus rhythm was performed if patients remained in AF after ablation.

Rhythm surveillance included, at a minimum, a 3-week extended rhythm monitor at 3 months post-ablation, followed by 24- and 48-hour Holter monitors at 6 month intervals, transmissions from implanted devices, and tracings from Kardia smartphone monitors (AliveCore, Mountain View, CA). 12-lead electrocardiograms were also obtained at each clinic visit. Additional monitoring was performed among patients with symptoms suggestive of AF recurrence. Recurrence of AF was defined as AF lasting >30 seconds occurring, as outlined by the Heart Rhythm Society/European Heart Rhythm Association/European Cardiac Arrhythmia Society.[14] We determined AF recurrence at 12 months based on this definition and after a 3-month blanking period from the date of ablation, at which time anti-arrhythmic drugs were stopped.

Statistical Analysis

Clinical variables were compared by H_2FPEF score using Chi-square tests for categorical variables and one-way analysis of variance tests for continuous variables. Probabilities of HFpEF were determined based on the derivation report of the H_2FPEF score.[5] Given their skewed distributions, H_2FPEF scores and BNP were log-transformed and standardized (expressed as per 1-standard deviation) for all analyses. We evaluated the association of H_2FPEF scores and BNP levels (dependent variable) using linear regression. Multivariable logistic regression was used to assess the association of H_2FPEF scores and recurrence of AF at 12 months. Two-sided $\propto$ levels <0.05 were considered statistically significant. Statistical analyses were performed using R version 3.5.0 (R Foundation for Statistical Computing).

Results

Of 611 patients who underwent cryoballoon ablation between 2011 and 2016, 126 patients had echocardiograms within 1 year prior to the procedure that contained sufficient data to calculate the H_2FPEF score. Among this group, 21 patients were excluded due to a history of reduced LVEF. Of the final analytic cohort (n=105), the median H_2FPEF score was 5 (interquartile range [IQR]: 4-6), corresponding to >80% probability of HFpEF (Figure 1). Compared to patients with H_2FPEF scores ≤4 (n=34), patients with H_2FPEF scores of 5 and 6 (n=46) and ≥7 (n=25) had a higher prevalence of diabetes (≤4: 0% vs. 5 and 6: 9% vs. ≥7: 32%, P=0.001) and obstructive sleep apnea (≤4: 3% vs. 5 and 6: 17% vs. ≥7: 24%, P=0.05) (Table 1). As expected, based upon the components of the H_2FPEF risk score, patients with higher scores were more likely to have hypertension (≤4: 21% vs. 5 and 6: 63% vs. ≥7: 88%, P<0.001). There were no differences in rates of persistent AF (≤4: 41% vs. 5 and 6: 52% vs. ≥7: 44%, P=0.59) or duration of AF (≤4: 65±91 months vs. 5 and 6: 46±61 months vs. ≥7: 49±49 months, P=0.50) by H_2FPEF score. Of note, there was no difference in LAV by H_2FPEF score (Table 1; Figure 2). Patients with higher aggregate H_2FPEF scores had significantly higher levels of all component variables, including age, BMI, PASP, and LV filling pressures as measured by E/e'. There were trends of lower GFR and higher rates of female sex with increasing H_2FPEF scores (Table 1).

Associations of H_2FPEF Score with Natriuretic Peptides and AF Recurrence

Among 44 patients with BNP levels available prior to cryoballoon ablation, median BNP levels were similar across H_2FPEF scores: (≤4: 128 [IQR: 95-227] pg/mL vs. 5 and 6: 193 [IQR: 106-279] pg/mL vs. ≥7: 192 [IQR: 111-314] pg/mL, P=0.75). There was no association between H_2FPEF score and BNP levels on linear regression analysis (β coefficient per SD-increase in H_2FPEF score: 0.06, 95% CI: -0.32, 0.44, P=0.76).

At 12 months post-procedure, the overall rate of recurrence of AF was 21%. The rates of recurrence of AF by H_2FPEF score

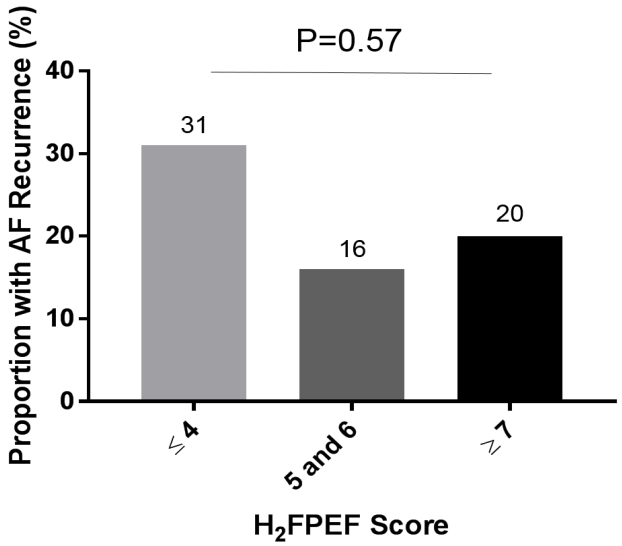

Figure 3: Recurrence Rates of Atrial Fibrillation at 12 Months By H_2FPEF Score. AF = atrial fibrillation.

groups were: ≤4 (31.2%, n=10), 5 and 6 (16.3%, n=7), and ≥7 (20.0%, n=5) (Figure 3). There was no association between H_2FPEF score and recurrence of AF at 12 months (OR per SD increase in log-transformed H_2FPEF score: 0.87, 95% CI: 0.54-1.40, P=0.57).

Discussion

In this analysis of a contemporary cohort of AF patients undergoing cryoballoon ablation, we describe the distribution of the H_2FPEF risk scores and BNP levels, and also evaluate the association of the H_2FPEF score with recurrence of AF post-procedure. The median H_2FPEF score in our study was 5, corresponding to a >80% probability of HFpEF. Patients with higher H_2FPEF scores represented an elderly cohort with higher prevalence of hypertension, diabetes, and obstructive sleep apnea and more adverse cardiac functional remodeling as indicated by higher PASP and E/e', but similar LA anatomic remodeling as evidenced by comparable LA volumes. There was no association of the H_2FPEF score with AF recurrence at 12 months in our study.

HFpEF remains a challenging syndrome to diagnose due to its heterogeneous clinical presentation and the inability of biomarkers or imaging studies to reliably identify patients burdened by this syndrome. Furthermore, AF and HFpEF often share overlapping symptoms, such as non-specific dyspnea and fatigue, which creates additional barriers to identify patients who truly possess both comorbidities.[15] Elevated BNP, a neurohormone of myocardial stretch, and increased LAV, an anatomic surrogate of presumed chronic pressure overload of the LA, are considered signs of HFpEF and serve as common inclusion criteria in clinical trials of HFpEF.[16, 17] However, the predictive abilities of BNP and LAV for diagnosing HFpEF were not strong enough for either variable to be incorporated into the H_2FPEF risk score.[5] In our study of AF patients undergoing cryoballoon ablation, the H_2FPEF risk score was not associated with BNP levels, and there was no significant difference in LA volumes across the spectrum of H_2FPEF scores. These findings suggest that the H_2FPEF risk score may be particularly useful for diagnosing HFpEF in the setting of pre-existing AF, as AF independently results in elevation in BNP and LA remodeling, which limits the clinical utility of these measurements. We demonstrate that AF patients undergoing ablation have high H_2FPEF scores, thus offering additive diagnostic information compared to natriuretic peptides or indices of LA anatomic remodeling. Given the high overall H_2FPEF scores among this population, our study suggests that AF patients who have symptoms requiring ablation represent a cohort that should be systematically screened for concomitant, occult HFpEF.

Optimal management strategies of AF in HFpEF remain unknown. Several concerning factors, including more advanced LA remodeling (i.e., LA fibrosis), high rates of persistent AF, and increased comorbidity burden have led to uncertainty regarding efficacy of AF ablation in HFpEF.[18] Further uncertainty has mounted given the potential for catheter ablation to increase LA pressure or result in stiff LA syndrome among a select AF population with multiple comorbidities,[19, 20] which may be poorly tolerated in the setting of HFpEF. Previous studies evaluating radiofrequency catheter ablation have suggested that the presence of diastolic dysfunction on echocardiography is associated with increased risk of AF recurrence.[21] Conversely, among a cohort patients with HFpEF, radiofrequency catheter ablation was associated with improvement in several indices of LV systolic and diastolic function and success was achieved in 73%, albeit after multiple procedures.[22] Additionally, AF radiofrequency ablation in HFpEF has been associated with reduced HF hospitalization compared with medical therapy.[23] The efficacy of cryoballoon catheter ablation in HFpEF has not been investigated in previous investigations. Additionally, these previous studies have typically defined HFpEF based on review of the electronic medical record, which may lack sensitivity and specificity in identifying true cases of HFpEF.[24] Our study, which defined risk of HFpEF on a continuum using a validated risk score, demonstrated that AF recurrence after cryoballoon ablation is similar regardless H_2FPEF risk score. Given the poor tolerance of loss of sinus rhythm among patients with HFpEF, these findings suggest that catheter ablation may be a reasonable therapeutic strategy, as its efficacy does not appear to be attenuated by increasing risk score. Indeed, dedicated randomized controlled trials evaluating the efficacy of catheter ablation for AF in HFpEF are needed to understand its role in mitigating symptoms and reducing clinical events in this vulnerable cohort.

Limitations

There are limitations to our study. Overall, the proportion of patients with data to calculate the H_2FPEF risk score was small, which introduces selection bias, raises the possibility that population may be underpowered to detect differences, and may account for the overall rates of AF recurrence in this study. Nonetheless, we were able to comprehensively quantify the H_2FPEF risk score in over 100 patients undergoing cryoballoon ablation and assess recurrence of AF. As the H_2FPEF score was initially derived in a population with dyspnea, its performance among an AF cohort undergoing ablation is unclear. However, participants with higher H_2FPEF scores in our study had increased rates of known risk factors for HFpEF, including diabetes and hypertension. BNP was drawn in a subset of the PVI cohort for clinical reasons, which may introduce bias in our findings of the lack of association between H_2FPEF scores and BNP. We did not assess the association of the H_2FPEF risk score and additional outcomes after ablation, including HF hospitalizations and symptom burden. Further investigations are required to evaluate the efficacy of catheter ablation with respect to these outcomes in HFpEF. Despite our comprehensive assessment of AF recurrence through clinic ECGs, Holter monitors, and smartphone and/or implantable device transmissions, the recurrence of AF in our study may have been underestimated due to the lack of continuous rhythm monitoring in all patients post-procedure. Continuous rhythm monitoring has become more frequent given recent technological advances. However, the method of AF detection in this study is reflective of guideline-prescribed clinical practice. Our procedural cohort was specific to cryoballoon-based PVI, as these patients are part of a prospectively maintained database, which may limit the generalizability of our findings. However, PVI using either cryoballoon or radiofrequency ablation has demonstrated similar long-term outcomes.[9] While the cryoballoon ablation protocol in our retrospective study was not specifically standardized, previous studies have demonstrated similar efficacies using a variety of procedural techniques.[25, 26] This study was performed among patients referred to a single tertiary care center

for PVI and thus our findings may not be generalizable to other AF populations. Specifically, the associations of the H_2FPEF risk score and recurrence of AF noted in our study may not be generalizable to older patients undergoing AF ablation or patients being treated through other methods (e.g., direct current cardioversion).

Conclusion

Among a cohort of AF patients undergoing cryoballoon ablation, H_2FPEF risk scores are generally high, and consideration of screening for occult HFpEF among this population may be warranted. While patients with high H_2FPEF risk scores were older and carried higher rates of diabetes, hypertension, and obstructive sleep apnea, there were no significant differences in BNP levels or LA volumes by H_2FPEF score. There was no association of the H_2FPEF risk score and AF recurrence at 12 months, suggesting efficacy of cryoballoon ablation even among patients with high H_2FPEF risk scores.

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Safety and Efficacy of Cryoballoon Ablation for the Treatment of Atrial Fibrillation in Diabetic Patients

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Abstract

Background: Cryoballoon based catheter ablation (CB-CA) is an established therapy for treatment of symptomatic atrial fibrillation (AF). However, data about AF ablation using the CB in the diabetic population is sparse. The aim of this single center retrospective study is to evaluate the safety and efficacy of CB ablation in patients with diabetes mellitus (DM) as compared to patients without DM.

Methods and results: Between July 2015 and December 2017, 397 consecutive patients underwent CB-CA for AF. Forty-eight consecutive patients with DM (DM group, study group) were compared with propensity score-matched patients without DM (n=48, control group). All patients underwent pulmonary vein isolation (PVI) using the second-generation CB (CB2). The mean age in the DM group was 66.9±9.5 years and 69.5±8.8 in the non-DM group (p=0.18). During a follow-up of 12.7±5.1 months, single procedure success rate for the DM and the non-DM group was 68.7% and 70.8%, respectively (p=0.82). The most common complication was transient phrenic nerve palsy (4 DM group vs. 0 non-DM group, p=0.04). No severe complication such as procedure related deaths, atrio-esophageal fistula or cerebrovascular embolic events occurred.

Conclusions: Our data strengthen the value of CB2 based ablation for the treatment of AF as an effective and safe procedure in DM patients, with similar success rates when compared with a non-DM population.

Introduction

The prevalence of atrial fibrillation (AF) is markedly increased in patients with diabetes mellitus (DM) [1,2]. This risk of AF occurrence is increased due to macro- and microvascular dysfunction, diabetic autonomic neuropathy and systemic inflammation leading consequently to atrial remodeling and fibrosis [1].

Key Words

Atrial fibrillation, Cryoballoon, Catheter ablation, Diabetes mellitus

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Catheter ablation (CA) of symptomatic patients with AF by targeting the pulmonary veins (PV) is widely used as recommended by current guidelines [3-5]. Single shot techniques such as the cryoballoon (CB) technology have been developed to facilitate the ablation procedure and to improve outcome [6-8]. In the last years, CB based PV isolation (PVI) is increasingly performed [7,8]. CB-CA has been proven to be non-inferior to the current gold standard of manual point by point mapping and radiofrequency (RF) CA for AF with respect to success and complication rates [6,9]. Additionally, CB-CA has recently been shown to be an effective strategy for paroxysmal as well as persistent AF [4, 6-8].

The necessity of treating DM patients with AF is noticeably growing, as the prevalence of DM population increases [10-12]. DM has been associated with worse outcome after cardiac surgery and interventions [2,10]. The abnormal glucose metabolism in DM patients, has been shown to affect the atrial substrate properties with an intra-atrial conduction delay and a low voltage area formation, resulting in higher AF recurrence rate after RF based CA [13]. Despite the fact that several non-randomized clinical studies have addressed the issue of CA in DM and have shown favorable rates of success [11,12], little is known about the results of CB-CA in this population.

In this study, we aimed to assess the safety and efficacy of AF ablation using the second-generation CB (CB2, Arctic Front Advance, Medtronic, Inc. Minneapolis, MN, USA) in patients with DM compared to a non-DM group of patients and to analyze predictors of arrhythmia recurrence.

Methods

Between July 2015 and December 2017, 397 patients with symptomatic paroxysmal or persistent AF and an indication for AF ablation according to current guidelines, who were scheduled for PVI using the CB2, were enrolled in this retrospective single center study. Patients with left atrial (LA) thrombus, uncontrolled thyroid dysfunction, contraindication to anticoagulation, pregnancy, previous AF-ablation, severe valvular disease and a LA size >60 mm were excluded. Severity of symptoms was recorded according to European Heart Rhythm Association (EHRA) score. Informed consent was taken from each patient before the procedure. The study was in compliance with the principals outlined in the Declaration of Helsinki and approved by the local Ethics Committee (No. 17-298). Patients were divided into a study group with diagnosed type 1 or type 2 DM (DM group) and a control group (non-DM group).

Preprocedural management

Transesophageal echocardiography was performed in all patients prior to the procedure. Apart from echocardiography, no additional pre-procedural imaging was performed. In patients on vitamin K antagonists, anticoagulation was continued throughout the procedure aiming at an INR of 2-3. In patients treated with novel oral anticoagulants (NOACs), the drug was discontinued up to 24 hours prior to the procedure and and re-initiated 6 h post-ablation at half the regular dose, and at full dose the following day.

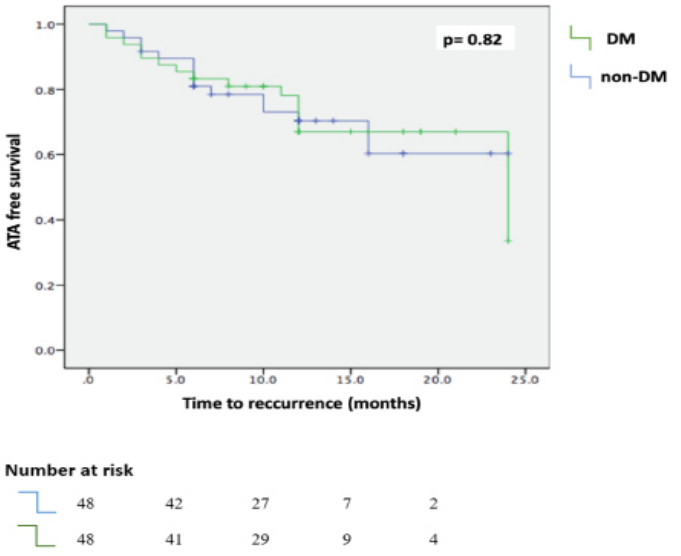

Figure 1: Comparison of ATA free survival for DM vs non-DM patients

Table 1: Baseline characteristics of study patients.

	Non-DM	DM	P value
Number of patients	48	48	
Age (years)	69.5 ± 8.8	66.9 ± 9.5	0.18
Male gender, n	27 (56.2%)	26 (54.1%)	0.83
Height (cm)	173.2±10.6	174.8±10.1	0.42
Weight (kg)	85.9±16.7	93.7±15.7	0.04
Hypertension, n	42 (87.5%)	44 (87.5%)	0.50
LA diameter (mm)	41.1±8.2	41.3±9.7	0.93
LVEF %	51.2±8.1	48.6±8.6	0.12
CHA2DS2VASc score	3.0±1.5	3.8±1.5	0.01
EHRA score	2.5±0.6	2.5±0.6	0.82
Previous Stroke/TIA,n	4 (8.3%)	5 (10.4%)	0.54
Previous MI, n	6 (12.5%)	14 (29.1%)	0.04
Cardiomyopathy, n	9 (18.7%)	11 (22.9%)	0.31
• Non-ischeamic	5 (10.4%)	7 (14.5%)	0.53
• Ischeamic	4 (8.3%)	4 (8.3%)	1.00
Mean duration of AF (months)	16.8±21.9	20.8±23.9	0.40
Follow up period (months)	11.8±4.7	13.6±5.55	0.87
Persistent AF, n	29 (60.4%)	35 (72.9%)	0.13

LA: left atrium, LVEF: left ventricular ejection fraction, MI: myocardial infarction, PCI: percutaneous coronary intervention, CABG: coronary bypass grafting operation, AF: atrial fibrillation. EHRA: European heart rhythm association. TIA: transient ischemic attack. CTI: cavotricuspid isthmus.

Procedural management

All procedures were performed under deep sedation using midazolam, fentanyl, and propofol [14]. One 10-pole diagnostic catheter (Webster® CS Uni-Directional, Biosense Webster, Inc., CA, USA) was introduced via the right femoral vein and positioned within the coronary sinus. A single transseptal puncture was performed via the right femoral vein under fluoroscopic guidance, using a modified Brockenbrough technique and an 8.5 French transseptal sheath (SL1, St Jude Medical, Inc., St Paul, MN, USA or PREFACE Biosense Webster). Heparin was administered after transseptal puncture to maintain an activated clotting time of ≥ 300 seconds. The transseptal sheath was then exchanged over a guidewire with a 12 French steerable sheath (Flexcath Advance, Medtronic). In order to identify all PV ostia, selective PV angiography was performed. In all patients, an esophageal temperature probe (Sensitherm, St Jude Medical, Inc. or CIRCA S-CATHTM) was inserted and positioned according to the individual CB position to facilitate esophageal temperature monitoring during energy delivery. All ablation procedures were conducted with the 28 mm CB2. The 28 mm CB2 was advanced into the LA via the 12 French steerable sheath and a spiral mapping catheter (20 mm diameter; Achieve, Medtronic) was advanced into the target PV to record electrical activity. The CB2 was inflated proximal to the PV ostium and gently pushed against the PV ostium to facilitate complete antral sealing. Contrast medium injected through the central lumen of the CB2 was used to verify complete occlusion of

Table 2: Baseline characteristics of study patients.

	Non-DM	DM	P value
Number of patients	48	48	
Additional CTI during the procedure, n	2 (4.1%)	2 (4.1%)	1.00
PV abnormality, n	14 (29.1%)	6 (12.5%)	0.03
• LCPV	8 (16.6%)	3 (6.2%)	0.10
• RMPV	6 (12.5%)	3 (6.2%)	0.62
Total procedure time (min)	122.5±33.3	127.5±38.3	0.50
Fluoroscopy time (min)	24.1±10.7	27.8±10.8	0.61
Freezes in LSPV (times)	1.2±0.4	1.3±0.7	0.23
Freezes in LIPV (times)	1.3±0.5	1.2±0.4	0.20
Freezes in RSPV (times)	1.3±0.5	1.3±0.5	0.85
Freezes in RIPV (times)	1.6±0.7	1.3±0.5	0.06
LSPV freeze duration (seconds)	251.8±95.6	264.7±126.7	0.57
LIPV freeze duration (seconds)	266.7±121.2	252.5±93.9	0.47
RSPV freeze duration (seconds)	250.9±138.9	257.5±143.5	0.82
RIPV freeze duration (seconds)	317.2±157.1	282.2±131.2	0.23
Minimum temperature in LSPV (°C)	48.6±6.2	48.6±6.6	0.98
Minimum temperature in LIPV(°C)	46.9±6.5	46.8±7.3	0.84
Minimum temperature in RSPV (°C)	48.8±6.5	48.8±6.7	0.97
Minimum temperature in RIPV (°C)	47.6±6.2	45.5±6.6	0.99
Balloon temperature <-60 °C (n)	8 (14.11%)	7 (12.2%)	0.42
Initial sinus rhythm, n	316 (92.9%)	52 (91.2%)	0.4
Cardioversion during procedure, n	24 (50.0%)	23 (47.9%)	0.83
Recurrence in blanking period, n	9 (18.7%)	8 (16.6%)	0.78
Late recurrence, n	14 (29.1%)	15 (31.2%)	0.82

LIPV: left inferior pulmonary vein; LSPV: left superior pulmonary vein; RIPV: right inferior pulmonary vein; RMPV: right middle pulmonary vein; RSPV: right superior pulmonary vein.

Table 3: Parameters included in univariate analysis

	P value
Gender	0.83
Age	0.79
hypertension	0.50
PV abnormality	0.03
LA diameter	0.32
LVEF	0.46
Early recurrence during BP	0.78
Diabetes mellitus	0.07
Cardiomyopathy of any type	0.31
Persistent AF	0.13
Mean duration of AF	0.26
Documented atrial flutter	0.56
Previous MI	0.04
CV during procedure	0.83

LA: left atrium, LVEF: left ventricular ejection fraction, MI: myocardial infarction, AF: atrial fibrillation, PV: pulmonary vein, CV: cardioversion, BP: blanking period.

Table 4: Cox regression analysis. Predictors of ATA recurrence after multivariate analysis.

	β	SE	Wald	df	Significance level	HR	CI 0.95	HR
Recurrence in blanking period	1.863	0.396	22.138	1	0.001	12.5	7.04	22.2
Persistent AF	1.171	0.543	4.662	1	0.03	2.45	1.41	4.27

SE: Standard error, df: degree freedom, HR: Hazard Ratio, AF: atrial fibrillation

the PV ostium. Each freeze cycle duration lasted 180 seconds. If the time to PVI was longer than 60 seconds or no real time PV isolation recording could be obtained, 240 seconds freeze cycle and one more 180 seconds bonus freeze cycle were applied as per discretion of the operator. In patients demonstrating AF at the time of the procedure, electrical cardioversion was performed after the final freeze cycle and PVI was re-confirmed in sinus rhythm (SR). During energy delivery along the right PVs, continuous phrenic nerve pacing at maximum output and pulse width (12 mA, 2.9 ms) at a cycle length of 1000 ms was performed, using a diagnostic catheter positioned in the superior vena cava. Phrenic nerve capture was monitored by intermittent fluoroscopy and by tactile feedback of diaphragmatic contraction by the operator's hand positioned on the patient's abdomen. In addition, the continuous motor action potential (CMAP) was monitored. Refrigerant delivery was stopped immediately if weakening or loss of diaphragmatic movement, or the reduction of CMAP amplitude was noted. If phrenic nerve palsy (PNP) occurred, no additional freeze cycle was applied along the septal PVs. Cavotricuspid isthmus ablation (CTI), using an open irrigated radiofrequency catheter (Celsius ThermoCool or ThermoCool -SF, Biosense Webster), was solely performed in patients with documented or induced common type atrial flutter during the index procedure. PV abnormality was defined as left common ostium and/or a right middle PV.

Postprocedural management

Following ablation, all patients underwent transthoracic echocardiography to rule out a pericardial effusion. All patients were treated with proton-pump inhibitors twice daily after the procedure until discharge and once daily for 6 weeks thereafter. Anticoagulation was continued for at least 3 months and thereafter based on the individual CHA_2DS_2-VASC score. To prevent early recurrence, antiarrhythmic drugs (ADD) were administered throughout a 3-month blanking period (BP). Our institutional approach strongly recommends the administration of AAD and discontinuation after BP. Due to patient preference or referring physician preference AAD was continued. Follow-up was performed either by the outpatient clinic or the referring cardiologist at 3, 6, and 12 months after the index procedure, as well as in case of symptoms suggestive of arrhythmia recurrence and included a ≥24 h-Holter recording and interrogations of implanted devices, if present. Symptoms suggestive of recurrent atrial tachyarrhythmia (ATA) prompted additional outpatient clinic visits.

Repeat ablation was offered to patients with symptomatic ATA recurrence after the BP, or symptomatic drug-refractory recurrent ATA within the BP that could not be managed without intervention. Repeat procedure was performed using a 3D Navigation system (CARTO-3, Biosense Webster). PVs were assessed for reconnection and re-isolation of the PVs was performed in case of recovered conduction. In case of AT, electro-anatomical mapping and entrainment mapping were performed to verify the mechanism and to guide the following RF ablation.

The primary endpoint of this study was any episode of documented ATA recurrence lasting longer than 30 seconds after a 3-month BP or triggering a repeat ablation within the blanking period. Secondary endpoints were complications related to the procedure, such as pericardial tamponade, PNP, cerebrovascular events, and groin complications.

Statistical Analysis

Continuous data are presented as mean ± standard deviation, skewed continuous parameters were expressed as median (interquartile range defined as Q1–Q3). Overall, 48 patients with DM were matched to 48 patients without DM. Propensity score matching was on a logistic regression model including age, sex, type of AF, hypertension, LVEF, LA size and prior transient ischemic attack (TIA)/stroke. Categorical data were summarized as frequencies and percentages and were compared using x2 test. Comparisons between baseline characteristics were performed by independent Student's t-test, Mann– Whitney rank-sum, Fisher exact, or x2 tests where appropriate. To analyze the association between baseline and procedural parameters on AF recurrence, binary logistic regression analysis was used. Parameters that were found to be univariately associated with the outcome and those that show a slight association with the outcome with P<0.20 were included in the multivariable analysis. Kaplan Meyer and cox regression analysis were performed to describe ATA free survival. Statistical analyses were performed using SPSS statistical software (version 22.0; SPSS Inc., Chicago, IL, USA). A 2-tailed P<0.05 was considered statistically significant.

Results

A total of 397 patients with paroxysmal (180/397; 45.4%) and persistent (217/397; 55.6%) AF [30 (7.5%) patients had concomitant documented typical atrial flutter] undergoing PVI using the 28mm CB2 were included in the analysis; 48/397 (12%) patients had DM. The control group was selected by propensity score matching from patients without DM. It was based on a logistic regression model including age, sex, type of AF, hypertension, LVEF, LA size, and prior TIA/stroke. Baseline characteristics of the study population are summarized in Table 1. Patients in the DM group had a higher CHA_2DS_2-VASC score (3.8± 1.5 vs 3.0±1.5 p=0.01) and a higher prevalence of previously known myocardial infarction (MI) (29.1% vs 12.5%, p=0.04). Additionally, there was a higher trend of persistent AF in DM group (72.9% vs 60.4 %, p=0.13). All targeted veins were isolated. Procedural characteristics are presented in Table 2. Anatomical PV abnormalities were observed in 6 patients (12.5%) in the DM group and 14 (29.1%) patients in the non-DM group (p=0.03). Total procedural time in the DM and non-DM groups were 127.5±38.3 vs 122.5±33.3 minutes (p=0.50).

Clinical follow-up

Overall, during 12.7± 5.4 months of follow-up, single procedure success rate was 70.8 % in the DM group and 72.9% in the non-DM group (p=0.82) (Figure 1). Early recurrence of ATA within the first 3 months after the index CB-CA occurred in 16.6% of patients in the DM group and 18.7% in the non-DM group (p=0.78). In multivariate analysis age, gender, hypertension, DM, PV abnormality, LA diameter, LVEF, cardioversion during procedure, early recurrence during the BP, Previous MI, cardiomyopathy of any type, documented atrial flutter, mean duration of AF and persistent AF, were included as these parameters had p<0.20 in univariate analysis (Table 3). After multivariable Cox regression analysis, persistent AF (p=0.03) and early recurrence during the BP (p=0.001), but not DM, were found to be predictors of recurrence of ATA (Table 4). AAD was prescribed to all patients after the index procedure.

Adverse events

Seven groin complications occurred (7 hematoma) in 4 DM patients and 3 in the non-DM group patients (p= 0.71). Transient PNP occurred in 4 patients in the DM group (4 vs 0, p=0.04). PNP had no effect on prolongation of hospital stay. All PNP cases resolved spontaneously during follow-up. In one case pericardial tamponade occurred, that was managed by pericardial puncture (one in the non-DM group, p=0.73), but hospital stay was not prolonged in this patient. There were no severe complications (procedure related deaths, atrio-esophageal fistula or cerebrovascular embolic events).

Discussion

This retrospective analysis investigated the safety and efficacy of CB2-CA in DM patients with paroxysmal and persistent AF and assessed predictors of ATA recurrence. The current analysis demonstrates that CB2-CA is a feasible and safe procedure in DM patients with similar success and complication rates as compared to a non-DM population. Persistent AF and early recurrence during the BP were found as predictors of recurrence of ATA.

Diabetic patients with AF have a worse cardiovascular outcome than those without, regarding mortality and hospitalizations [15,16]. Consequently, a rhythm control approach may be preferred in this group of patients to improve cardiovascular outcome [10,17].

However, data investigating the effect of CB_2-CA in DM patients were limited by non-randomized small studies and limited number of patients [2,11,17].

The long-term outcome of CA in patients with AF and DM was studied in a meta-analysis by Anselmino and colleagues [11]. In this meta-analysis 15 studies with 1464 patients were included. Mean follow-up was 27 months. The overall complication rate was between 1.5–5.0 % and overall long-term success rate of maintaining SR was 66 (58–73) %. Advanced age, higher body mass index, and higher basal glycated haemoglobin level were found to be predictors of recurrence of ATA. In our analysis, the complication and success rates were similar to previous publications without significant differences between the both groups [11, 18, 19].

Recently, Bogossian et al. evaluated the efficacy and safety of CA for AF and atrial flutter (AFlut) in patients with DM [2]. Between 2007 and 2010, 8175 patients who underwent CA for AFlut or AF were included in this multicenter prospective registry. Patients with DM (n=944) were compared to patients without DM (n=7231). After a follow-up period of 366 days, there was no significant difference between AF groups in terms of major adverse cardiac and cerebrovascular events. CA of AF was mostly done with RF CA. CB-CA was the most frequent alternative energy source (DM:17.1%, non-DM: 17.5%) [2].

The AF prevalence and the risk of AF recurrence are increased in

patients with DM due to atrial remodeling and fibrosis [1, 10]. This correlation was also proven in our analysis where patients with DM presented more often with persistent AF and persistent AF was a predictor of recurrence of ATA. However, during our follow-up, single procedure success rate was similar between both groups. Similar ATA free survival in diabetic patients with more complex substrate can be attributed to additional ablative effects of CB-2. Besides ostial PV isolation, application of CB-2 results in large atrial lesion formation causing substrate modification, especially in the posterior LA wall. The spherical shape of CB-2 may cause a mismatch between the balloon and PV ostia during optimal contact causing additional atrial wall ablation that may eliminate components responsible for more diseased LA such as CFAEs, rotors, and vagal ganglia as well [20]. Recently the left atrial appendage was identified as a possible target for catheter ablation and radiofrequency and CB-2 based LAAI has been shown to improve clinical outcome. [21, 22, 23]

Phrenic nerve palsy was found to be more common in DM patients. In all cases, PNP resolved spontaneously during follow-up and did not prolonged hospital stay. However, DM itself may cause neuropathy and phrenic nerves of diabetic patients may be more sensitive to cryoenergy compared to nondiabetic individuals [1,2].

The results of our analysis as well as of the abovementioned studies suggest that in patients with DM, CB2-CA is a safe and effective treatment strategy for symptomatic AF. Moreover, DM patients with good functional status and controlled glycemic levels [19] should be carefully evaluated and highly considered to receive CB2-CA with a favorable success rate and similar complication rate in comparison to non-DM patients.

There are some limitations of this study that need to be acknowledged. This analysis is retrospective in nature with moderate number of patients and without preprocedural cardiac imaging. Moreover, our follow-up did not include routine continuous monitoring with implanted devices or 7-day Holter recording and therefore our success rate may be overestimated. Nevertheless, follow up included 24-hour Holter monitoring, and/or device interrogations (if present), at three, six and 12 months. The effect of DM type, duration of DM, and HbA1c levels on CB2-CA outcome has not been assessed. Finally, no systematical esophagoscopy was performed in this study. Consequently, no data about the incidence of esophageal injury is available.

Conclusions

Our data strengthen the value of CB2-CA for the treatment of AF as an effective and safe procedure in DM patients, with similar success and complications rates compared to non-DM population.

Conflicts of interests

CHH received travel grants and research grants by Medtronic, Pfizer, Novartis, Claret Medical, SentreHeart, Biosense Webster, Boston Scientific and Cardiofocus. He received speaker's honoraria from Cardiofocus, Boston Scientific and Novartis. RRT received travel grants from St. Jude Medical, Topera, Biosense Webster, Daiichi Sankyo, SentreHeart and speaker's honoraria from Biosense Webster, Biotronik, Pfizer, Topera, Bristol-Myers Squibb; Bayer, Sano Aventis and research grants by Cardiofocus. CE received travel grants and educational grants by Medtronic. KHK received travel grants and research grants from Biosense Webster, Stereotaxis, Prorhythm, Medtronic, Edwards, Cryocath, and is a consultant to St. Jude Medical, Biosense Webster, Prorhythm, and Stereotaxis. He received speaker's honoraria from Medtronic. All other authors have no relevant disclosures.

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Anatomy Versus Physiology-Guided Ablation for Persistent Atrial Fibrillation

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Abstract

Background: Pulmonary vein isolation remains the cornerstone of atrial fibrillation (AF) ablation. However, due to high recurrence rates, especially in patients with persistent AF, PV antral isolation, complemented by linear ablation, autonomic modulation, and ablation of complex fractionated electrograms, have been attempted to increase the odds of success. However, the optimum approach for a complementary strategy in addition to PVI for persistent AF is unknown.

Methods: We performed a prospective randomized trial by assigning 92 patients with persistent AF in 1:1 ratio to pulmonary-vein isolation plus ablation of electrograms showing complex fractionated activity (45 patients), or pulmonary-vein isolation plus additional linear ablation across the left atrial roof and mitral valve isthmus (47 patients). The duration of follow-up was five years. The primary endpoint was freedom from any documented recurrence of atrial fibrillation after a single ablation procedure.

Results: At a 12-month follow-up, 9 (23%) patients had AF recurrence in the linear ablation and 8 (21%) patients in the CFAE groups. At a mean follow-up duration of 59±36 months, 48.3% of patients in the linear ablation group and 44.6% of patients in the CFAE group were free from AF (p=0.403). There were no significant differences between the two groups for independent predictors of freedom from AF. The overall procedure time and radiation exposure were higher in the PVI+linear ablation group. There were five adverse events noted, two in the linear group (pericardial effusion not requiring drain) and 3 in the CFAE group (1 pseudoaneurysm, one effusion requiring pericardiocentesis and one effusion nor requiring drain).

Conclusion: Among patients with persistent atrial fibrillation, we found no difference in maintenance of sinus rhythm in either linear ablation or ablation of complex fractionated electrograms was performed in addition to pulmonary vein isolation in short- and long-term follow-up.

Introduction

Since the seminal report by Dr. Michel Haïssaguerre, catheter-based ablation for atrial fibrillation (AF) has evolved and been highly effective for the elimination of atrial fibrillation (AF) compared to antiarrhythmic medications.[1] The overall freedom from AF is dependent on the duration of AF, with success rates ranging between 75% and 90% in patients with paroxysmal AF. [1, 2] In contrast, the success rate is lower in the setting of persistent AF.[3]. PV isolation has been the cornerstone of AF ablation. However, due to a relatively high recurrence rate, especially in patients with persistent AF, other ablation techniques have been developed, involving a PV antral isolation, often complemented by ablation lines, and ablation of complex fractionated atrial electrograms. (CFAE)[2 4]

Furthermore, several randomized studies have produced conflicting results regarding the benefit of adding linear ablation lines, CFAE ablation, both or none. [5-8] Methods of targeting left, and right atrial areas of complex, fractionated or high-frequency electrograms have been developed to improve AF success rates.[9-13] Thus a broad spectrum of approaches ranging from strictly anatomical to more physiology-guided ablation has been utilized. However, the optimum approach for a complementary strategy in addition to PVI for persistent AF remains elusive.

Hence we designed a prospective study to establish freedom from AF with combined wide area circumferential ablation and linear ablation, vs. combined wide area circumferential ablation and CFAE ablation.

Key Words

Atrial Fibrillation, Post-Operative Atrial Fibrillation, Valvular Heart Surgery, Time Varying Risk.

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Methods

Study design

We prospectively randomized patients undergoing pulmonary vein isolation to either additional linear ablation, versus the adjunctive ablation targeting fractionated or high-frequency electrograms ablation for the treatment of AF. Ninety-two patients with symptomatic persistent AF were randomized to PVI+ additional linear ablation group vs. PVI + physiology guided CFAE ablation. Inclusion criteria consisted of a history of symptomatic persistent AF, age ≥21 years, the recommendation for catheter-based, wide-area pulmonary vein isolation, and provision of informed consent. Patients with an unstable medical condition including, but not limited to, acute myocardial infarction, recent stroke, decompensated congestive heart failure, or recent major surgeries, pregnant or breastfeeding women, those unable to give informed consent and those for whom it was not feasible to be followed up at Mayo Clinic were excluded from the study.

Ablation procedures

Patients presented to the clinical electrophysiology laboratory in the fasting stage. All patients underwent general anesthesia. Multiple 5-8 Fr sheaths were placed in the femoral veins; Catheters were positioned in the coronary sinus, left atrium, and other chambers as necessary with electrodes coupled to the input amplifiers of a multi-channel recording system. Catheter positioning and ablation were guided with fluoroscopy. Two long 8 Fr sheaths were advanced, crossing the interatrial septum into the left atrium. An 8 Fr open irrigation-tipped catheter was advanced via one sheath, with a 15 - 25 mm lasso catheter advanced via the second. All patients were heparinized to maintain an ACT of 300 - 400 throughout the entire procedure using both bolus and infusion heparin.

An electroanatomic mapping system (CARTO, Biosense Webster Inc.) was used to create geometries of each ostium of the four pulmonary veins. After that, LA mapping was performed in AF, which was induced if not already present, incorporating 75-100 points into the LA surrogate geometry. The venoatrial junction was taken as the point of confluence between each pulmonary vein and the left atrium; the intracardiac ultrasound was used to confirm that specific location. Multiple electrical and anatomic features were registered, and off-line analyzed to assess left atrial substrate.

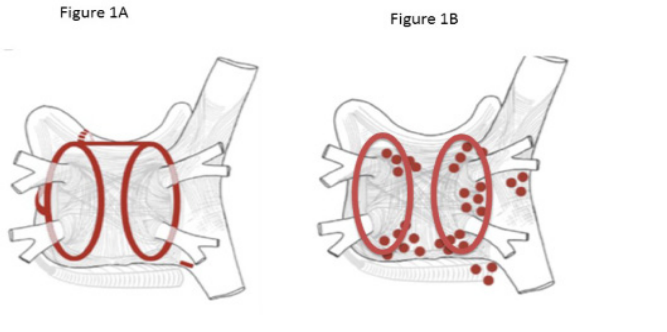

Figure 1: Schematic of common lesion sets employed in AF ablation. A: The circumferential ablation lesions that are created in a circumferential fashion around the right and the left PVs and linear ablation line in the left atrial room and mitral isthmus. B: Ablation targeting complex fractionated activity electrograms (CFAE). Modified with permission from Calkins et al. Heart Rhythm 2012; 9:632–696.e21.2

Table 1: Patient Demographics and Clinical Characteristics

Variable	Linear (N=47)		CFAE (N=45)		P-value
Age (years)	60.9	(8.3)	60.5	(10.2)	0.85
Gender, n (%)					0.15
. Male	41	(87%)	34	(76%)	
. Female	6	(13%)	11	(24%)	
Body Mass Index	34.9	(6.8)	34.4	(7.8)	0.73
LA Volume (cc/m^2)	44.4	(11.9)	45.9	(11.5)	0.56
Duration of Ablation	41.7	(23.4)	34.4	(16.2)	0.09
Diabetes, n (%)	5	(11%)	10	(23%)	0.16
Coronary Artery Disease, n (%)	7	(16%)	5	(11%)	0.53
Chronic Kidney Disease, n (%)	3	(6%)	1	(2%)	0.33
Hypertension, n (%)	27	(61%)	27	(61%)	1.00
Congestive Heart Failure, n (%)	5	(11%)	5	(11%)	1.00
Chronic Obstructive Pulmonary Disease, n (%)	3	(6%)	3	(7%)	0.96
RV Systolic Pressure	28.8	(7.9)	28.4	(7.6)	0.81
Antiarrhythmic Drug Therapy, n (%)	14	(30%)	9	(20%)	0.28
ACE Inhibitor/ARB, n (%)	14	(30%)	12	(27%)	0.74
Beta Blocker, n (%)	35	(74%)	36	(80%)	0.53
Calcium Channel Blocker, n (%)	11	(23%)	10	(22%)	0.89
Statin, n (%)	25	(53%)	31	(69%)	0.12
Rhythm, n (%)					0.43
. Sinus	4	(9%)	2	(4%)	
. AFib/Flutter	43	(91%)	43	(96%)	
LV Ejection Fraction	53.7	(12.5)	53.4	(12.7)	0.90
LV End Diastolic Diameter	52.0	(7.3)	52.1	(6.6)	0.93
LV End Systolic Diameter	36.1	(8.7)	35.6	(7.1)	0.78
LV Volume Mass	103.5	(29.8)	94.9	(22.9)	0.15
Right Atrial Enlargement, n (%)					0.89
. Normal	5 (11%)		9	(20%)	
. Mild	11(24%)		7	(16%)	
. Moderate	14(30%)		11	(25%)	
. Severe	16(35%)		17	(39%)	
Mitral Regurgitation, n (%)					0.12
. Normal	29	(62%)	21	(48%)	
. Mild	15	(32%)	16	(36%)	
. Moderate	3	(6%)	7	(16%)	
Tricuspid Regurgitation, n (%)					0.23
. Normal	31	(67%)	25	(56%)	
. Mild	12	(26%)	15	(33%)	
. Moderate	3	(7%)	4	(9%)	
. Severe	0	(0%)	1	(2%)	

Table 2: Approach to Linear Ablation

Variable	Linear group (N=47)		CFAE group (N=45)		P-value
1C Line Completed, n (%)					
. Yes	45	(96%)			
. No	2	(4%)			
IC line Bidirectional Block, n (%)					
. Yes	29	(64%)			
. No	16	(36%)			
1A Line Completed, n (%)					
. Yes	46	(98%)			
. No	1	(2%)			
IA line Bidirectional Block, n (%)					
. Yes	39	(85%)			
. No	7	(15%)			
CTI, n (%)					0.62
. Yes	38	(83%)	38	(86%)	
. No	8	(17%)	6	(14%)	
CTI Bidirectional Block, n (%)					0.56
. Yes	37	(95%)	38	(97%)	
. No	2	(5%)	1	(3%)	
AF termination					
. During PVI, n (%)	5	(11%)	2	(5%)	0.28
. During Linear Ablation, n (%)	2	(4%)	0	(0%)	0.37
. During CFAE Ablation, n (%)	0	(0%)	3	(7%)	0.79
Spontaneous ERAF, n (%)	3	(6%)	5	(11%)	0.42

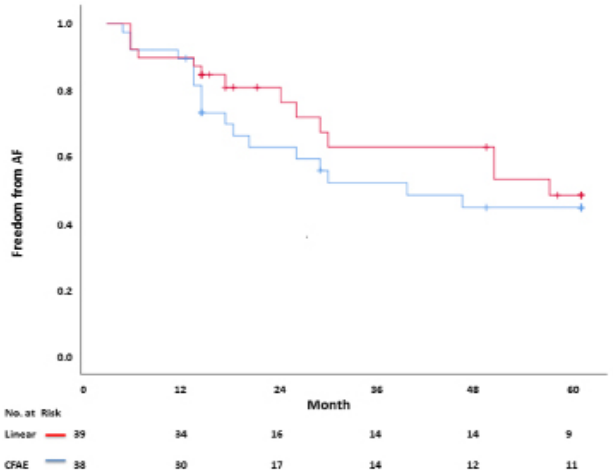

Figure 2: shows Kaplan-Meier AF free rate at short-term and long-term follow-up post PVI+linear and PVI+CFAE ablations.

Table 3: Voltage Mapping Area

Variable	Linear (N=47)		CFAE (N=45)		P-value
Total Mapping Points	84.4	(25.5)	103.3	(30.6)	0.003
Minimum Voltage	0.1	(0.1)	0.1	(0.0)	0.17
Median Voltage	0.6	(0.4)	0.5	(0.2)	0.16
Maximum Voltage	3.5	(2.9)	3.1	(1.6)	0.51
Mean Total Voltage	0.5	(0.2)	0.5	(0.2)	0.93
Left WACA					
Mapping Points	7.3	(9.8)	10.8	(10.0)	0.10
CFAE Points	5.4	(11.0)	7.1	(7.4)	0.39
% CFAE Points	71.0	(64.2)	72.2	(33.6)	0.92
Mean Voltage	0.5	(0.3)	0.5	(0.3)	0.71
Right WACA					
Mapping Points	8.9	(12.1)	11.0	(8.6)	0.33
CFAE Points	5.3	(9.5)	6.6	(5.2)	0.40
% CFAE Points	65.1	(37.9)	68.2	(33.0)	0.71
Mean Voltage	0.4	(0.1)	0.5	(0.2)	0.16
Roof					
Mapping Points	10.7	(7.8)	16.3	(11.2)	0.007
CFAE Points	2.3	(2.8)	3.9	(4.0)	0.026
% CFAE Points	26.3	(28.9)	21.0	(20.4)	0.36
Mean Voltage	0.6	(0.4)	0.6	(0.5)	0.77
Area of Low Voltage (cm2)	8.6	(8.0)	11.1	(8.5)	0.18
Posterior Wall					
Mapping Points	9.2	(8.1)	15.9	(9.6)	<.001
CFAE Points	4.1	(4.3)	5.8	(5.2)	0.10
% CFAE Points	42.3	(30.2)	34.6	(26.8)	0.25
Mean Voltage	0.5	(0.2)	0.4	(0.2)	0.52
Area of Low Voltage (cm^2)	12.7	(7.9)	12.2	(7.1)	0.76
Septum					
Mapping Points	5.7	(5.6)	10.6	(7.8)	<.001
CFAE Points	1.2	(2.0)	3.1	(3.5)	0.001
% CFAE Points	19.7	(25.0)	26.3	(29.7)	0.35
Mean Voltage	0.6	(0.3)	0.6	(0.3)	0.89
Area of Low Voltage (cm^2)	7.7	(7.7)	10.1	(7.0)	0.15

Ablation: PV isolation + linear lines

Each patient in the linear group underwent wide area circumferential pulmonary vein isolation and then adjunctive left atrial lines. In all, one ablative ring was placed around the left pulmonary veins at a distance of 5-15 mm outside the venoatrial junction. The second ring was placed around the right pulmonary veins at an equivalent distance. All energy deliveries were made using 25 - 50 watts of radiofrequency energy delivered via a 3.5 mm irrigation tip catheter with 0.9 NS flow infused at 10 - 30 ml/min. Each ablative lesion was juxtaposed to the immediately preceding lesion using 3-mm marker annotation on the surface of the CARTO map (figure 1A). The endpoint of the circumferential ablation was the elimination of all PV potentials as assessed by lasso catheter mapping (entrance block and exit block if pulmonary vein ectopy was present). The termination of AF during ablation was recorded. Mitral isthmus linear lesion was created from the mitral valve annulus to the left wide area circumferential ablative ring. Coronary sinus ablation was undertaken to facilitate the mitral isthmus line block when needed. An additional left atrial roof lesion was created from the left superior to the right superior pulmonary veins with care taken to maintain this line of block well anteriorly and superiorly to the region of the

Table 4: Procedure Time and Dosage

Variable	Linear (N=47)		CFAE (N=45)		P-value
WACA					
Procedure Time, min	99.3	(42.2)	90.2	(33.8)	0.26
Flouro Time, min	30.9	(24.2)	30.0	(19.0)	0.86
Radiation Dose, mgy	917.8	(817.6)	904.9	(729.5)	0.94
RF Time, min	55.6	(21.3)	54.7	(15.1)	0.82
Linear or CFAE Ablation					
Procedure Time, min	43.9	(31.6)	34.4	(16.2)	0.08
Flouro Time, min	10.8	(4.4)	8.6	(7.4)	0.37
Radiation Dose, mgy	537.3	(420.4)	255.0	(220.0)	<.001
RF Time, min	26.0	(14.9)	21.8	(29.5)	0.42
Total Procedure Time, min	369.5	(97.9)	352.3	(100.0)	0.41
Total Flouro Time, min	88.5	(37.5)	80.6	(34.7)	0.31
Total Radiation Dose, mgy	2689.6	(1588.7)	2501.1	(1509.0)	0.56
Total RF Time, min	98.1	(33.4)	84.0	(18.8)	0.023

esophagus. Additional linear ablation in the form of the left atrial septal line and anterior mitral annulus line was undertaken as an option per operator's discretion.

PV isolation + ablation of complex fractionated electrograms

Patients randomized to the CFAE group underwent wide area circumferential pulmonary vein isolation, and ablation targeting CFAE manifested as repetitive firing at any site of point-to-point mapping with an electrogram cycle length 50-120 msec, with or without intervening return to baseline between each electrogram component using CARTO CFAE software. The wide area circumferential ablation of each pulmonary vein was performed first. CFAE were identified using an approach as described by Nadamanee.[12] The search for complex, fractionated, or rapid electrograms specifically targeted regions superior and medial to the left superior pulmonary vein, inferior and medial to the left inferior pulmonary vein, superior and lateral to the right superior pulmonary vein, and inferior and lateral to the right inferior pulmonary vein. Left atrial septal and roof were also evaluated for CFAE. Figure 1B shows the 5 CFAE mapping regions. The region of CFAE was annotated on the surface of the electroanatomic map. The low voltage mapping point was defined as ≤0.5 mV. RF applications were delivered at those identified CFAE sites until the local potentials were eliminated.

DC cardioversion was allowed when AF persists after completion of WACA and LA linear or CFAE ablation. AF was reinitiated by using rapid atrial pacing up to 300 bpm with isoproterenol infusion. If AF was inducible, repeat DCCV was undertaken to assess the presence of early recurrence of AF.

The patients underwent a cavotricuspid flutter ablation for a documented typical atrial flutter or empiric linear ablation based on the operator preference. The lesions were performed in a linear manner connecting the tricuspid annulus and the IVC. The bidirectional block was confirmed by differential pacing and reversal of activation sequence by pacing on either side of the line of the block.

Table 5: Univariate analysis for AF free at 12 months

Variable	Odds Ratio	95% CI	P-value
Age (years)	0.965	(0.903, 1.031)	0.287
Gender	1.047	(0.256, 4.280)	0.949
Body Mass Index	0.998	(0.927, 1.075)	0.964
LA Volume (cc/m²)	0.960	(0.916, 1.005)	0.080
CFAE (vs. Linear) Ablation	1.125	(0.383, 3.308)	0.831
Duration of CFAE Ablation	0.989	(0.940, 1.042)	0.688
Duration of Linear Ablation	1.005	(0.973, 1.037)	0.768
Diabetes	0.267	(0.076, 0.938)	0.039
Coronary Artery Disease	0.346	(0.084, 1.421)	0.141
Chronic Kidney Disease	0.842	(0.082, 8.656)	0.885
Hypertension	1.140	(0.362, 3.593)	0.823
Congestive Heart Failure	0.808	(0.147, 4.446)	0.806
Chronic Obstructive Pulmonary Disease	>999.999	(<0.001, >999.999)	0.974
LA Volume Index	0.935	(0.851, 1.026)	0.156
RV Systolic Pressure	0.978	(0.916, 1.045)	0.509
Antiarrhythmic Drug Therapy	1.250	(0.378, 4.133)	0.715
ACE Inhibitor/ARB	0.718	(0.206, 2.504)	0.603
Beta Blocker	1.420	(0.356, 5.661)	0.619
Calcium Channel Blocker	0.172	(0.021, 1.403)	0.100
Statin	1.500	(0.491, 4.584)	0.477
LV Ejection Fraction	1.030	(0.989, 1.074)	0.158
LV End Diastolic Diameter	0.945	(0.873, 1.022)	0.155
LV End Systolic Diameter	0.923	(0.859, 0.991)	0.028
LV Volume Mass	0.992	(0.972, 1.012)	0.424
Right Atrial Enlargement	0.502	(0.266, 0.948)	0.034
Mitral Regurgitation	0.659	(0.307, 1.417)	0.286
Tricuspid Regurgitation	0.506	(0.227, 1.130)	0.097
Mean Total Voltage	5.764	(0.253, 131.193)	0.272
Left WACA % CFAE Points	0.993	(0.975, 1.011)	0.441
Left WACA Mean Voltage	0.504	(0.059, 4.304)	0.531
Right WACA % CFAE Points	0.982	(0.963, 1.002)	0.072
Right WACA Mean Voltage	4.006	(0.039, 406.988)	0.556
Avg. Left/Right WACA % CFAE Points	0.987	(0.968, 1.006)	0.181
Avg. Left/Right WACA Mean Voltage	0.635	(0.038, 10.569)	0.752
Roof % CFAE Points	0.970	(0.946, 0.995)	0.018
Roof Mean Voltage	15.923	(0.883, 286.977)	0.061
Posterior Wall % CFAE Points	0.990	(0.970, 1.011)	0.357
Posterior Wall Mean Voltage	147.429	(0.857, >999.999)	0.057
Septum % CFAE Points	0.983	(0.962, 1.005)	0.123
Septum Mean Voltage	0.330	(0.037, 2.927)	0.319

Monitoring During Ablation

Esophageal position and temperature were monitored during all left atrial ablations using a nasogastric tube containing a temperature probe continually repositioned in the esophagus at the level of the ablation catheter to avoid any temperature rise above 38˚C. The

pacing was performed through the ablation catheter at all locations before ablation in the anterior right PVs at ten mA output and 10 ms pulse duration to ensure a lack of phrenic nerve capture. Patients were on heparin throughout the procedure with target ACT 300-400.

Post-procedure care and follow-up

All the patients were monitored in the hospital for at least 24 hours. An additional inpatient stay was permitted if an antiarrhythmic medication was added. All patients received heparin overnight and resume warfarin after the procedure. 12-lead ECG and Chest X-ray were obtained on the next day. Patients were dismissed within 24-48 hours after ablation. Antiarrhythmic drugs were prescribed as per the physician's discretion. All patients were followed up at 3 and 12 months with an ECG and a Holter to assess AF recurrence. The long-term follow-up results were evaluated by ECGs or Holter monitoring documented in the medical records. For patients with recurrent AF or atrial flutter, redo pulmonary vein isolation may be undertaken to reisolate the reconnected pulmonary veins. Any other atypical or typical flutters were mapped and ablated. Sustained attempts were made to achieve bidirectional block across the linear ablation lesion set.

Statistical Analysis

Continuous variables are presented as mean (SD). Discrete variables are summarized as frequency (percentage). Comparisons between groups are made using the Student t-test for continuous variables and the Pearson X^2 test for categorical variables. Further assessment of potential associations with freedom from documented recurrence of AF was assessed utilizing a logistic regression model. Statistical significance is defined as a 2-tailed P value of less than 0.05. Statistical analyses were completed with SAS 9.4 (SAS Institute Inc, Cary, North Carolina).

Results

Patient characteristics

A total of 92 patients were enrolled between September 2009 and January 2013 and were randomly assigned to PVI + linear ablation (47 patients) and PVI + CFAE group (45 patients). Baseline demographics, medication use, comorbidities, and echo characteristics were balanced between the two groups, as shown in Table 1. The mean age was 60.7 years (male sex 81.5%). More than half of the study patients (61%) had hypertension. On average, the LV systolic function was preserved. More than ninety percent of patients were in AF at the time of ablation. The majority of patients were taking beta-blockers or calcium channel blockers. Twenty percent of patients in the CFAE group were on AAD compared to 30% in the linear group. Among the antiarrhythmic medications, 8/92 were on propafenone, 7/92 were on amiodarone, 5/92 were on sotalol, 1/92 on dofetillide, 2/92 flecainde. There was no significant difference of specific antiarrhythmic in both groups.

Acute ablation results

All patients underwent pulmonary vein isolation. There was an entrance block noted in all the veins.

In the linear group, mitral isthmus ablation was attempted in 96% of the patients, and the bidirectional block was confirmed in 64% of these patients. The left atrial roof line was attempted in 98 % of the patients, and the bidirectional block was confirmed in 85% of these patients. Eighty-three percent of this group underwent a CTI line with a bidirectional block confirmed in 95 % of these patients. (Table 2)

In the CFAE group, the average LA mapping point taken was higher than the linear ablation group (mean points 103.3 vs. 84.4, p=0.003). The total points obtained and CFAE points were higher on the anterior wall and septum in the CFAE group than in the linear group. Yet, the percent of CFAE points remained similar in these areas between the two groups. Among the five regions of left WACA ring, right WACA ring, left atrial roof, posterior wall, and septum, the CFAE points were more frequently seen within the WACA rings than other LA areas (65-72% vs. 20-42%, p<0.0001 Table 3). In AF, the mean voltage was highest at the roof and septum (0.6 mv) and lowest on the posterior wall (CFAE group) (0.4 mv). (Table 3) All CFAE points were ablated.

In the linear group, termination of AF was seen in 11% during PVI and 4% during linear ablation, and early recurrence of AF (ERAF) was observed in 6% of the patients. In the CFAE group, termination of AF was seen in 5% of patients during PVI and 7% during CFAE ablation, and ERAF was observed in 11 % of patients. If AF was not terminated during ablation, cardioversion was performed in remaining patients.

Procedure time and complications

The mean time for performing WACA was 94.9 minutes. Besides, the mean time for linear ablation was 43.9 minutes in addition to PVI. The mean time for CFAE ablation was 34.4 minutes in addition to PVI. The total radiation dose was 2689.6 ± 1588.7 mGy in the linear ablation group and 2501.1 ± 1509.0 mGy in the CFAE group. (P=0.56) There was no difference in total procedure time (linear group 369.5 ±97.9 minutes vs. CFAE 352.3±100.0 minutes, p=0.41). The total RF ablation time was longer in the linear group 98.1±33.4 minutes compared to the CFAE group 84.0±18.8 minutes (p=0.023) (Table 4).

There were five adverse events noted, 2 in the linear group (pericardial effusion not requiring drain) and 3 in the CFAE group (one pseudoaneurysm, one effusion requiring pericardiocentesis and one effusion nor requiring drain). There was no procedure-related death, atrioesophageal fistula, stroke, or pulmonary vein stenosis (>70% pulmonary vein narrowing).

Ablation outcomes

At a 12-month follow-up, 9 of 39 (23%) patients had AF recurrence in the linear ablation and 8 of 38 (21%) patients in the CFAE groups (p=0.83) after 3-month blanking time. Twelve (32%) patients in the linear group and 13 (34 %) in the CFAE group were taking AADs to achieve rhythm control. One patient in the linear group and 7 patients in the CFAE group underwent redo ablation at 12 months

(P=0.023). Thirteen (33%) patients in the linear ablation group and 16 (42%) patients in the CFAE group had AF related hospitalization within 12 months (P=0.43). Rehospitalizations for AF included 3-month blanking time.

On univariate analysis and multivariate analysis, neither PVI+linear nor PVI+CFAE group independently predicted freedom from AF at short-term follow-up. There were no specific demographic, clinical, or ablation related characteristics predictive for maintenance of sinus rhythm. (Table 5)

At a mean follow-up duration of 59±36 months, 48.3% of patients in the linear ablation group and 44.6% of patients in the CFAE group were free from AF (p=0.403, Figure 2). There was no significant difference between the two groups. The Cox regression analysis showed hazard ratio 1.34 (95% CL, 0.666-2.695, p=0.412).

Discussion

In a prospective, randomized study, we report no difference in the maintenance of sinus rhythm with PVI+linear ablation vs. PVI + CFAE ablation in short- and long-term follow-up. The overall freedom from AF was 77 % in the PVI+linear group and 79 % in the PVI + CFAE group in one year of follow-up. This outcome was achieved by concurrent use of AADs in one thirds of and repeat ablation in 8% of study patients. Approximately one-third of patients required hospitalization to manage recurrent AF, including within 3-month blanking time. The wide range of clinical presentation of AF and targeted therapy is fundamentally governed by the variable extent of interaction between AF triggers (or drivers) and the necessary "substrate" created by electrophysiologically and structurally remodeled atrial tissue capable of supporting and maintaining AF.14 The pathogenesis of AF is complex and multifactorial. Pulmonary vein (PV) triggers have been demonstrated to play a critical role in both the initiation and perpetuation of AF. Although elimination of PV arrhythmogenicity has been highly effective for paroxysmal AF, it has modest efficacy in the long-term for persistent AF, suggesting that mechanisms beyond the PVs also contribute to the perpetuation of AF in these patients. AF-free survival after catheter ablation is significantly lower for patients with persistent AF. A systematic review of outcomes following ablation found an approximately 20% AF-free survival at 12 months with pulmonary vein isolation alone.[15] The focus has been directed to deciphering AF mechanisms, including targeting non-pulmonary vein triggers, rotors, complex fractionated atrial electrograms, and cardiac autonomic ganglia activity. Several ablation strategies have been proposed including linear ablation, ablation of complex fractionated atrial electrograms, a "stepwise" approach of the incremental extent of atrial ablation until AF terminates, targeting rotors using proprietary software, and the abolishment of autonomic ganglia.[4]

The STAR-AF study of ablation strategies for persistent AF showed no improvement in ablation efficacy for linear lesions plus PVI vs. PVI alone.[5] The RASTA AF trial also concluded that that additional substrate modification beyond PVI does not improve single-procedure efficacy in patients with persistent AF.[13]

The Catheter Ablation of Persistent Atrial Fibrillation (CHASE-AF) study also revealed that the addition of linear lesions and defragmentation of PVI did not improve outcomes for the ablation of persistent AF compared with PVI alone.[16] Our study showed similar short-term, and long-term ablative results with additional left atrial lines vs. CFAE targeted ablation. It has been widely demonstrated that incomplete block across the ablation lines can be responsible for atrial tachycardia /atrial flutter recurrence. In our cohort, we were able to demonstrate that bidirectional block was confirmed in mitral isthmus in 64%, roofline in 85%, and CTI in 95% of cases. The most considerable difficulty with linear ablation is in achieving and confirming complete block across the lesions. It is particularly difficult for the mitral isthmus line, which may require extensive ablation within the coronary sinus to accomplish. Incomplete linear lesions may be proarrhythmic and may lead to refractory atrial flutters that are often highly symptomatic.

Meta-analysis has reported long-term success rates of 80%, with significant heterogeneity in the success of single-procedure outcomes.[17] The stepwise approach for ablation for long-standing persistent AF has been championed by the Bordeaux group. [18] In a recent study that used a stepwise ablation strategy, including isolation of thoracic veins, ablation of CFAEs, and linear ablation until AF was terminated, linear ablation was necessary in more than 85% of the patients for termination of persistent AF. [19] Our study had a meager acute AF termination rate despite pulmonary isolation with concomitant left atrial substrate modification. Yet, AF recurrence rate is not high with a low AF termination rate during the ablation at 12 months follow up.

In the original study by Nademanee and associates, ablation of CFAEs without routine isolation of the PVs was reported to result in freedom from AF in 91% of the 121 patients with paroxysmal or chronic AF. Despite these encouraging acute outcomes, the follow-up data were disappointing, with a 1-year single procedure efficacy of 35% and a 5-year efficacy of 17%.[19]. Unfortunately, improved results with CFAE ablation in patients with persistent AF have not been uniformly reported, and the scientific basis for CFAE ablation is not universally accepted. An approach using PVI and CFAE ablation has been reported as producing success rates of 29% to 74% after a single procedure. [4, 20] Moreover, results from the STAR AF II trial have shown that the addition of further ablation (lines or CFAEs) to PVI increased ablation time but did not reduce the recurrence of AF in 589 patients with persistent AF.[5] At 18 months, the percentage of patients who were free from AF recurrence after one procedure without antiarrhythmic medication did not significantly differ among groups. Similar findings were reported in the CHASE-AF trial, which indicated that the addition of defragmentation and linear ablation to PVI did not improve ablation outcomes for persistent AF compared with PVI alone. [16]However, the findings of the long-term results of CFAEs and linear ablation for persistent AF were uncertain. Our study found no significant difference in AF recurrent rate between CFAEs and linear ablation group at a mean follow-up duration of 5 years. Less than 50% of patients who had persistent AF and underwent ablative therapy remained in sinus rhythm in either additional linear or CFAE ablation groups. A difficulty in targeting CFAEs is that most may be due to passive activation and lack specificity to indicate drivers of AF. Thus primary CFAE-guided ablation may lead to excessive and unnecessary ablation in the LA. As

mentioned, the target sites for antral PVI overlap considerably with CFAE sites in many patients. In our study, the majority of the CFAE points were noted in the left and right WACA regions compared to the rest of the left atrium. The ring of WACA, including these CFAE points, may have the advantage of maintaining sinus rhythm and minimize unnecessary ablation. More selective targets may be needed to characterize an individual patient's specific arrhythmic substrate.

We acknowledge certain important limitations. This is a single center, small randomized study. We did not include a group assigned to pulmonary vein isolation only. The mechanism of recurrence of AF could not be ascertained whether it was dependent on PVs. Maneuvers to improve the durability of pulmonary vein isolation (e.g., adenosine provocation), use of contact force, pacing on ablation lesions may have influenced outcomes. However, we did not use such maneuvers, and data supporting the utility of this approach were not available at the time of this study. Recurrence was noted on 24-hour Holter, whether the recurrences could have been higher due to continuous monitoring remains to be seen. Quality of life data and long term data and findings on repeat ablation could not be ascertained. The accuracy of long-term AF recurrence could be dampened from retrospective data collection.

Conclusion

In conclusion, we report no difference in the maintenance of sinus rhythm rates in patients undergoing PVI+CFAE vs. PVI+linear ablation in short- and long-term follow-up periods.

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Cognitive Screening in Geriatric Patients with Atrial Fibrillation Evaluated for Falls

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Abstract

Background: Atrial fibrillation (AF) is associated with cognitive decline and dementia. This study investigates whether the Montreal Cognitive Assessment (MoCA) detects more cognitive decline than the Mini Mental State Examination (MMSE) in patients with AF. Secondary aims were to assess the rate of white matter hyperintensities (WMH) and mesotemporal atrophy (MTA) in patients with AF.

Methods: Observational cohort study. Patients of 65 years and older that visited the Fall and Syncope Clinic were eligible. Patients were included if both a MoCA and MMSE were completed. In patients of whom an MRI was performed WMH were assessed with the Fazekas score and MTA was assessed with the MTA score. To assess frailty a Frailty Index (FI) was calculated.

Results: 428 patients were included. Mean age was 80 years, 66% was female. The mean FI was 0.28 (CI 0.11 to 0.45), indicative of severe frailty. In 90 patients AF was known and in 9 patients it was first diagnosed, overall prevalence 23%. Cognitive impairment was found with the MoCA in 80% of patients with persistent AF, versus in 33% with the MMSE. Patients with paroxysmal AF had more WMH than patients with SR (p 0.04). No differences were found in relevant MTA between patients with AF or SR.

Conclusion: Cognitive decline in patients with AF is better detected using the MoCA than the MMSE. This means that in daily clinical practice, the MOCA should be used instead of the MMSE for patients with AF.

Introduction

Atrial fibrillation (AF) is an arrhythmia associated with severe outcomes such as stroke, heart failure, and death [1]. Furthermore, there is an increasing amount of evidence that shows an association between atrial fibrillation (AF) and dementia [2-9]. Several studies describe possible mechanisms and pathways through which AF could cause or contribute to cognitive decline and dementia [5, 7, 8, 10, 11]. AF is associated with both vascular dementia and Alzheimer's disease [5, 7, 8, 10, 11].

The three main hypotheses on the relationship between AF and cognitive decline are that: 1. AF leads to a prothrombotic state and subsequent thromboembolisms, 2. AF leads to cerebral hypoperfusion through reduced cardiac output, and 3. AF results in malfunctioning of cerebrovascular regulation through systemic inflammation.

Key Words

Cognition, Frailty, Geriatric cardiology.

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The prothrombotic state can cause vascular or post-stroke dementia [11]. Studies show that thromboembolism related cognitive decline may be prevented by the use of oral anticoagulation (OAC) [12, 13]. An association between AF and dementia exists also in patients without clinical stroke [4, 7], which suggests other etiologic mechanisms.

The second suggested mechanism is cerebral hypoperfusion, mainly through the development of heart failure and consequently lower cardiac output, as well as through beat to beat variations in perfusion [14]. Patients with AF indeed have a lower cerebral blood flow and brain perfusion than those with SR, and this seems more pronounced in patients with persistent AF compared to those with paroxysmal AF [15]. Chronic cerebral hypoperfusion and hypoxia may lead to a reduced clearance of amyloid-beta and form a stimulus for the phosphorylation of tau, leading to Alzheimer-like neuropathological changes [7, 10].

Thirdly, systemic inflammation possibly leads to malfunctioning of cerebrovascular regulation which has been associated to Alzheimer's and vascular dementia [7], and AF is also associated with chronic, low grade systemic inflammation [5, 11].

Table 1: Baseline characteristics

	Total	SR	Persis AF	PAF	p1	p2	p3
n (%)	428	329 (76.9)	46 (10.7)	53 (12.4)			
Female, n (%)	284 (66.4)	227 (69.0)	23 (50.0)	34 (64.1)	0.01	0.48	0.16
Age in years , mean (std.)	79.6 (6.6)	79.2 (6.5)	81.6 (7.1)	80.4 (6.3)	0.02	0.20	0.39
Number of morbidities, mean (std.)	10.7 (5.3)	10.0 (4.9)	13.8 (6.0)	12.3 (6.3)	<0.01	<0.01	0.24
Number of drugs, mean (std.)	6.7 (3.6)	6.4 (3.6)	7.9 (3.4)	7.9 (3.8)	<0.01	<0.01	0.99
Polypharmacy (>5 drugs), n (%)	266 (62.1)	191 (58.1)	36 (78.2)	39 (73.6)	0.01	<0.01	0.59
Hypertension, n (%)	294 (68.7)	215 (65.3)	39 (84.8)	40 (75.5)	0.01	0.15	0.25
Hypercholesterolemia, n (%)	129 (30.1)	95 (28.9)	18 (39.1)	16 (30.2)	0.16	0.85	0.35
Diabetes mellitus, n (%)	87 (20.3)	65 (19.8)	9 (19.6)	13 (24.5)	0.98	0.42	0.55
Stroke or TIA, n (%)	99 (23.1)	67 (20.4)	15 (32.6)	17 (32.1)	0.06	0.06	0.96
Ischemic heart disease, n (%)	108 (25.2)	73 (22.2)	19 (41.3)	16 (30.2)	0.01	0.20	0.25
Congestive heart failure, n (%)	44 (10.3)	16 (5.0)	16 (34.9)	12 (22.6)	<0.01	<0.01	0.18
Valvular disease, n (%)	53 (12.4)	33 (10.0)	10 (21.7)	10 (18.9)	0.02	0.06	0.72
CHA2DS2VASc, mean (std.)	4.0 (1.5)	3.8 (1.4)	4.7 (1.4)	4.5 (1.5)	<0.01	<0.01	0.54
HAS-BLED, mean (std.)	2.9 (1.1)	2.8 (1.1)	2.9 (0.9)	3.0 (1.2)	0.73	0.46	0.74
Chronic respiratory disease, n (%)	88 (20.6)	64 (26.8)	14 (30.4)	10 (18.9)	0.09	0.91	0.18
Chronic kidney disease, n (%)	52 (12.1)	30 (9.1)	9 (19.6)	13 (24.5)	0.03	<0.01	0.55
Thyroid disease, n (%)	61 (14.3)	44 (13.4)	8 (17.4)	9 (17.0)	0.46	0.48	0.96
Alcohol daily use, n (%)	212 (49.5)	160 (48.6)	25 (54.3)	27 (50.9)	0.77	0.66	0.69
Smoking or former smoker, n (%)	181 (42.3)	134 (40.7)	24 (52.2)	23 (43.4)	0.14	0.71	0.38
History of fractures, n (%)	171 (40.0)	135 (41.0)	19 (41.3)	17 (32.1)	0.97	0.22	0.34
Osteoporosis, n (%)	65 (15.2)	51 (15.5)	6 (13.0)	8 (15.1)	0.66	0.94	0.77
Parkinson's disease, n (%)	16 (3.7)	14 (4.3)	1 (2.2)	1 (1.9)	0.50	0.41	0.92
Parkinsonism other cause, n (%)	29 (6.8)	23 (7.0)	2 (4.3)	4 (7.5)	0.50	0.88	0.51
Dementia (all forms), n (%)	14 (3.4)	10 (3.0)	3 (6.5)	1 (1.9)	0.23	0.64	0.24

Abbreviations: SR: Sinus Rhythm, Persis AF: persistent AF, PAF: paroxysmal AF. 1Persistent AF versus Sinus Rhythm, 2Paroxysmal AF versus Sinus Rhythm, 3Persistent AF versus Paroxysmal AF.

Patients with cognitive decline or dementia are often frail, have a higher risk of falling, polypharmacy, dependency in daily activities, and difficulty managing their medications [16]. Cognitive decline can have an important impact on the compliance to treatment and overall prognosis [17]. To diagnose cognitive disorders can be difficult and often requires the expertise of a neurologist or geriatrician. Common screening tools are the Mini Mental State Examination (MMSE) and the Montreal Cognitive Assessement (MoCA) [18, 19]. The MoCA was developed to detect mild cognitive impairment (MCI), a condition that the MMSE can detect with less accuracy [19]. Also, since the MoCA has items testing executive functions, it might be more sensitive to vascular cerebral damage [20, 21]. Vascular cerebral damage can be detected with a MRI of the brain, scoring white matter hyperintensities (WMH) with the Fazekas score [22].

Recently we have shown that in a group of elderly patients with falls or syncope the MoCA is more sensitive to cognitive decline than the MMSE [23]. Taking the possible mechanisms into account through which AF could cause cognitive decline, our hypothesis is that the MoCA is more sensitive to cognitive decline than the MMSE in geriatric patients with AF. The primary objective of this study is to assess whether the MoCA detects more cognitive decline than the MMSE in patients with AF who are referred to a Falls and Syncope Day Clinic (FSC). Secondary objectives are to investigate the relationship between AF and white matter hyperintensities (WMH) and mesotemporal atrophy (MTA) as found on MRI scanning of the brain.

Methods:

We conducted an observational cohort study at a Fall and Syncope day Clinic (FSC), North West Clinics Alkmaar, The Netherlands. Including consecutive patients aged ≥65 years that visited the FSC from November 2011 until the end of May 2017 in whom cognitive function was screened with both the MMSE and MoCA. Patients were excluded if no 12 lead electrocardiogram (ECG) or 24 hour Holter monitor were performed.

The FSC is a two-day diagnostic program that evaluates elderly patients with unexplained falls with or without transient loss of consciousness (TLC). It is conducted by a multidisciplinary team led by a geriatrician and includes a physiotherapist, nurse practitioners, cardiologist and neurologist. Details and outcomes of this two-day program have been reported earlier [23, 24, 25]. In brief, all patients underwent a comprehensive geriatric assessment including laboratory testing, a 12 lead ECG, and assessment of mental, cognitive and functional state. Cognitive function was screened using Dutch validated versions of both the MMSE and MoCA [19, 26, 27]. If cognitive dysfunction was found with either the MMSE or

Table 2: Cognitive and functional state

	Total	SR	Persis AF	PAF	p1	p2	p3
MMSE score, mean (std.)	27.2 (2.4)	27.3 (2.4)	26.5 (2.3)	27.3 (2.4)	0.02	0.95	0.08
MoCA score, mean (std.)	23.7 (3.8)	23.7 (3.9)	22.6 (3.2)	24.2 (3.4)	0.06	0.40	0.02
MMSE below 26 points, n (%)	78 (18.2)	57 (17.3)	15 (32.6)	6 (11.3)	0.01	0.27	0.01
MoCA below 26 points, n (%)	278 (65.0)	209 (63.5)	37 (80.4)	32 (60.4)	0.02	0.66	0.03
Fazekas score, mean (std.)	1.9 (1.0)	1.8 (1.0)	2.1 (1.0)	1.9 (0.9)	0.22	0.65	0.53
MTA score, mean (std.)	1.7 (0.8)	1.7 (0.8)	2.1 (0.7)	1.6 (0.7)	0.02	0.43	0.01
MTA score, above cut-off*, n (%)	120 (38.1)	95 (37.8)	11 (36.7)	14 (41.2)	0.90	0.71	0.71
Frailty Index, mean (std.)	0.28 (0.1)	0.27 (0.1)	0.34 (0.1)	0.31 (0.1)	<0.01	0.01	0.19
Low handgrip strength, n (%) (n=304)	207 (68.1)	159 (68.2)	20 (64.5)	28 (70.0)	0.68	0.83	0.62
Gait disturbance, n (%)	69 (16.1)	51 (15.5)	7 (15.2)	11 (20.8)	0.96	0.34	0.48
Abnormal Tinetti score (n=391), n (%)	257 (65.7)	196 (65.3)	29 (72.5)	32 (62.7)	0.37	0.72	0.33
Dependent in ADL, n (%)	80 (18.7)	61 (18.5)	12 (26.1)	7 (13.2)	0.01	0.35	0.14
Dependent in instrumental ADL, n (%)	136 (31.8)	102 (31.0)	17 (37.0)	17 (32.1)	0.42	0.88	0.61
Use of a walking aid, n (%)	216 (50.5)	158 (48.0)	27 (58.7)	31 (58.5)	0.18	0.16	0.98
Visual impairment, n (%)	189 (44.2)	145 (44.1)	19 (41.3)	25 (47.2)	0.72	0.67	0.56
Institutionalized, n (%)	22 (5.1)	15 (4.6)	4 (8.7)	3 (5.7)	0.23	0.73	0.56

Abbreviations: SR: Sinus Rhythm, Persis AF: persistent AF, PAF: paroxysmal AF. MMSE: Mini Mental State Examination, MoCA: Montreal Cognitive Assessment, MTA: mesotemporal atrophy, ADL: Activities of Daily Living. 1Persistent AF versus Sinus Rhythm, 2Paroxysmal AF versus Sinus Rhythm, 3Persistent AF versus Paroxysmal AF. *Age adjusted cut-off.

MoCA patients were offered an analysis of cognitive function by a neuropsychologist, but outcomes of that analysis were not available for this study. Patient consent and ethical board approval were not required, since this study used archival data of standard geriatric evaluations and had no implications on therapeutic decisions.

Baseline characteristics were collected from all patients including their gender, age, medical history and medication use. All baseline ECGs were assessed by an experienced cardiologist (JR), to determine if patients had sinus rhythm (SR) or AF. To determine the rhythm on the Holter monitor the judgement of the clinically consulted cardiologists was retrieved from the medical files. A frailty index (FI) was created based on the accumulation of deficit model, as proposed by Searle and colleagues, and Rockwood and colleagues [17, 28]. In this study, we created a FI using a total of 45 deficits, comprised of 29 somatic items, 3 items of cognitive function and 13 items of basic daily functioning. Patients were considered frail at an FI of 0.18 to 0.24, and severely frail with an FI of 0.25 or higher.

Patients were classified as having SR if they were not known with AF and both their ECG and Holter monitor showed SR. Patients were classified as having persistent AF if their medical history notes AF and both the ECG and Holter showed AF as well. Paroxysmal AF was defined as having AF in the medical history, but either or both the ECG and Holter showed SR. In the case of first diagnosed AF, it was considered persistent when both the ECG and Holter showed AF, and was classified as paroxysmal when either the ECG or Holter showed SR.

The scores of the MMSE and MoCA were compared between the groups (SR, persistent AF and paroxysmal AF). Also whether patients scored below the common threshold for cognitive impairment was compared between these groups. For both the MMSE and MoCA this threshold is less than 26 out of 30 points. There were several reasons to perform an MRI of the brain, such as abnormalities in the neurological examination, walking disorders, suspected epilepsy and cognitive deficits, see also the published description of the FSC protocol [23, 24]. If an MRI of the brain was available, WMH were assessed with the Fazekas score, a categorical visual rating scale with a range from 0 to 3 points [22]. Furthermore, mesotemproal atrophy (MTA) was assessed using a categorical visual rating score with a range from 0 to 4 [29]. Age adjusted cut-off scores were used to identify patients with relevant MTA [30].

Statistical analysis

Analyses were performed using SPSS for Windows, version 20 (SPSS, Inc, Chicago, IL). Categorical variables were expressed as counts and percentages, continuous variables as mean value with standard deviation. Comparisons between participants were conducted using the Pearson Chi square for categorical variables and T test for continuous variables. P values of 0.05 or smaller were considered statistically significant. Possible confounders were analysed using the Mantel-Haenszel test for conditional independence.

Results

Participants

In total, 518 patients aged 65 years or older visited the FSC. In 493 patients a MMSE was performed and in 428 patients also a MoCA was performed. In all of these 428 patients both an ECG and a 24 hour Holter monitor was performed and consequently these 428 patients were included in this analysis. An MRI was performed in 332 patients. The medical history is shown in Table 1. The mean age was 80 ± 7 years, 66% were female and cardiovascular disease was very prevalent. Patients were on average known with 11 ± 5 morbidities

Table 3: Medication use

	Total	SR	Persis AF	PAF
ACE or ARB, n (%)	192 (44.9)	136 (41.3)	26 (56.5)	30 (56.6)
Beta blocker, n (%)	142 (33.2)	98 (29.8)	22 (47.8)	22 (41.5)
Anti platelet agent, n (%)	143 (33.4)	131 (39.8)	4 (8.7)	8 (15.1)
Vitamin K antagonist, n (%)	93 (21.7)	15 (4.6)	39 (84.8)	39 (73.6)
Diuretics, n (%)	141 (32.9)	102 (31.0)	19 (41.3)	20 (37.7)
Lipid lowering drugs, n (%)	202 (47.2)	151 (45.9)	20 (43.5)	31 (58.5)
Dihydropyridines, n (%)	71 (16.6)	53 (16.1)	8 (17.4)	10 (18.9)
Anti arithmetic, not Beta blocker, n (%)	62 (14.5)	14 (4.3)	24 (52.2)	24 (45.3)
Proton pump inhibitor, n (%)	178 (41.6)	136 (41.3)	23 (50.0)	19 (35.8)
Pulmonary agents, n (%)	74 (17.3)	56 (17.0)	9 (19.6)	9 (17.0)
Vitamin supplements, n (%)	183 (42.8)	139 (42.2)	18 (39.1)	26 (49.1)
Thyroid hormone, n (%)	42 (9.8)	30 (9.1)	6 (13.0)	6 (11.3)
Bisphosphanate, n (%)	34 (7.9)	28 (8.5)	4 (8.7)	2 (3.8)
Oral antidiabetics, n (%)	65 (15.2)	49 (14.9)	8 (17.4)	8 (15.1)
Insulin, n (%)	24 (5.6)	17 (5.2)	2 (4.3)	5 (9.4)
Pain relievers, n (%)	116 (27.1)	88 (26.7)	12 (26.1)	16 (30.2)
Benzodiazepine, n (%)	82 (19.2)	62 (18.8)	8 (17.4)	12 (22.6)
Antidepressants, n (%)	61 (14.3)	52 (15.8)	3 (6.5)	6 (11.3)
Antipsychotics, n (%)	9 (2.1)	7 (2.1)	1 (2.2)	1 (1.9)

Abbreviations: SR: Sinus Rhythm, Persis AF: persistent AF, PAF: paroxysmal AF. 1Persistent AF versus Sinus Rhythm, 2Paroxysmal AF versus Sinus Rhythm, 3Persistent AF versus Paroxysmal AF.

and used 7 ± 3 different drugs. 90 patients were known with AF and 9 patients were first diagnosed with AF, constituting to an overall prevalence of AF of 23%. Of all AF cases, 53 were paroxysmal AF (54%) and 46 were persistent AF (46%). Patients with persistent and with paroxysmal AF were known significantly more often with heart failure (35% and 23% respectively, versus 5% in patients with SR, p <0.01) and chronic kidney disease (20% and 25% respectively, versus 9% in patients with SR, p 0.03 and p <0.01).

Functional state and frailty

Functional and cognitive state is shown in Table 2. The mean FI was 0.28 (95% CI of the mean 0.11 to 0.45), indicative of severe frailty in the entire cohort. In total only 26 patients (6%) were not frail, with an average FI of 0.13, and all of these 26 patients were known with SR. Patients with persistent AF were the frailest, with an FI of 0.34 (95% CI of the mean 0.16 to 0.51). Those with paroxysmal AF had an FI of 0.31 (95% CI of the mean 0.15 to 0.48), and patients with SR an FI of 0.27 (95% CI of the mean 0.11 to 0.44). Both the patients with persistent and paroxysmal AF had a significantly higher FI than the patients with SR (p <0.01 for persistent AF versus SR, p 0.01 for paroxysmal AF versus SR). The Tinetti test for gait and balance was abnormal in 66% of all patients and a gait disorder was present in 16% [31]. Furthermore, 51% uses a walking aid. For their age and gender, handgrip strength was less than expected in 68% of patients. Most of the patients live at home, 5% live in an elderly or nursing home, 19% need help performing activities of daily living (ADL) and 32% are dependent on others in respect to the instrumental ADL. In 20% of the patients there was a risk for malnourishment, 20% had problems hearing and 44% were known with visual impairment.

Cognitive state

At baseline, 14 patients (3%) of the studied cohort were known with dementia and 60 patients (14%) with mild cognitive impairment (MCI). The rate of known dementia or MCI was not statistically different between patients with SR, paroxysmal AF or persistent AF. Overall, the mean score of the MMSE was 27 points, and of the MoCA 24 points. In general, cognitive decline was found with the MMSE in 17% of patients with SR, 11% of patients with paroxysmal AF and in 33% of patients with persistent AF. With the MoCA, cognitive decline was found in 64% of patients with SR, 60% of patients with paroxysmal AF and 80% of patients with persistent AF. Supplementary Table A shows the associations between morbidities and cognitive decline as found on the MMSE or MoCA. Cognitive decline was found with the MMSE more often in patients known with persistent AF (33%, p = 0.01), parkinsonism (36%, p = 0.003), and chronic kidney disease (33%, p = 0.007). With the MoCA, cognitive decline was found more often in patients with persistent AF (80%, p = 0.02), chronic kidney disease (81%, p = 0.013), heart failure (77%, p = 0.094), and parkinsonism (78%, p = 0.069). Since both heart failure and chronic kidney disease are associated with cognitive decline, they are possible confounders in the association between AF and finding cognitive decline on the MMSE or MoCA. Controlling for confounding shows that in patients with paroxysmal AF finding cognitive decline on the MMSE or MoCA is independent of the presence of heart failure or chronic kidney disease (Mantel-Haenszel test p = 0.107 and p = 0.219 respectively). However, in patients with persistent AF, finding cognitive decline on the MMSE is dependent on the presence of heart failure or chronic kidney disease (Mantel-Haenszel test p = 0.021), but with the MoCA it is not (Mantel-Haenszel tests of conditional independence p = 0.103).

Imaging outcomes

In 332 patients (78%) an MRI of the brain was performed, the mean Fazekas score was 1.9 ± 1.0 points and the mean MTA score was 1.7 ± 0.8 points. In patients with SR the Fazekas score was 1.8 points, and in patients with either paroxysmal AF or persistent AF the Fazekas score was higher, respectively 1.9 and 2.1 points (p = 0.22 and p = 0.65, respectively, compared to SR). Heart failure, comprised of both heart failure with reduced ejection fraction and with preserved ejection fraction, was present in 26 of the patients that underwent MR imaging. In patients with heart failure the Fazekas score was 2.2 ± 0.9 and in those without 1.8 ± 1.0 (p = 0.07). And in patients with chronic kidney disease the Fazekas score was 2.1 ± 0.9, compared to 1.8 ± 1.0 in those without (p = 0.15).

The MTA score was significantly higher in patients with persistent AF compared to those with SR (2.1 vs 1.7, p 0.02), and compared to those with paroxysmal AF (2.1 vs 1.6, p<0.01). Relevant MTA was present in 95 patients with SR (38%), 11 patients with persistent AF (37%) and 14 patients with paroxysmal AF (41%). No statistically significant differences were found in the rate of relevant MTA between patients with AF or SR.

Patients with a MMSE below the cut-off had a significantly higher MTA score (2.1 vs 1.6, p = <0.001), but not a higher Fazekas score (2.1 vs 1.8, p = 0.11). Patients with a MoCA score below the cut-off

too had a significantly higher MTA score (1.8 vs 1.6, p = 0.01), but not a higher Fazekas score (1.9 vs 1.8, p = 0.53). Also, patients with a MMSE below the cut-off had more relevant MTA (53 vs 35%, p = 0.02) but patients with a MoCA below the cut-off did not have relevant MTA more often (40 vs 36%, p = 0.55).

Discussion

As hypothesized, the sensitivity to detect cognitive decline in geriatric patients with AF is much higher for the MoCA than for the MMSE. Of patients with paroxysmal AF 60% score abnormally on the MoCA, and of those with persistent AF 80% score abnormally on the MoCA, compared to an abnormal score on the MMSE in only 11 and 33% respectively. Both the MMSE and MoCA are validated instruments to identify cognitive decline, but the MoCA is known has a higher sensitivity for identifying MCI compared to the MMSE [19,20]. It is therefore likely that the MoCA produced a better estimate of the prevalence of cognitive decline in this cohort than the MMSE.

In patients with persistent AF, cognitive decline can be identified with the MoCA independently of the presence of heart failure or chronic kidney disease, while our analysis suggests that to identify patients with persistent AF and cognitive decline with the MMSE was dependent on the presence of heart failure or chronic kidney disease. For patients with paroxysmal AF, finding cognitive decline on the MMSE was not dependent on the presence of heart failure or chronic kidney disease. This indicates that the MoCA is better suited to detect cognitive decline in patients with AF than the MMSE, possibly due to its higher sensitivity to subcortical vascular damage compared to MMSE [20].

In this cohort of very elderly and severely frail patients, we found no differences in prevalence of dementia at baseline between those with and without AF, and the prevalence of dementia was low. Probably this is explained by a referral and selection bias. Cognitive disorders can contribute greatly to an individual's risk of falling [32-34], but cognitive decline itself might not have been noticed by caretakers or diagnosed by the general practitioner before visiting the FSC. To find a high rate of cognitive decline in a population referred specifically because of falling is therefore not surprising.

The studied cohort has a high average Fazekas score, indicative of that most patients had relevant WMH. We found small differences on MR imaging were found between patients with SR or AF. More WMH were found in patients with paroxysmal or persistent AF, compared to patients with SR, but these differences were not statistically significant. In patients with cognitive decline as found on either the MMSE or the MoCA, more MTA was found, but not more WMH. Only in patients with a MMSE below cut-off significantly more relevant MTA was found. Since MTA is a biomarker for Alzheimer's disease, the combination of relevant MTA and cognitive decline found by means of a MMSE, could be suggestive for the presence of dementia in these patients. This is in contrast with the patients who scored below the cut-off of the MoCA, in whom relevant MTA was not seen more often. Most likely, this is explained by the MoCA being more sensitive to MCI compared to the MMSE [19,20]. Since both patients with persistent or paroxysmal AF were significantly more often known with heart failure, and patients with heart failure in general had more WMH in this cohort, it is possibly hypoperfusion as consequence of heart failure that lead to WMH.

The study of Glotzer and colleagues found a higher rate of adverse events in patients with a high burden of AF [35]. Also our findings show that cognitive outcomes of patients with persistent or paroxysmal AF are different, and we encourage that future research to study the influence of the burden of AF on cognitive outcomes.

This study has several limitations. The cross-sectional design only allows a description of the population and possible associations between patient characteristics, but cannot provide conclusions about causality. Only the cognitive screening tests were used in this study and not the outcomes of a full multidisciplinary cognitive assessment that often include biomarkers, and therefore we could only detect cognitive decline. Nonetheless, both the MMSE and the MoCA are screenings tools for the identification of patients with cognitive decline [18-20]. They can aid the physician with the selection of patients that should be referred for a full cognitive assessment. Our results most of all show the need to assess cognitive function in elderly patients with AF, but is not a reliable reflection of the prevalence of cognitive disorders within this population.

The data describes the patients' health status up until the moment of inclusion but follow up data of adverse events were not available. This study used the medical history as it was reported by the referring physician, combined with what was retrieved from the hospital files and therefore might be incomplete or otherwise imprecise. It is possible that a higher prevalence of white matter hyperintensities is found in the very elderly in general because of cardiovascular disease [36], which is reflected in the high mean Fazekas score of 1.9 points in the studied cohort.

Conclusion

In this study we found that cognitive decline in patients with AF is better detected using the MoCA than the MMSE. Based on these findings we urge physicians to screen their AF patients for cognitive decline, preferably using the MoCA instead of the MMSE.

The marked differences between patients with persistent or paroxysmal AF could suggest that the burden of AF influences long term cognitive outcomes, possibly in interaction with heart failure, which should be addressed in future research.

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Supplementary Tables

Table A: Factors associated with cognitive decline

		MMSE < 26 points, n (%)	p	MoCA < 26 points, n (%)	P
Sinus Rhythm	present	57 (17,3)	0,376	209 (63,5)	0,281
	absent	21 (21,2)		69 (69,7)	
Paroxysmal AF	present	6 (11,3)	0,187	32 (60,4)	0,447
	absent	72 (19,2)		246 (65,6)	
Persistent AF	present	15 (32,6)	0,014	37 (80,4)	0,022
	absent	63 (16,5)		241 (63,1)	
Hypertension	present	54 (18,4)	1,000	197 (67,0)	0,192
	absent	24 (17,9)		81 (60,4)	
Diabetes mellitus	present	17 (19,5)	0,756	62 (71,3)	0,208
	absent	61 (17,9)		216 (63,3)	
Ischemic heart disease	present	22 (20,4)	0,564	74 (68,5)	0,415
	absent	56 (17,4)		204 (63,7)	
Heart failure	present	8 (18,2)	1,000	34 (77,3)	0,094
	absent	70 (18,2)		244 (63,5)	
Parkinsonism	present	16 (35,6)	0,003	35 (77,8)	0,069
	absent	62 (16,2)		243 (63,4)	
Chronic kidney disease	present	17 (32,7)	0,007	42 (80,8)	0,013
	absent	61 (16,2)		236 (62,8)	
Gait disorder	present	16 (23,2)	0,238	50 (72,5)	0,170
	absent	62 (17,3)		228 (63,5)	

Abbreviations. AF: Atrial fibrillation.

Table B: Cognitive screening and cognitive disorders among patients using beta blockers.

	Beta blocker			Persis AF Beta blocker			PAF Beta blocker		
	No (n=286)	Yes (n=142)	p	No (n=24)	Yes (n=22)	p	No (n=31)	Yes (n=22)	p
MMSE below 26, n (%)	49 (17.1)	29 (20.4)	0.406	6 (25.0)	9 (40.9)	0.250	3 (9.7)	3 (13.6)	0.654
MoCA below 26, n (%)	180 (62.9)	98 (69.0)	0.215	19 (79.2)	18 (81.8)	0.821	17 (54.8)	15 (68.2)	0.328
MCI diagnosis, n (%)	39 (13.6)	21 (14.8)	0.746	3 (12.5)	1 (4.5)	0.339	3 (9.7)	1 (4.5)	0.486
Dementia diagnosis, n (%)	8 (2.8)	6 (4.2)	0.434	0 (0.0)	3 (13.6)	0.061	1 (3.2)	0 (0.0)	0.395

Abbreviations: Persis AF: persistent atrial fibrillation, PAF: paroxysmal atrial fibrillation. MMSE: Mini Mental State Examination, MoCA: Montreal Cognitive Assessment, MCI: Mild Cognitive Impairment.

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Meta-Analysis of Catheter Ablation versus Medical Therapy in Patients with Atrial Fibrillation Without Heart Failure

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Abstract

Introduction: Catheter ablation has shown to reduce mortality in patient with atrial fibrillation (AF) and heart failure (HF) with reduced ejection fraction. Its effect on mortality in patients without HF has not been well elucidated.

Methods: Thirteen randomized controlled trials encompassing 3856 patients were selected using PubMed, Embase and the CENTRAL till April 2019. Estimates were reported as random effects risk ratio (RR) with 95% confidence intervals (CI).

Results: Compared with medical therapy, catheter ablation did not reduce the risk of all-cause mortality (RR, 0.86, 95% CI, 0.62-1.19, P=0.36; I^2=0), stroke (RR, 0.55, 95% CI, 0.18-1.66, P=0.29; I^2=0), need for cardioversion (RR, 0.84, 95% CI, 0.66-1.08, P=0.17; I^2=0) or pacemaker (RR, 0.59, 95% CI, 0.34-1.01, P=0.06; I2=0). However, ablation reduced the RR of cardiac hospitalization (0.37, 95% CI, 0.18-0.77, P=0.01; I^2=86), and recurrent atrial arrhythmia (0.46, 95% CI, 0.35-0.60, P<0.001; I^2=87). There were non-significant differences among treatment groups with respect to major bleeding (RR, 1.89, 95% CI, 0.59-6.08, P=0.29; I^2=15), and pulmonary vein stenosis (RR, 3.00, 95% CI, 0.83-10.87, P=0.09; I^2=0), but had significantly higher rates of pericardial tamponade (RR, 4.46, 95 % CI, 1.70-11.72, P<0.001; I^2=0).

Conclusions: Catheter ablation did not improve survival compared with medical therapy in patients with AF without HF. Catheter ablation reduced cardiac hospitalization and recurrent atrial arrhythmia at the expense of pericardial tamponade.

Introduction

Atrial fibrillation (AF) is the most common type of cardiac rhythm disorder, associated with increased morbidity and mortality [1–3]. AF has an estimated prevalence of ~ 34 million people worldwide [4]. Guidelines for the management of AF recommends medical therapy (MT) (rate control or rhythm control) as an initial management, however in case of unstable, symptomatic or drug refractory conditions, catheter ablation (CA) is the recommended management [5,6]. MT for sinus rhythm (SR) restoration has not shown significant survival advantage over a rate-control strategy [7]. Moreover, literature adds that use of antiarrhythmic drugs is associated with increased re-hospitalization. [7–10]. Since anti arrhythmic drugs show moderate results in maintaining SR, pro arrhythmic, and causes significant side effects, therefore, physicians need to focus on the safety profile other than efficacy while prescribing them [5]. Moreover, the selection of antiarrhythmic drug becomes limited when the comorbidity, cardiovascular risk, side effects, and preference of the patient is taken into account. Literature has shown significant efficacy of CA both as an initial and secondary approach in management to maintain SR in case of MT failure, improvement in functional status, and cardiac function [11–15]. Catheter ablation has shown reduction in mortality with AF and systolic heart failure (HF), however no survival benefit in patients without HF has been observed [16]. Since previous meta-analysis [16], new randomized data has provided further insight on this topic and has the potential to impact clinical outcomes [17, 18]; therefore, we sought to update the meta-analysis in subjects with AF without HF.

Key Words

Catheter Ablation; Atrial Fibrillation; Medical Therapy; Meta-Analysis.

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Table 1: Baseline characteristics of the randomized clinical trials.

First Author/Study (Year)	Groups (Ablation vs AAD Class)	N	Mean Age (yrs)	Male (%)	SHD (%)	LAD (mm)	DM (%)	CAD (%)	Prior Stroke (%)	LVEF (%)	Cross over to RFA (%)	AF Pattern (%)		Blanking (weeks)	Follow-Up (months)
												Paroxysmal	Persistent		
Krittayaphong et al. (2003)	Ablation	15	55	73	13	40	6.7	NR	NR	64	NR	73	27	NR	12
	Amio	15	49	53	13	39	20	NR	NR	62		60	40		
Wazni et al. (2005)	Ablation	33	53	NR	28	41	NR	NR	NR	53	NR	97	3	8	12
	Class I, III	37	54	NR	28	42	NR	NR	NR	54		95	5		
Oral et al. (2006)	Ablation	77	55	87	08	45	NR	NR	NR	55	77	95	5	12	12
	Amio	69	58	90	09	45	NR	NR	NR	56		0	100		
APAF (2006)	Ablation	99	55	70	07	40	5.1	NR	NR	60	42	100	0	6	12
	Class I, III	99	57	65	04	38	4	NR	NR	61		100	0		
Stabile et al. (2006)	Ablation	68	62	62	63	46	NR	NR	NR	59	52	62	38	4	12
	Class I, III	69	62	64	62	45	NR	NR	NR	58		72	28		
A4 study (2008)	Ablation	53	50	85	19	39	1.9	5.7	NR	63	63	100	0	12	12
	Class I, III	59	52	83	24	40	3.4	10	NR	66		100	0		
Forleo et al. (2009)	Ablation	35	63	57	46	44	NR	20	NR	55	NR	46	54	5	12
	Class I, III	35	65	66	54	45	NR	20	NR	53		37	63		
Wilber et al. (2010)	Ablation	106	55.5	68.9	9.5	NR	9.5	NR	1.9	62.3	NR	NR	NR	12	9
	Class I, III	61	56.1	62	15	NR	12	NR	3	62.7		NR	NR		
MANTRA PAF (2012)	Ablation	146	56	68	5	40	4	4	NR	NA	36	100	0	12	24
	Class I, III	148	54	72	10	40	7	1	NR	NA		100	0		
SARA (2014)	Ablation	98	55	76	NR	NR	NR	3.1	3.1	61.1	47.9	NR	NR	12	12
	Class I, III	48	55	37	NR	NR	NR	2.1	2.1	60.8		NR	NR		
RAAFT2 (2014)	Ablation	66	56	77	NR	40	1.5	9.1	4.6	61.4	47	98.5	96.7	12	21
	Class I, III	61	54	74	NR	43	6.6	3.3	6.6	60.8		1.5	3.3		
CAPTAF (2019)	Ablation	79	55.8	73.4	1.3	41.7	3.8	2.5	5.1	56.2	10.1	70.9	29.1	12	12
	Class I, III	76	56.3	81.6	1.3	41.7	3.9	3.9	0	56.1		75	19		
CABANA (2019)	Ablation	1108	68	62.7	NR	NR	25.3	18.8	6.1	-	27.1	42.4	47.3	12	12
	Class I, III	1096	67	63	NR	NR	25.7	19.7	5.3	-		43.5	47.3		

A4 Study=A Comparison of Antiarrhythmic Drug Therapy and Radio Frequency Catheter Ablation in Patients With Paroxysmal Atrial Fibrillation; AF = atrial fibrillation; Amio = amiodarone; APAF=Ablation for Paroxysmal Atrial Fibrillation; CABANA= The Catheter Ablation vs Antiarrhythmic Drug Therapy for Atrial Fibrillation Trial; CAD=coronary artery disease; CAPTAF= Catheter Ablation compared with Pharmacological Therapy for Atrial Fibrillation; class I, III = class I, III antiarrhythmic agents; DM = diabetes mellitus; LAD = left atrial diameter; LVEF = left ventricular ejection fraction; MANTRA-PAF = Medical Antiarrhythmic Treatment or Radiofrequency Ablation in Paroxysmal Atrial Fibrillation: A Randomized Prospective Multicenter Study; NA = not available; NR = not reported; RAAFT2 = Radiofrequency Ablation vs Antiarrhythmic Drugs as First-Line Treatment of Paroxysmal Atrial Fibrillation; RFA = radiofrequency ablation; SARA = Study of Ablation Versus antiarrhythmic Drugs in Persistent Atrial Fibrillation; SHD = structural heart disease

Methods

This meta-analysis was conducted as per the guidelines of Cochrane Collaboration [19], and it is reported in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) report [20].

Data Sources And Searches

An updated literature search was conducted to select randomized controlled trials using PubMed, Embase and the CENTRAL till April 2019 using key search terms, "atrial fibrillation", "catheter ablation", "pulmonary vein isolation" and "antiarrhythmic drugs". The PubMed search algorithm is reported in the [Table]. A gray literature [21,22] search was carried out by searching www.clinicaltrialresults.com, www.clinicaltrials.gov, www.cardiosource.org, www.esccardio.org, and abstracts and presentations from major cardiovascular meetings. Reference lists of the relevant articles were also reviewed. All citations were downloaded into EndNote X7 (Thompson ISI ResearchSoft, Philadelphia, Pennsylvania), and duplicates were removed electronically and manually.

Study Selection

Two independent reviewers (M.Z.K. and M.Z.) analyzed the citations at the level of title and abstract, and the studies were considered on the basis of following criteria: 1) RCTs investigating CA versus MT (rhythm- or rate-control medications) in patients with AF; and 2) studies reporting at least 1 event for outcomes of interest in an adult population. Moreover, the inclusion criteria for studies was not limited to sample size, language preference, follow up duration or availability of the full text. The whole process was supervised by a third author (S.U.K.), and any discrepancies were resolved by consensus.

Quality Assessment And Data Extraction

Two independent authors (M.U.K and A.A.) used a structured data collection form to abstract the data for baseline characteristics, techniques of the procedure, events, nonevents, mode of medical treatment, sample size, mean, standard deviations, crude point estimates or standard error estimates, and follow-up duration. Additionally, the continuous outcomes were extracted as per the differences between the 2 groups during the follow up in addition

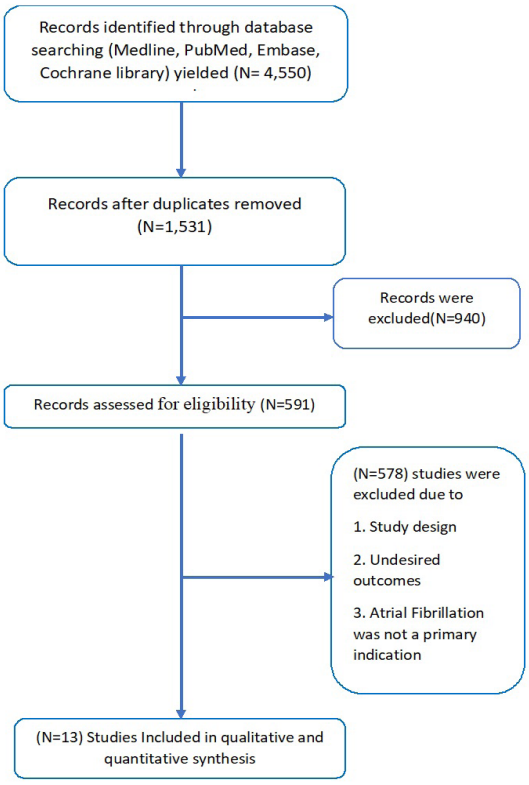

Figure 1: **Flow Chart of our study**

to any changes from baseline. For all estimates, adjusted estimates were extracted. Intention-to-treat principle was used as basis for the acquisition of data. Data adjudication was done by 1 author (S.U.K.). Methodological quality or risk bias assessment was done at study level using the Cochrane bias risk assessment tool [23] (Table).

Outcome Measures

The primary endpoint was all-cause mortality. The secondary endpoints were stroke, cardiac hospitalization, recurrent atrial arrhythmia, need for cardioversion or pacemaker, major bleeding, pulmonary vein stenosis and pericardial complications. The definitions of the endpoints were taken as reported in the included trials.

Statistical Analysis

Estimates were assessed by using a DeSermonian and Laird random effects model. We preferred a random effects model to account for any study heterogeneity [24]. Binary outcomes were calculated as risk ratio (RR) or risk difference, and continuous estimates were expressed as mean difference (MD) with 95% confidence interval (CI). Because both the RR and risk difference represent the same data, we focused on RR estimates in this review. A p value of 0.05 was set as significant. Heterogeneity was assessed using Q statistics and quantified by I2 with values >50% consistent with a high degree of heterogeneity [25]. Publication bias was assessed using Egger's regression test. All analyses were conducted using Comprehensive Meta-analysis software version 3.0 (Biostat, Englewood, New Jersey).

Results

The initial search yielded 4,550 records, of which 3,019 citations were removed as duplicates; of the remaining 1,531 articles, 940 studies were excluded if the title and/or abstract suggested that the studies were not relevant. A total of 591 records were assessed for eligibility, of which 578 studies were excluded because of their study design or undesired outcomes or when AF was not a primary indication. Ultimately, 13 RCTs (3856) met the inclusion criteria (Figure 1). Baseline characteristics of the trials are shown in Table 1 [18,19,26–36].

In 13 trials (3856 patients), the pooled mean age of patients was 56.8±4.8 years, 69% were males and 8.8% had coronary artery disease. The mean left ventricular ejection fraction (LVEF) was 59.1±3.8%, 67% patients had paroxysmal AF and 33% had persistent AF. The average follow-up duration was 19 months. Compared with medical therapy, ablation did not reduce the RR of all-cause mortality (0.86 [95% CI, 0.62-1.19], P=0.36; I^2=0; Figure 2) and stroke (0.55 [95% CI, 0.18-1.66], P=0.29; I^2=0). However, ablation reduced the RR of cardiac hospitalization (0.37 [95% CI, 0.18-0.77], P=0.01; I^2=86), and recurrent atrial arrhythmia (0.46 [95% CI, 0.35-0.60], P<0.001; I^2=87). There were non-significant differences among treatment groups with respect to safety outcomes (figure 3) such as major bleeding (1.89 [95% CI, 0.59-6.08], P=0.29; I^2=15), need for cardioversion (0.84 [95% CI, 0.66-1.08], P=0.17; I^2=0) or pacemaker (0.59 [95% CI, 0.34-1.01], P=0.06; I^2=0) and pulmonary vein stenosis (3.01 [95% CI, 0.83-10.92], P=0.09; I^2=0). However, pericardial complications were more common among the ablation group (4.44 [95% CI, 1.69-11.68], P<0.001; I^2=0). Egger's regression test did not detect publication bias for primary endpoint (P=0.94).

Discussion

In this meta-analysis, ablation did not reduce the risk of total mortality, stroke, need for cardioversion or pacemaker compared with medical therapy in patients with AF without HF. However, ablation was associated with 63% RR reduction of for cardiac hospitalization and 54% for recurrent atrial arrhythmia. Previous meta-analysis [13-16] addressed a mix of both HF and non-HF population, however those studies were limited by low power for hard outcomes and brief follow-ups of non-HF trials. Whereas, current meta-analysis was updated with the CABANA (Catheter Ablation Vs Antiarrhythmic Drug Therapy for Atrial Fibrillation) trial, the largest and longest follow-up study powered to assess effect of catheter ablation on mortality in subjects with AF without HF [17], and the CAPTAF (Catheter Ablation compared with Pharmacological Therapy for Atrial Fibrillation) trial [18] to confirm catheter ablation's lack of benefit on hard clinical endpoints in this subset of patients. Ablation was not significantly associated with stroke prevention but most of the patients with stroke risk factors were on anticoagulation even after ablation, therefore, making it difficult to assess actual stroke risk change with ablation. It remains uncertain whether after ablation anticoagulation can be safely discontinued. Ongoing the OCEAN (Optimal Anticoagulation for Higher Risk Patients Post Catheter Ablation for Atrial Fibrillation) trial (NCT02168829) will shed further light on this issue. Our analysis showed ablation had statistically significance reduction for cardiac hospitalization, the persistent benefits of having reduced risk for cardiac hospitalization

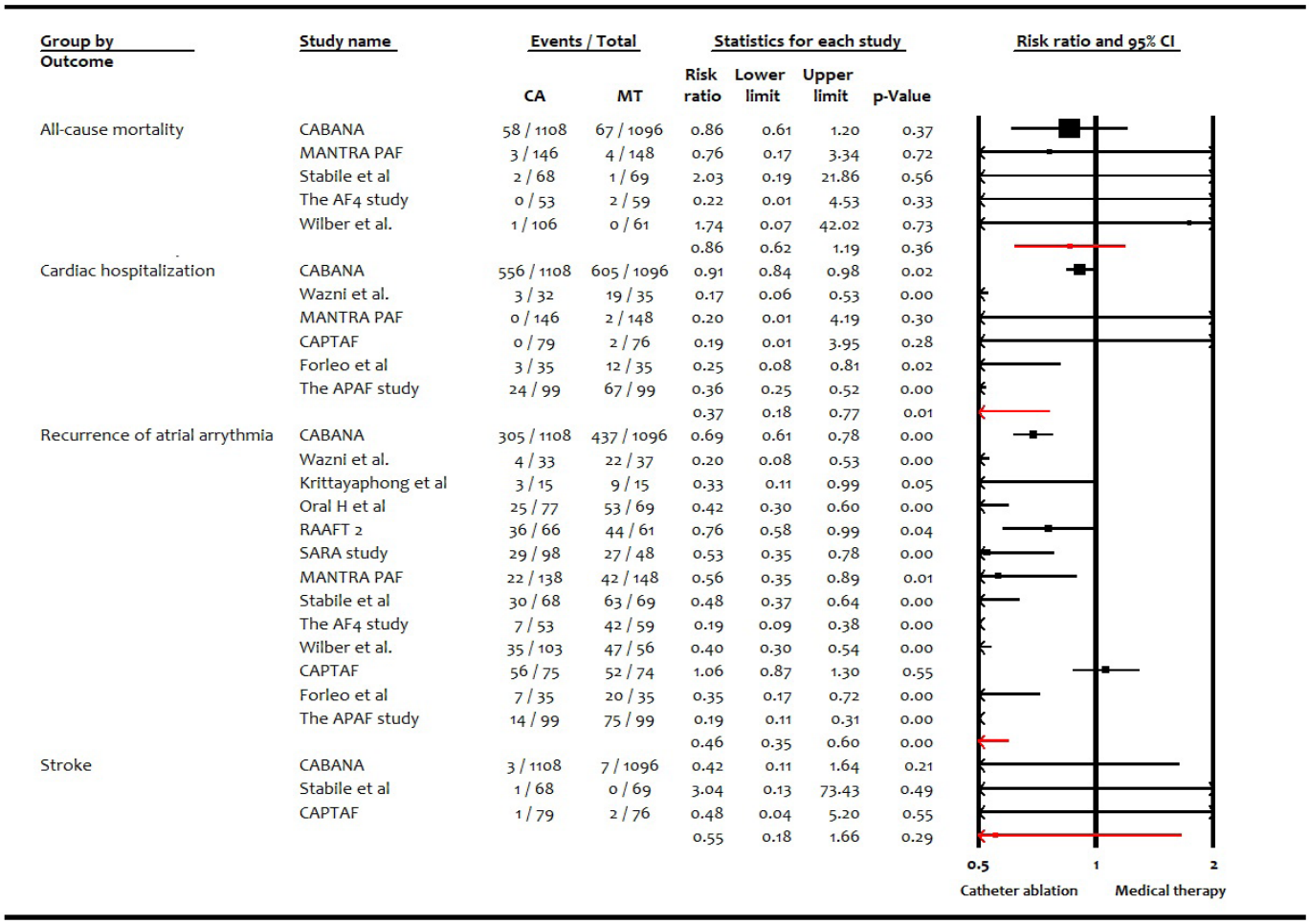

Figure 2: **Forest Plot Showing Results of Catheter Ablation versus Medical Therapy in Patients with Atrial Fibrillation Without Heart Failure**

and recurrent atrial arrhythmia with ablation are reassuring and carry significant implications for quality of life and health care expenditures. Finally, although, ablation was generally safe in terms of major bleeding or pulmonary vein stenosis, the benefits of reduced hospitalization and recurrent arrythmias were somewhat counterbalanced by higher rates of pericardial complications like cardiac tamponade, although infrequent, can be serious complications with significant mortality and morbidity [36].

Study Limitations

Considerable limitations of this meta-analysis include variations in ablation strategies, duration of treatment, post ablation antiarrhythmic therapy, methods of AF surveillance, CHA_2D-VAS_2c scores and follow-up durations. In addition to lack of blinding, protocol adherence and cross over were not random across most of the trials, therefore a high degree of selection bias was noticed. All-cause mortality was not adequately powered in any of the included individual trials. We refrained from assessment of Quality of Life due to paucity of data and heterogeneity in measurement scales. The safety endpoints were not powered and lacked precision. Moreover, this analysis is mainly driven by the CABANA trial as it had the highest number of participants.

Conclusions

Although among patients with AF without HF, ablation was associated with lower rates of cardiac hospitalization and recurrent atrial arrhythmia compared with medical therapy, subjects receiving ablation did not experience mortality benefit. Therefore, perceived advantages of ablation in "healthy" subjects with AF must be closely weighed against potential complications and health care use costs [37].

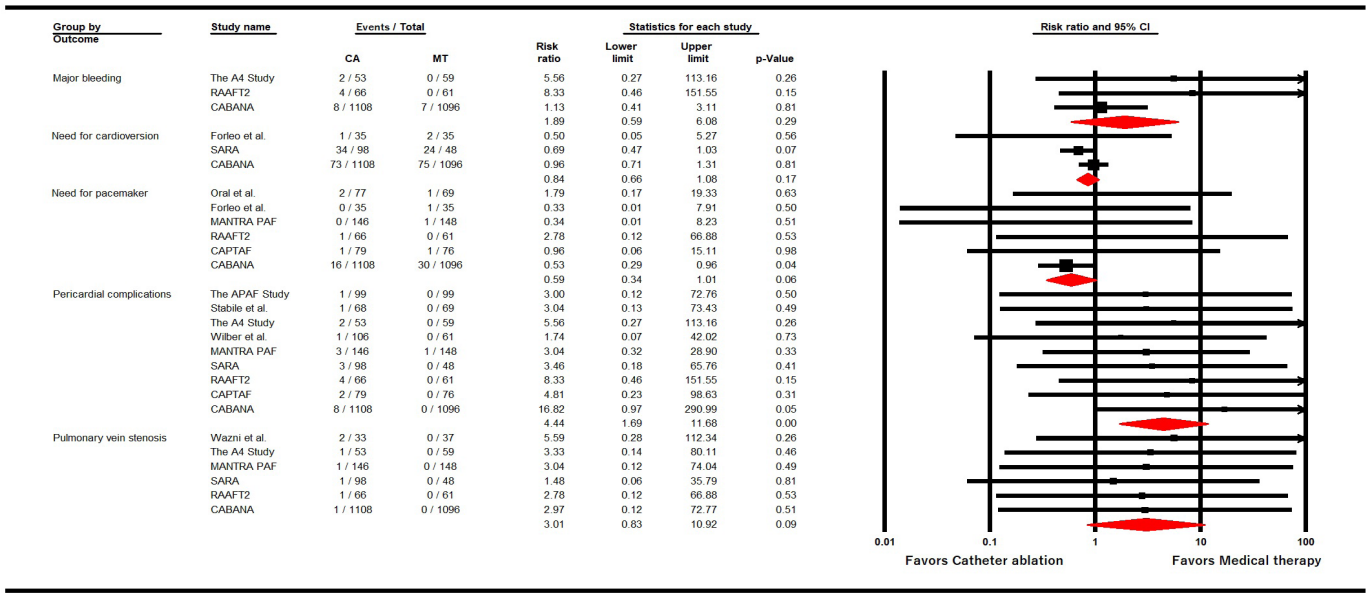

Figure 3: **Forest Plot showing safety analysis between Catheter Ablation versus Medical Therapy in Patients with Atrial Fibrillation Without Heart Failure**

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Pulmonary Vein Isolation Using Ablation Index Improves Outcome in Patients with Atrial Fibrillation

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Abstract

Aims: To evaluate the clinical outcome of pulmonary vein isolation (PVI) in radiofrequency ablation of atrial fibrillation (AF) comparing a strategy using Ablation Index (AI) and lesion contiguity with Contact Force (CF) only.

Methods: In a single-center retrospective design, we included 479 patients with AF (n=341 (71.2%) paroxysmal AF (PAF) and n=138 (28.8%) persistent AF (PeAF)) treated with first time radiofrequency ablation. In 2015, 210 patients underwent PVI based on a drag-and-ablate technique using CF only. In 2017, 269 patients underwent point-by-point PVI using AI and a maximum inter-lesion distance of 6 mm ensuring contiguity. Follow-up was performed after 12 months. Outcome was freedom from documented AF/atrial tachycardia (AT) after single procedure without use of anti-arrhythmic drugs at follow-up.

Results: There was no significant difference in baseline characteristics between the groups. The median procedure time and mean ablation time were significantly longer in the AI-group compared to the CF-group (131.5[113;156] min vs. 120.0[97;140] min, P < 0.01) and (44.1±10.0 min vs. 37.1±13.3 min, P < 0.01), respectively. Freedom from documented AF/AT was significantly higher in the AI-group compared to the conventional CF –group (71.0% vs. 62.4%, P = 0.046). The improvement in clinical outcome in the AI group is mainly driven by the outcome in patients with PeAF (64.9% vs. 50.0%, P = 0.078) and not PAF.

Conclusion: An ablation strategy combining AI and lesion contiguity improves the clinical outcome after first time PVI in patients with AF compared to a strategy using CF only.

Introduction

Catheter ablation is a recognized treatment of symptomatic atrial fibrillation (AF). Various ablation strategies have been suggested, but pulmonary vein isolation (PVI) remains the cornerstone of radiofrequency ablation (RFA) in both paroxysmal AF (PAF) and persistent AF (PeAF).[1, 2] New catheter technologies providing real-time measurement of Contact Force (CF) sensing between the catheter tip and endocardium[3] and automated ablation lesion tagging technology based on catheter stability have been introduced to optimize the ablation lesions and thereby achieve durable isolation of the pulmonary veins (PV).[4, 5] Recently, the Ablation Index (AI) algorithm that incorporates CF, time and power has been developed as a marker of adequate ablation lesion.[2, 6]

Key Words

Radiofrequency ablation - Pulmonary vein isolation - Persistent atrial fibrillation - Contact Force – Ablation Index

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AI accurately predicts lesion depth in animal models[7] and has shown improved clinical success rates when used in PVI ablation.[6, 8] A new concept using an automated ablation tagging module which combine AI values and a maximum distance of 6 mm between lesions to ensure contiguity has been investigated, and recent data show that this ablation strategy improves PVI durability and clinical outcome in patients with both PAF and PeAF.[9, 10]

The purpose of this study is to evaluate the efficacy and feasibility of this ablation concept in a population of PAF and PeAF patients compared to a conventional CF-guided PVI strategy.

Methods

Study population

Patients with symptomatic PAF or PeAF, who underwent first-time RFA during the year 2015 and 2017, were included. Patients with left ventricular ejection fraction (EF) <30%, age >80 years, previous major heart surgery (valve surgery, coronary artery bypass graft), congenital heart disease or additional lines during

PVI procedure (except cavotricuspid isthmus ablation for typical flutter) were excluded. Patients with interrupted procedure due to complications were excluded in the analysis of outcomes. PAF and PeAF were defined according to guidelines.[1]

The study was approved by the Danish Data Protection Agency (J.nr. 2018-41-5401 Dok.nr. 468739) and performed according to the declaration of Helsinki.

Ablation Technique

All procedures were performed with uninterrupted anticoagulant therapy (Warfarin or New Oral Anticoagulants (NOAC)). Before the procedure a CT scan of the left atrium was done. Pre-procedural transesophageal echocardiography was performed to exclude thrombus formation in the left atrium. The procedure was performed under minimal sedation using a combination of Midazolam and Fentanyl. After transseptal puncture, Heparine was administered with a target activated clotting time of 300-350 s. Electroanatomical mapping was performed with a multipolar mapping catheter (LASSO®, Biosense Webster Inc.). In 2015 (CF-group), PVI was performed with a CF catheter (SmartTouch™, Biosense Webster Inc.) and a drag-and-ablate technique using the CARTO® 3 system (version 6). During ablation, each ablation point was deployed using the VISITAG™ module (settings: stability 3 mm for 5 s., CF 25 % > 5 grams). In 2017 (AI-group), we performed point-by-point PVI using the SmartTouch™ catheter and AI (VISITAG™ setting: stability 3 mm for 5 s., CF 25% > 5 grams, an AI of 550 (anterior/superior) and 400 (posterior/inferior)) and lesion contiguity with a maximum inter-lesion distance of 6 mm (Figure 1). The AI formula was described in the PRAISE study as a weighted formula , with constants replaced by letters [10]

$$AblationIndex = (K * \int_0^t CF^a(\tau)P^b(\tau)d\tau$$

where CF = contact force, P = power and d = application duration.

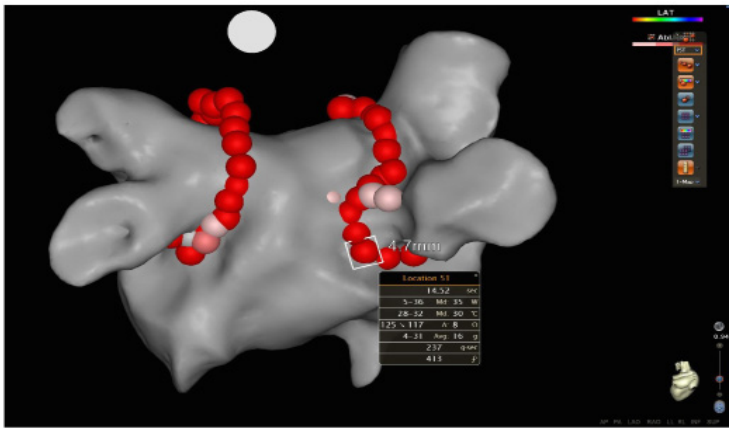

Figure 1: illustrates a 3-dimensional electroanatomical map of the left atrium and adjacent pulmonary veins in a posterior-anterior projection. The red dots correspond to each ablation point obtained during pulmonary vein isolation using the VISITAG™ Module and Ablation Index target settings. The inter-lesion distance between the points is also measured.

Table 1: Baseline Characteristics

	Contact Force (n=210)	Ablation Index (n=269)	P-value
Age	60.6±9.1	61.8±9.3	0.16
BMI	28.2(24.7;31.6)	27.2(24.8;31.0)	0.27
Sex (Male)	142(67.6%)	191(71.0%)	0.43
Hypertension	112(53.3%)	131(48.7%)	0.31
Congestive heart failure	14(6.7%)	12(4.5%)	0.29
Diabetes	18(8.6%)	24(8.9%)	0.89
TCI	17(8.1%)	14(5.2%)	0.20
Vascular disease	15(7.1%)	29(10.8%)	0.17
CHA_2DS_2-VASc score	1.6±1.3	1.6±1.4	0.97
Type of AF			
PAF	146(69.5%)	195(72.5%)	
PeAF	64(30.5%)	74(28.8%)	0.51

(BMI: "Body Mass Index". TCI: "Transitory Cerebral Ischemia". PAF: "Paroxysmal atrial fibrillation". PeAF: "Persistent atrial fibrillation". Congestive heart failure: "Defined as left ventricular ejection fraction (EF) less than 40% but higher than 30%").

Cavo-tricuspid isthmus (CTI) ablation was performed if patients had documented typical atrial flutter before or during procedure. The endpoint of procedure was bi-directional block in the PVs confirmed by the LASSO® catheter. Patients with PeAF underwent cardioversion during the procedure.

Clinical follow-up

All patients were seen in the outpatient clinic after a 3 months blanking period and at 12 months of follow-up. The clinical visits included ECG, recording of symptoms and adjustments in medications. If no symptoms were presented and ECG showed sinus rhythm at the 3-month follow-up, all antiarrhythmic drugs (AAD) were discontinued. Patients underwent 7 days holter-monitoring to confirm any atrial arrhythmias if AF recurrence was suspected and the ECG was normal. In case of documented symptomatic AF recurrence, patients were scheduled for re-ablation. Patients with palpitations but no documented AF/AT continued AAD treatment. Patients with any AF symptoms between the clinical follow-up were advised to seek medical attention to confirm AF by ECG.

The primary outcome was freedom from documented AF or atrial tachycardia (AT) lasting more than 30 seconds verified on ECG at any time between 3- and 12 months without re-ablation or use of AAD, except betablockers.[1] Secondary outcome was the rate of re-ablation.

Statistical analysis

Continuous variables are presented as mean ±SD if they were normally distributed or median and [25th;75th] percentiles if the data are not normally distributed. For comparison we used Students t-test for normally distributed data. For comparison of non-normally distributed data we used Mann Whitney U-test or logistic transformation. Categorical data are presented as frequency and percentage and compared with chi-square test.

Logistic and multivariate logistic regression analyses were used to

identify predictors of recurrence. Results are presented as relative risk ratio (95% confidence interval).

A P-value of < 0.05 was considered statistical significant.

All analysis was performed in Stata/IC (Version 15.1, StataCorp LLC, College Drive, USA)

Results

Patient characteristics

In total, 479 patients who underwent first time PVI procedure for symptomatic AF were included (n=341 (71.2%) PAF and n=138 (28.8%) PeAF). There were no differences in baseline characteristics between the CF-group: (n=210 (43.8%)) and the AI-group: (n=269 (56.2%)) (see Table 1).

Procedural evaluation results

Successful PVI was achieved in 476 (99.4%) patients. Three procedures were interrupted before complete PVI isolation due to excessive pain during ablation. The total procedural- and ablation times were significantly longer in the AI-group compared to the CF-group (135.5[114;160] min vs. 120.0 [99;144.5] min, P ≤ 0.01) and (44.7±11.3 min vs. 37.1±13.4 min, P ≤ 0.01), respectively. The fluoroscopy time was shorter in the AI-group (11.4±7.1 min vs. 15.1±8.4 min, P ≤ 0.01) (Table 2). Four procedural complications were registered (0.8%). In the CF-group, one patient had cardiac tamponade that required pericardial drainage and one patient experienced a minor stroke. In the AI-group, two patients had cardiac tamponade requiring drainage.

In 94 patients, CTI ablation was performed. CTI was equally distributed between the AI-group and CF-group (21.9% vs. 16.8%, P = 0.157). Subgroup analysis of patients with PAF (24.6% vs. 19.3%, P = 0.246) and PeAF (14.9% vs. 10.9%, P = 0.495) showed no significant difference between the AI-group and CF-group.

Primary and secondary outcomes

The proportion of patients in sinus rhythm without any documentation of AF/AT after single PVI procedure was significantly higher in the AI-group compared to the conventional CF-group (71.0% vs. 62.4%, P = 0.046) (Figure 2). Fewer patients underwent re-ablation in the AI-group compared to the CF-group although not statistically significant (16.8% vs. 23.3%, P = 0.071).

Subgroup analysis (Table 3) showed a trend toward improved outcome with AI especially in patients with PeAF compared to the CF-group (64.9% vs. 50.0%, P = 0.078). Significantly less patients with PeAF underwent re-ablation in the AI-group (18.9% vs. 34.4%, P = 0.039). In contrast, the re-ablation rate in patients with PAF was similar in the AI-group and CF-group (15.9% vs. 18.5%, P = 0.528).

Logistic regression of prognostic factors for AF recurrence

In a multivariate analysis we tested for significant predictors for recurrence of AF. We tested gender, age, CHA_2DS_2-VASc, EHRA-score, AADs before procedure, type of AF, ablation time, X-ray dose, CTI ablation and procedure time. The only significant predictor of outcome was the type of AF (P = 0.006).

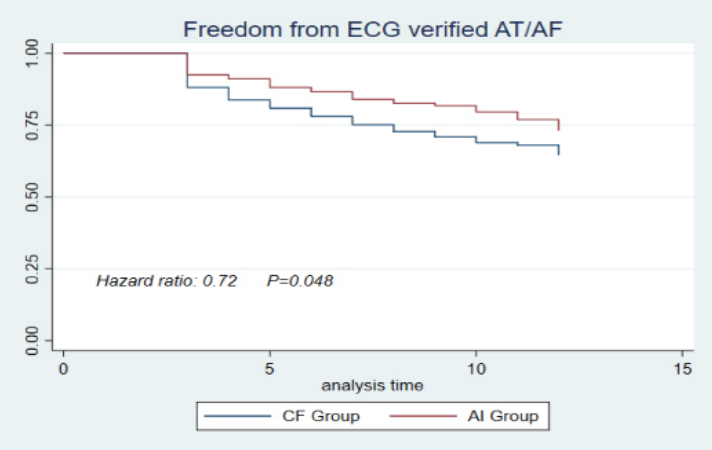

Figure 2: Freedom from documented recurrence of any atrial tachycardia or re-ablation or anti-arrhythmic drugs after a 3 months blanking period.

Table 2: Procedural Data

	Contact Force	Ablation Index	P-value
Xray time(min)	15.1±8.4	11.4±7.1	<0.01
Xray dose (cGY/m^2)	10(5;21)	7(4;16)	<0.01
Ablationtime(min)	37.1±13.4	44.7±11.3	<0.01
Total proceduretime(min)	120.0(99;144.5)	135.5(114;160)	<0.01
Procedural complications	2(1.0%)	2(0.7%)	0.80

(AF: "Atrial Fibrillation". PAF: "Paroxysmal atrial fibrillation". PeAF: "Persistent atrial fibrillation".).

Table 3: Clinical outcomes

Primary outcomes	Contact Force (n=210)	Ablation Index (n=269)	P-value
Success	131(62.4%)	191(71.0%)	0.046
Success by AF type:			
PAF	99(67.8%)	143(73.3%)	0.266
PeAF	32(50.0%)	48(64.9%)	0.078
Freedom from ECG verified AT	136(64.8%)	195(72.5%)	0.069
Freedom from anti arrhythmic drugs at 12 months	174(89.2%)	241(92.6%)	0.015
Secondary outcome			
No of re-ablations	49(23.3%)	45(16.7%)	0.071

(AF: "Atrial Fibrillation". PAF: "Paroxysmal atrial fibrillation". PeAF: "Persistent atrial fibrillation").

Discussion

This study compared an ablation strategy combining AI and lesion contiguity to CF alone in AF patients scheduled for first-time PVI ablation. The main finding was a significant lower recurrence of AF/AT at 12 months follow-up in the AI-group. There was no difference regarding complication rate between the two ablation methods.

The primary goal in AF ablation is a durable PVI. The CF sensing

catheters were introduced to optimize force feedback and produce more effective lesion sets to achieve the goal. A meta-analysis on CF-guided ablation found a success-rate of 80.1% in PAF patients and only 48.9% in PeAF patients.[11] In our subgroup analysis we found a success-rate in PAF and PeAF after CF-guided ablation of 67.8% and 50.0% respectively, indicating that our data are representative. In the STAR-AF2 trial, a similar outcome was found after PVI in patients with PeAF, and there were no clinical effect of additional linear ablation or ablation of complex fractionated electrograms.[12] The importance of a durable PVI has pushed the technology further in developing algorithms which incorporate various information such as CF, time and power into each lesion set during RFA. The TOCCASTAR and EFFICAS I/II studies have shown that CF technology combined with force-time integral improve the rate of isolated PV after 3 months of follow-up and long-term clinical outcome compared to non-CF ablations.[3, 5] The AI algorithm which incorporates CF, time and power into each lesion set was developed as a marker of ablation outcome. AI was evaluated in animal and human studies and has shown a rate above 90% of isolated PV in both PAF and PeAF patients at scheduled re-interventions 3 months after index ablation.[8, 10] The recent PRAISE trial reported 93% isolated PV at re-evaluation after 3 months in 40 patients with PeAF scheduled for PVI only.[10] Freedom from AT after 12 months of follow-up was 80%, which is higher than our results. This may be explained by a difference in our sedation protocol and PV isolation control maneuvers. We used minimal sedation, but patients undergoing AF ablation in general anaesthesia have a higher success rate.[13] Furthermore, we did not check for dormant reconduction with adenosine which in some studies have shown a better clinical outcome.[14] Nevertheless, our data supports that PVI only in patients with AF undergoing first time ablation is a reasonable strategy, and AI is effective, probably due to durable PVI. Furthermore, focus on lesion contiguity by checking the lesion sets around the PV for gaps above 6 mm may also explain the improvement in clinical outcome. Studies have shown that non-contiguity between point-by-point lesions along the ablation lines results in PV reconduction even with effective lesion sets.[3, 15] Ablation- and total procedural time were longer in the AI group. This indicates that operators use more time creating and placing the lesions which might lead to more sustainable lesions leading to higher success rates.[16] This finding is consistent with other studies.[8]

Our overall improvement in clinical outcome in the AI group is mainly driven by the improvement for patients with PeAF and not PAF. Previous studies have found that the PV often are reconducting even in patients without AF recurrences, and maybe a strategy using CF only is sufficient to achieve reasonable clinical freedom from AF/AT in PAF patients[17]. It is uncertain if the AI strategy in our population increased the PVI durability compared to the CF-group since we did not re-evaluate this during follow-up. Notably, the PRAISE trial found that only 1 of 8 patients with recurrent AF had PV re-conduction.[10] This emphasizes the need for other strategies to treat patients with recurrent AF after PVI such as targeting extrapulmonary triggers, low-voltage areas or rotors.

Limitations

There are several limitations to this study. Although the study reflects real life outcome in consecutive patients undergoing PVI procedure in a high volume center, the two interventions are compared in a retrospective design. We characterized the AF type according to the definition in guidelines, but some misclassification cannot be ruled out. We only used ECG to evaluate the patients at follow-up, and more frequent ECG monitoring could probably have documented episodes of asymptomatic AF/AT during follow-up. Furthermore, follow-up was limited to 12 months thus long-term success rates are not available. Patients did not follow a strict protocol of AAD withdrawal after the procedure. We considered the use of AAD at the 12 months clinical control as a recurrence of AF/AT, however theoretically a patient could have stopped AAD the day before 12 months clinical control.

Conclusion

This retrospective study shows that an ablation strategy combining AI and lesion contiguity improves the clinical outcome after first-time PVI in patients with paroxysmal or persistent AF.

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Extreme Obesity is Associated with Low Success Rate of Atrial Fibrillation Catheter Ablation

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Abstract

Background: Catheter ablation (CA) is an established treatment for patients with symptomatic atrial fibrillation (AF). The purpose of this study was to evaluate the safety and efficacy of single CA in AF patients with extreme obesity (body mass index [BMI] ≥ 40 kg/m²) and its long-term impact on body weight.

Methods: Patients with BMI ≥40 kg/m² who underwent CA at the Ohio State University between 2012 and 2016 were included. The primary efficacy endpoint was no atrial arrhythmia lasting > 30 seconds without anti-arrhythmic drugs during 1-year follow-up after a single procedure.

Results: Out of 230 AF patients with BMI ≥ 40 kg/m² undergoing CA, pulmonary vein isolation was achieved in 226 (98%) patients. Seventeen patients (7.4%) experienced acute major complications, including pericardial effusion, vascular complications and respiratory failure. Patient characteristics for 135 patients with complete 1-year follow-up were as follows: mean age 58.6 ± 9.6 years, mean BMI 44.5± 4.7 kg/m², female 63 (47%), non-paroxysmal AF 100 (74%), median CHA_2DS_2-VASc score 2 (IQR:1-3). In this cohort, the primary efficacy endpoint was achieved in 44 (33%) patients. Paroxysmal AF was associated with higher CA success compared to non-paroxysmal (51 vs. 26% [p < 0.01]).There was no significant weight change even in patients with successful AF CA.

Conclusions: Extreme obesity is associated with low AF CA success, particularly in those with non-paroxysmal AF. Successful AF CA was not associated with long-term weight reduction. A better treatment strategy is needed in this population of AF and extreme obesity

Introduction

Atrial fibrillation (AF) remains the most common sustained arrhythmia and has been progressively increasing with the estimated prevalence of over >5 million in the United States and > 30 million globally.[1-3] Numerous risk factors for AF have been identified, including hypertension, diabetes, coronary artery disease, and sleep apnea.[4] Recently, obesity has been recognized as a critical AF risk factor due to its adverse structural, functional, electrophysiological, and neurohormonal effects in the human atria.[5,6] Conversely, sustained weight reduction has been shown to be associated with reduced AF burden.[7,8]

Catheter ablation (CA) is an established treatment strategy for patients with symptomatic AF, and associated with drug-free 1-year AF free survival of 60-80% and 50-60% in patients with paroxysmal AF and persistent AF, respectively.[9-12] Prior studies have demonstrated that obesity negatively impacts AF CA outcomes.[13-16] However, the number of patients with extreme obesity defined as body mass index (BMI) ≥ 40 kg/m² enrolled in these studies is relatively small.[17]

The purpose of this study was to evaluate the efficacy and safety of CA in AF patients with extreme obesity in a high-volume tertiary care electrophysiology program.

Key Words

Atrial fibrillation; Catheter ablation; Body mass index; Obesity.

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Methods

Patient population

Consecutive patients with BMI ≥ 40 kg/m² who underwent index AF CA at the Ohio State University Medical Center (OSUMC) between 1/2012 and 6/2016 were included. Baseline demographic, clinical, procedural, and follow-up data were collected. Patients who did not complete 1-year follow-up at OSUMC or through affiliated clinics were excluded from efficacy analysis (Figure 1). Baseline patient characteristics at the time of ablation included age, weight, height, gender, AF type (paroxysmal vs. non-paroxysmal), history of atrial flutter, electrical cardioversion, congestive heart failure, chronic kidney disease, diabetes mellitus, hypertension, coronary artery disease, peripheral vascular disease, stroke, thromboembolism,

prior Class I or III anti-arrhythmic drug (AAD) use, and echocardiographic parameters (left ventricular ejection fraction [EF] and left atrial size on trans-esophageal echocardiography [TEE]). The CHA_2DS_2-VASc scores were calculated for all patients. Patients who had undergone prior cardioversion and/or had at least one AF episode lasting > 7 days were classified as having "non-paroxysmal" AF. Transesophageal echocardiography performed at OSUMC 1-3 days prior to the AF CA was reviewed. Informed consent for inclusion in any retrospective study was obtained from the patients prior to CA. The Ohio State University Institutional Review Board approved the study.

Pre-Procedural Management

Patients underwent a TEE and cardiac computed tomography (CT) (or cardiac magnetic resonance imaging) 1-3 days prior to AF CA. Generally, warfarin was continued without interruption and direct oral anticoagulants (DOACs) were held 24 hours prior to the CA in accordance with local practice. Perioperative management of class I and III AAD was left to the discretion of the electrophysiologist and were generally discontinued after 1 month.

Echocardiographic Measures

Two-dimensional TEE images of the left atrium (LA) were obtained in the standard 2-, 3- and 4-chamber views. The anterior-posterior diameter, LA area and LA volume (using the Method of Discs) were measured in each view at the end of ventricular systole.[18] Estimated LA volume (ml) was calculated as a mean of 2-chamber and 4-chamber volume measurements using biplane Simpson method. All LA volumes were indexed by body surface area (BSA).

Ablation Procedure

Catheter ablation was performed using either radiofrequency (RF) or cryoballoon under general anesthesia. Trans-septal puncture was guided by intracardiac echocardiogram and fluoroscopy. An esophageal temperature probe was used for all patients. Active clotting time was maintained above 300 seconds. The procedural endpoint was electrical isolation of all pulmonary veins (PV). RF ablation procedures were performed using a 3.5-mm tip irrigation catheter (Thermocool or Thermocool Smarttouch, Biosense Webster Diamond Bar, CA, USA) to achieve wide area circumferential ablation. Additional ablation strategies were left to the discretion of the operator, including empiric linear lines, electrical isolation of superior vena cava, ablation of complex fractionated electrograms and mapping and ablation of rotors using a proprietary mapping algorithm.[19] Power was titrated to 20-25 watts in the left atrial posterior wall and 30-40 watts in other areas. A force-sensing

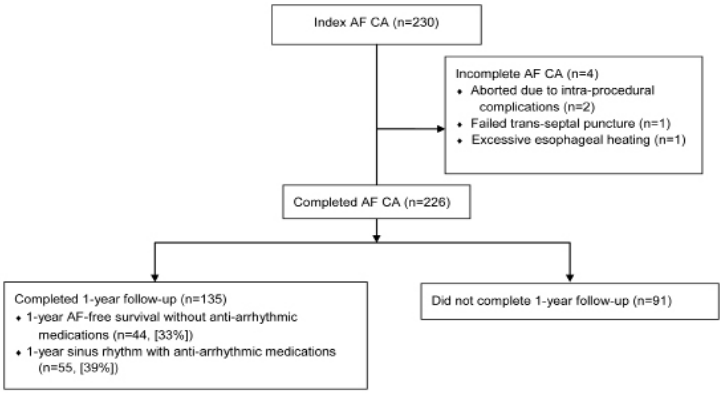

Figure 1: Patient flow diaphragm

Table 1: Baseline characteristics of the total patients, patients with complete 1-year follow-up, and patients who were lost to follow-up (total n= 226)

Characteristic	Completed Follow Up (n=135)	Lost to Follow Up (n=91)	P Value
Age-yr	58.5 ± 9.6	57.8 ± 9.9	0.60
Weight (kg)	135.9 ± 20.8	135.6 ± 18.7	0.90
BMI (kg/m²)	44.5 ± 4.7	45.1 ± 5	0.38
Female	63 (46.7)	40 (44)	0.69
AF Type			0.10
Paroxysmal	35 (25.9)	33 (36.3)	
Non-Paroxysmal	100 (74.1)	58 (63.7)	
Ablation Type			0.93
RFA	118 (87.4)	76 (83.5)	
Cryo	14 (10.4)	13 (14.3)	
Phased RFA	3 (2.2)	2 (2.2)	
Medical History			
Atrial flutter	23 (17)	18 (19.8)	0.60
CHF	25 (18.5)	22 (24.2)	0.30
CKD	6 (4.4)	6 (6.6)	0.48
Diabetes	51 (37.8)	28 (30.8)	0.28
Hypertension	115 (85.2)	78 (85.7)	0.91
CVA/TIA	6 (4.4)	4 (4.4)	1
CAD/PVD	17 (12.6)	22 (24.2)	0.06
Number of AAD use (Median [IQR])	1	1	0.36
0	13 (9.6)	9 (9.9)	
1	79 (58.5)	53 (58.2)	
2	34 (25.2)	17 (18.7)	
3	7 (5.2)	9 (9.9)	
4	1 (0.7)	3 (3.3)	
5	0 (0)	0 (0)	
6	1 (0.7)	0 (0)	
CHA_2DS_2-VASc score (Median [IQR])	2 (1-3)	2 (2-3)	0.64
0	2 (1.5)	4 (4.4)	
1	33 (24.4)	18 (19.8)	
2	45 (33.3)	26 (28.6)	
3	35 (25.9)	26 (28.6)	
4	13 (9.6)	10 (11)	
5	4 (3)	6 (6.6)	
6	2 (1.5)	1 (1.1)	
7	1 (0.7)	0 (0)	
Echocargiographic Parameters			
Ejection Fraction	60 (50-60)	55 (50-60)	0.27
Left atrial volume (ml/m²)	28.0 ± 9.7	29.6 ± 9.6	0.25

AAD = antiarrhythmic drug; AF = atrial fibrillation; BMI = body mass index; CAD= coronary artery disease; CHF= congestive heart failure; CKD=chronic kidney disease; CVA=cerebrovascular accident; IQR=interquartile range; RFA=radiofrequency ablation; PVD=peripheral vascular disease; TIA=transient ischemic attack

catheter (Thermocool Smarttouch, Biosense Webster, Diamond Bar, CA, USA) has been primarily used since 2014. A small number of patients (N=5) underwent phased RF ablation as part of VICTORY AF trial (ClinicalTrials.gov Identifier: NCT01693120. The study was terminated due to lower than expected enrollment rate).[20] Antral cryoballoon ablation was performed with 2nd generation 28 mm cryoballoon using standard two 3-minute freeze applications. (Arctic Front, Medtronic Inc., Minneapolis, MN, USA). During cryoballoon application to the right PVs, right phrenic nerve capture was monitored with abdominal palpation and diaphragmatic compound motor action potentials (CMAP).[21] A circular mapping catheter (Lasso: Biosense Webster; Achieve: Medtronic Inc.) or a multipolar mapping catheter (Pentaray: Biosense Webster) was used to confirm PV isolation. Warfarin was continued perioperatively and DOACs were resumed after venous hemostasis was confirmed; regardless of indication, anticoagulation was continued indefinitely. Aspirin and proton pump inhibitor were prescribed for minimum 1-month post ablation.

Outcomes

The primary efficacy endpoint of AF CA was no atrial arrhythmia recurrence lasting > 30 seconds off AAD (class I and class III drugs) during 1-year follow-up following a single CA procedure. Atrial arrhythmia recurrence was corroborated based on review of routine 30-day event monitors performed approximately 3 and 6 months after the index CA and any ECG performed during the 1-year months of follow up. In patients with implantable loop recorders and cardiac implantable devices, periodic device interrogation was used to assess for atrial arrhythmia recurrence.[22] Adjudication of atrial arrhythmias was performed by one of nine board-certified cardiac electrophysiologists. The secondary efficacy outcome was sinus rhythm maintenance after the index CA procedure with the aid of an AAD at 1-year follow-up. Safety endpoints include any major periprocedural adverse events, including myocardial infarction, stroke, pericardial effusion/tamponade, phrenic nerve paresis, atrial-esophageal fistula, acute respiratory failure, or vascular complications requiring a surgical or percutaneous intervention. Early arrhythmia recurrence within the first 3-month blanking period was not included in the efficacy endpoints. Patients' weights were recorded at baseline and at each follow-up visit.

Follow-up

Patients were routinely followed at 3, 6, and 12 months, including detailed history, exam, weight, EKG, and 30-day continuous rhythm monitor. Outpatient visits between 11 and 13 months were considered the 1-year follow-up for this study. AF/atrial tachycardia episodes were reviewed if patients had a cardiac implantable electronic device and implantable loop recorders. Patients were queried regarding any adverse complications or arrhythmia episodes that may have occurred at another health care center.

Statistical analysis

Statistical analysis: Continuous variables were compared using Student's t-test after normality was verified with histogram analysis or the Shapiro-Wilkins test; categorical variables were compared using the chi-square test or Fisher's Exact test as appropriate. Continuous variables are expressed as the mean ± SD and categorical variables are expressed n (%). The effect of incremental increase in BMI on AF CA outcome was assessed by grouping subjects with BMI ≤ 45 into one group and BMI > 45 into a second group. Student's t-test was used to compare subjects' weights on the day of AF CA and final day of follow-up. All analyses were considered significant if $p < 0.05$. Univariate predictors of AF CA success with $p < 0.20$ were included as candidate predictors in a multivariate model.

Table 2: Demographic and clinical characteristics of 135 patients with complete 1-year follow-up according to AF recurrence.

Characteristic		AF recurrence n = 91	No AF recurrence n = 44	P Value
Age-yr		58.7 ± 9.0	58.1 ± 10.7	0.76
Weight (kg)		138.1 ± 21.4	131.3 ± 19.0	0.07
BMI (kg/m^2)		44.7 ± 5.2	44.0 ± 3.6	0.35
Female		38 (60.3)	25 (39.7)	0.10
AF Type				0.01
Paroxysmal		17 (18.7)	18 (40.9)	
Non-Paroxysmal		74 (81.3)	26 (59.1)	
Ablation Type				0.95
RFA		80 (87.9)	38 (86.4)	
Cryo		9 (9.9)	5 (11.4)	
Phased RFA		2 (2.2)	1 (2.3)	
Medical History				
Atrial flutter		17 (18.7)	6 (13.6)	0.46
CHF		19 (20.9)	6 (13.6)	0.31
CKD		6 (6.6)	0 (0)	0.08
Diabetes		56 (61.5)	28 (63.6)	0.81
Hypertension		14 (15.4)	6 (13.6)	0.79
CVA/TIA		4 (4.4)	2 (4.5)	1
CAD/PVD		10 (11)	7 (15.9)	0.42
Number of AAD use (Median [IQR])		1 (1-2)	1 (1-2)	0.47
	0	7 (7.7)	6 (13.6)	
	1	54 (59.3)	25 (56.8)	
	2	25 (27.5)	9 (20.5)	
	3	3 (3.3)	4 (9.1)	
	4	1 (1.1)	0 (0)	
	5	0 (0)	0 (0)	
	6	1 (1.1)	0 (0)	
CHA_2DS_2-VASc score (Median [IQR])		2 (1-3)	2 (2-3)	0.60
	0	2 (2.2)	0 (0)	
	1	24 (26.4)	9 (20.5)	
	2	28 (30.8)	17 (38.6)	
	3	25 (27.5)	10 (22.7)	
	4	7 (7.7)	6 (13.6)	
	5	3 (3.3)	1 (2.3)	
	6	2 (2.2)	0 (0)	
	7	0 (0)	1 (2.3)	
Echocargiographic Parameters				
Ejection Fraction		60 (50-60)	60 (50-60)	0.27
Left atrial volume (ml/m^2)		29.6 ± 10.8	26.8 ± 7.6	0.13

AAD = antiarrhythmic drug; AF = atrial fibrillation; BMI = body mass index; CAD= coronary artery disease; CHF= congestive heart failure; CKD=chronic kidney disease; CVA=cerebrovascular accident; IQR=interquartile range; RFA=radiofrequency ablation; PVD=peripheral vascular disease; TIA=transient ischemic attack

Results

Patient population

Two hundred and thirty consecutive patients with BMI ≥ 40 kg/m^2 underwent attempted AF CA between 1/2012 and 6/2016. The mean weight was 135.8 ± 19.9 kg (299.4 ± 43.9 pounds) and the mean BMI was 44.8 ± 4.9 kg/m^2. PV isolation was acutely successful in 226 (98%) patients. Out of 226 patients with complete PVI, 135 patients completed 1-year follow-up at the OSUMC and were included in the efficacy analyses (Figure 2). There were no significant differences between 135 patients with complete 1-year follow-up and 91 patients with incomplete follow-up with regards to baseline demographics and clinical factors (Table 1).Baseline patient characteristics for 135 patients with one-year follow-up were as follows: mean age 58.5 ± 9.6 years, mean weight 135.9 ± 20.8 kg, mean BMI 44.5 ± 4.7 kg/m2, female 63 (47%), non-paroxysmal AF 100 (74%), median CHA2DS2-VASc score 2 (IQR:1-3), and median EF 60% (IQR: 50-60). Patients tried median 1 AAD (IQR:1-2) before AF CA. (Table 2)

Peri-procedural complications: AF CA was aborted in 2 patients due to intraprocedural complications (acute respiratory failure and cardiac tamponade) and could not be completed in 2 others due to failed trans-septal catheterization and excessive esophageal heating. Among the patients who completed PVI, there were 17 additional procedural complications in 15 patients. These complications included 5 cases of pericardial effusion requiring pericardiocentesis, 11 cases of groin pseudoaneurysm or AV fistula requiring a procedural intervention and one case of acute post-procedural respiratory failure requiring re-intubation and mechanical ventilation. In total, 17 out of 230 patients (7.4%) experienced acute major procedural complications.

Primary efficacy endpoint: Among the 135 obese patients included in this study, the primary efficacy endpoint of single AF CA success (no atrial arrhythmia recurrence lasting > 30 seconds off AAD during 1-year follow-up) was achieved in 44/135 patients (33%) (Table 2). Paroxysmal AF was associated with a higher CA success rate compared to non-paroxysmal AF (51% vs. 26%, p<0.01). The ablation technique (cryoablation versus radiofrequency ablation) did not impact AF CA success (Table 3) (p=0.95). Additionally, patients with paroxysmal AF had a longer median AF-free survival (300 days) than those with non-paroxysmal AF (278 days) (p < 0.01). By multivariate analysis, AF type (paroxysmal vs. non-paroxysmal) remained the only independent predictor of AF CA success. In this cohort of extremely obese patients, incremental increase in BMI above 40 kg/m^{2}did not impact AF CA outcomes (p=0.55). The secondary efficacy outcome (sinus rhythm maintenance with AF CA ± an AAD at 1-year follow-up) was observed in 53 (39%) patients, meaning the addition of AAD to CA increased sinus rhythm maintenance by 6%.

Impact of successful CA on weight: There was no significant weight change among all patients with 1-year follow-up (135.8 kg at AF CA vs.135.3 kg at last follow up, p = 0.39); this finding persisted when considering only the 53 patients maintaining sinus rhythm with CA ± AAD (131.8 kg at AF CA vs. 131.8 kg at last follow up, p = 0.96).

Discussion

Major findings

Major findings: In the present study of extremely obese patients (BMI ≥ 40 kg/m2) undergoing AF CA, sinus rhythm maintenance was only 39% at 1-year follow-up even with the use of class I or III AAD. Patients with non-paroxysmal AF had even lower success rate. Furthermore, there was no significant weight loss, with or without maintenance of sinus rhythm during the 1-year follow-up.

Overweight and obesity are generally defined as BMI 25-29.9, and ≥ 30 kg/m^2, respectively.[17] In Europe and North America, over 60% of adults are at least overweight, and of these 20-30% are obese.[23] In the Framingham Heart Study, every unit increase in BMI correlated with a 4-5 % increase in AF diagnosis.[24] The interplay between excess body weight and AF is complex. In addition to its close association with other cardiovascular risks and sleep disordered breathing (SDB), obesity appears to modulate underlying arrhythmogenic substrates,[25,26] exacerbating atrial dilatation,[27,28] diastolic dysfunction,[28-30] inflammation[31-33], fibrosis,[34] and conduction heterogeneity.[35] More recently, the pro-arrhythmic roles of pericardial fat and obesity-associated biomarkers (leptin, adiponection) have been implicated in the pathogenesis of AF.[6,23,36]

Excess body weight has been shown to negatively impact AF CA outcomes. Winkle et al evaluated AF CA outcomes in 2715 patients, including 129 patients with BMI > 40 kg/m2.15After multiple AF CA procedures, the reported 1-year AF free survival (no AAD) was 67% with an increase in the rate of complications. Sivasambu et al examined AF CA outcomes for 701 patients, including 84 patients with BMI > 40 kg/m^2.[14] In this subgroup with BMI > 40 kg/m^2, the 1-year AF free survival after CA was 42%, similar to the results of our current study. Compared to prior publications, the current study population was younger, and had a lower CHA_2DS_2-VASc score, yet the success of a single AF CA procedure was lower (33%) at 1-year follow-up. This may be due to the more intensive arrhythmia monitoring, the strict definition of single AF CA success, and higher rate of non-paroxysmal AF (74%) in our cohort. The relatively high rates of AF CA procedural complications observed in this study are consistent with complication rates observed by Winkle et al. in patients with BMI ≥ 4015.

Despite advances in mapping, imaging and ablation technologies, the success rates for AF CA remain rather constant for 60-80% and 50-60% in patients with paroxysmal AF and persistent AF, respectively.[9-12] Consequently, there has been a growing interest in comprehensive management of AF risk factors including body weight, SDB, and other cardiovascular comorbidities as therapeutic targets for AF management. In the ARREST-AF (Aggressive Risk Factor Reduction Study for Atrial Fibrillation and Implications for the Outcome of Ablation) and LEGACY (Long-Term Effect of Goal Directed Weight Management on an Atrial Fibrillation Cohort) studies, the investigators demonstrated that a structured, physician driven, and goal-directed weight and risk factor management strategy can lead to reduced AF burden and higher AF CA success rates.[7,8] In the LEGACY study, sustained > 10% weight loss was associated with lower AF recurrence, compared to those with < 3% weight loss, indicating a dose-dependent effect of weight loss on AF burden.[8]

In the sub-analysis of the LEGACY cohort, the investigators also observed regression of persistent AF to either paroxysmal or no AF among patients with more substantial weight loss and, 52% of patients with AF and > 10% weight loss achieved no AF after the mean 48-month follow-up.[37]

Lastly, the lack of weight loss even among patients with successful sinus rhythm maintenance is discouraging since one of the incentives for the patient and the physician to pursue AF CA in this cohort is that with long-term sinus rhythm maintenance, the patient will feel more motivated to pursue active lifestyle and to achieve sustained weight loss.

Given the incomplete understanding of AF pathogenesis, the increased risk of complications and the low success of AF CA in extreme obesity, electrophysiologists should incorporate other strategies for managing atrial arrhythmias before considering CA, such as enrollment and active participation in a monitored weight reduction program, and perhaps consideration of bariatric surgical options. Once the patient demonstrates successful lifestyle changes and sustained weight loss, then AF CA may be considered and would likely have greater success.

Limitations

Several limitations of this study should be noted. First, this is a single-center retrospective analysis. Second, 91 out of 230 patients did not complete follow-up through our system. Yet, the study population data show no significant differences between patients completing vs. not completing 1-year follow-up. Thus, it seems unlikely that the patients completing follow-up elsewhere would have significantly different outcomes. Third, diagnosis and treatment status of SDB were not captured in this study. The adverse impact of OSA on AF CA outcomes has been well described.[38,39] Fourth, continuous rhythm monitoring was not systematically utilized, yet monitoring and follow up was consistent with published guidelines. Fifth, we compared cohorts with BMI ≥ 40 and <45 against those with BMI ≥ 45 but did not include those with BMI ≤ 30 in this analysis. However, the single-procedure freedom from AF in this population has consistently been shown to be 60-70% in several large trials. Lastly, there may have been more AF episodes that were noted at outside hospitals without the knowledge of primary electrophysiologists.

Conclusions

Extreme obesity is associated with low AF CA success, particularly in those with non-paroxysmal AF. Successful sinus rhythm maintenance after AF CA was not associated with long-term weight reduction. A better treatment strategy is needed in this population of AF and extreme obesity.

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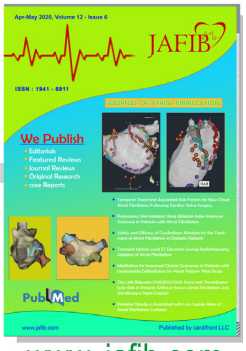

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Temporal Trend and Associated Risk Factors for New-Onset Atrial Fibrillation Following Cardiac Valve Surgery

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Abstract

Aims: Post cardiac surgery atrial fibrillation (POAF) is common, with adverse implications. However, relatively little is known regarding the time varying nature of risk factors associated with POAF. We describe variation in POAF along with its associated risk factors.

Methods: Medical records of adult patients undergoing cardiac valve surgery from 2003-13, without a history of pre-operative AF were analyzed retrospectively. POAF was adjudicated using inpatient and outpatient electrocardiograms (EKG). Risk of AF over time along with time-varying risk factors were estimated using multiphase non-linear logistic mixed effects model.

Results: 10,461 patients with 100,149 EKGs were analyzed [median follow-up 4 months (IQR 48 hours-2 years)]. AF prevalence changed with time since surgery and two distinct phases were identified. Prevalence peaked to 13% at 2 weeks (early phase) and 9% near 7 years post-operatively (late phase). Older age, greater severity of preoperative tricuspid valve (TV) regurgitation, mitral valve replacement and prior cardiac surgery were time-independent risk factors for POAF. TV repair was associated with a decreased risk of early phase POAF. Pre-operative blood urea nitrogen, peripheral vascular disease and hypertension were associated with a higher risk of late phase POAF.

Conclusion: POAF risk shows two distinct phases with an early peak and a late gradual rise, each associated with a different set of risk factors.

Introduction

Atrial fibrillation (AF) is the commonest post-cardiac surgery arrhythmia with an estimated incidence between 30-50% and is associated with a significant increase in morbidity, mortality and healthcare costs[1]. Post-operative atrial fibrillation (POAF) following cardiac surgery is invariably noted within the first 5 days and commonest on the 2nd post-operative day[2]. Given the adverse impact of POAF, effective strategies for targeting POAF risk factors are expected to have momentous impact in decreasing post-operative morbidity and healthcare costs.

Risk of POAF is associated with risk factors related to surgery as well as conventional risk factors. Theoretically, these risk factors are expected to vary with time since surgery. For example, electrolyte abnormalities would be expected to have a pro-arrhythmogenic effect in the early post-operative stage, while incision related inflammation will tentatively have both short-term and long term (from scarring) implications. This is in contrast to conventional risk factors such as diabetes and hypertension, the effect of which is expected to be time-independent[3]. Characterization of this time-varying risk and identification of associated risk factors is integral to synthesizing effective programs for POAF monitoring, diagnosis and prevention.

Multiple studies have previously described POAF burden following cardiac surgery, but few have addressed its temporal pattern and the time-varying nature of risk factors influencing POAF[4-9]. The aim of this study is to describe the time-varying prevalence of POAF along with its associated time-varying and constant risk factors in patients undergoing cardiac valve surgery in a tertiary care hospital in the United States, without a previous history of atrial fibrillation.

Key Words

Atrial Fibrillation, Post-Operative Atrial Fibrillation, Valvular Heart Surgery, Time Varying Risk.

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Materials and methods

This is a single-center, retrospective cohort study analyzing data

of patients who underwent cardiac valve surgery at a tertiary-care center.

Population

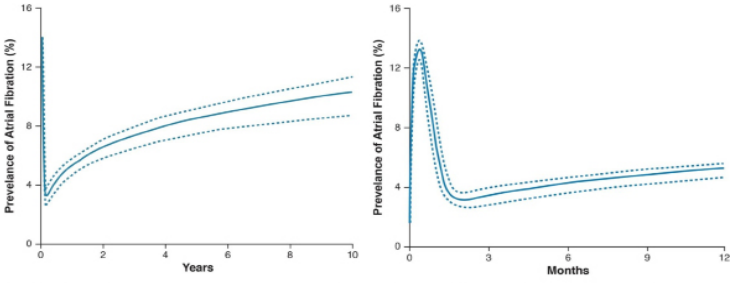
Patients older than 18 years undergoing cardiac valve surgery from 2003-2013, alone or in combination with coronary artery surgery were selected. Patients with a history of AF prior to surgery were excluded. Patients without at least one adjudicated pre-operative and post-operative electrocardiogram (ECG) were excluded. Patient consent for the surgical procedure was obtained prior to surgery. A waiver of informed consent for utilizing electronic medical records (EMR) was allowed by the institutional review board (IRB) since this was an observational study without any anticipated patient harm.

Definitions

AF was defined utilizing AATS recommendations as its presence on an ECG lasting for greater than 30 seconds or for the duration of the reading, if less than 30 seconds[10]. History of AF was defined as either patient reported diagnosis of AF, documented history of AF in EMR or presence of a cardiologist adjudicated preoperative ECG with AF. POAF was described as the presence of a post-operative cardiologist adjudicated 12-lead ECG showing AF, either during an outpatient visit or inpatient hospitalization. Echocardiographic data was extracted from echocardiogram reports read by board qualified cardiologists.

Statistical Methods

Continuous data is described using means with standard deviations (SD) or medians with interquartile range (IQR). Categorical data is described using frequencies and percentages. Transformation of continuous variables was performed when necessary. 5-fold multiple imputation using Markov Chain Monte Carlo technique was employed to impute missing values (SAS PROC MI). In multivariate modeling, for each imputed complete dataset, their regression coefficients and variance-covariance matrices were estimated and final regression coefficient estimates, variance-covariance matrices and p-values were computed by combining estimates from the 5 models (SAS PROC MIANALYZE).



Time since surgery	2 weeks	3 months	6 months	1 year	2 years	3 years	5 years	7 years	10 years
Percentage of POAF	13	3	4	5	6	7	8	9	10

Figure 1: **Temporal trend of post-operative atrial fibrillation. The table shows the corresponding values varying with time surgery.**

1a: Temporal trend of prevalence of post-operative atrial fibrillation. Solid lines represent the estimated parametric model of percentage of atrial fibrillation (mean effect) enclosed within a 95% bootstrap percentile confidence interval.
1b: Zoomed in version of figure 1a showing the temporal trend of post-operative atrial fibrillation following valve surgery for the first year since surgery.

Table 1: **Baseline characteristics of the study population.**

Variable	Measure/ % of n	Available data n (% of N)
Age	61.1±13.9	10,461 (100)
Females (%)	4,131 (39%)	10,461 (100)
Race (%)		10,461 (100)
Caucasian	9,364 (90%)	
African-American	548 (5.3%)	
Other	476 (4.6%)	
Hypertension (%)	6,354 (61%)	10,461 (100)
Peripheral artery disease (%)	708 (6.8%)	10,461 (100)
Diabetes mellitus (%)	1,646 (15.8%)	10,391 (99)
Insulin treated	665 (6.4%)	
Non-insulin treated	981 (9.4%)	
COPD (%)	1,636 (16%)	10,461 (100)
Smoking history (%)	4,896 (47%)	10,450 (99.8)
CHF (%)	3,371 (32%)	10,461 (100)
Myocardial infarction (%)	2,054 (20%)	10,461 (100)
Dialysis (%)	201 (2%)	10,461 (100)
CVA (%)	808 (7.7%)	10,461 (100)
Preoperative NYHA (%)		10,011 (96)
Class I	2,705 (27%)	
Class II	4,403 (44%)	
Class III	2,455 (25%)	
Class IV	448 (4.5%)	
Endocarditis (%)	979 (9.4%)	10,461 (100)
SURGICAL PROCEDURE		
Coronary artery bypass graft	2,900 (28%)	10,461 (100)
Mitral valve surgery	9,873 (94%)	10,461 (100)
Mitral valve repair	7,731 (74%)	
Mitral valve replacement	2,142 (20%)	
Aortic valve surgery	2,234 (21.3%)	10,461 (100)
Aortic valve repair	190 (1.8%)	
Aortic valve replacement	2,044 (19.5%)	
Tricuspid valve surgery	2,019 (19%)	10,461 (100)
Tricuspid valve repair	1,877 (18%)	
Tricuspid valve replacement	142 (1%)	
ECHO parameters		
Mitral valve regurgitation	9,469 (91%)	10,411 (99.5)
Severity		
1	586 (5.6%)	
2	1,172 (11%)	
3	2,563 (25%)	
4	5,148 (49%)	
Mitral valve stenosis	592 (6.7%)	8,734 (83)
Aortic valve stenosis	1,417 (25%)	5,701 (54)
Aortic valve regurgitation	2,631 (26%)	10,275 (98)
Tricuspid valve regurgitation	5,008 (49%)	10,321 (99)
Posterior wall thickness (mm)	1.1±0.3	9,287 (89)
LVEDV Index (mL/m2)	67.8±27	9,058 (87)
LVESV Index (mL/m2)	27.4±19.8	8,911 (85)
LVEF (%)	52.9±12.9	10,344 (99)
Left ventricle mass index (g/m2)	126±43	8,995 (86)
Biochemistry		
Creatinine (mg/dL)	1.2±0.9	10,450 (99.9)
Blood urea nitrogen (mg/dL)	21.6±15.3	10,450 (99.9)
eGFR (MDRD) (mL/min/m2)	75.7±27.1	10,450 (99.9)
Total cholesterol (mg/dL)	175±44.3	9,073 (87)
HDL cholesterol (mg/dL)	52.2±17.7	9,070 (87)
LDL cholesterol (mg/dL)	99.3±36.1	9,070 (87)

LDL cholesterol (mg/dL) 99.3±36.1 9,070 (87)
COPD: Chronic obstructive pulmonary disease
CHF: Congestive heart failure
CVA: Cerebrovascular accident
LVEDV: Left ventricle end diastolic volume
LVESV: Left ventricle end systolic volume
LVEF: Left ventricle ejection fraction
eGFR: Estimated glomerular filtration rate
HDL: High density lipoprotein
LDL: Low density lipoprotein

To assess the temporal trend of the prevalence of POAF (repeated binary measurements), post-operative ECG data was analyzed longitudinally for changes in prevalence of AF over time. A multiphase non-linear logistic mixed-effects model was used to resolve a number of time phases to form a temporal decomposition model and to estimate the shaping parameters at each phase[11-13]. PROC NLMIXED (SAS) was used to implement the temporal decomposition model. The prevalence of POAF over time was estimated by averaging the patient-specific profiles. Due to limited capabilities of variable selection in PROC NLMIXED, variable screening was done using ordinary multivariable logistic regression (PROC LOGISTIC) and a computer-intensive machine learning "bagging" method, with the assumption of independence of observations with entry criteria (.10) and stay criteria (.05)[14]. Isolated variables and their transformations were entered into the repeated measurements multivariable model one by one and a two-sided P value <0.05 was considered significant. All analyses used SAS statistical software (SAS v9.4, SAS Institute, Cary, NC).

Results

Baseline Characteristics

10,461 patients undergoing cardiac valve surgery from 1/1/2003 to 12/31/2013 without a history of pre-operative AF, with at least one pre-operative and one post-operative adjudicated ECG were selected for this study. The baseline characteristics of the study cohort are described in Table 1.

The mean age of patients undergoing surgery was 61 (±13.9) years, 39% of the patients were females and majority were Caucasians (90%). Hypertension was the most prevalent risk factor (61%) at baseline followed by congestive heart failure (32%). Almost half of the patients (44%) had NYHA class II symptoms. Mean ejection fraction was 53% (±13). Majority of surgeries were elective, with <1% being emergent. Mitral valve (94%) surgeries in isolation or in combination with other valves was the commonest valve surgery with three quarters being mitral valve repair. Yearly distribution of surgeries is given in Supplementary table 1.

100,149 post-operative ECGs were available with a median follow-up time of 4 months (25th-75th centile 2 days- 2 years) with a range of half day to 14 years. Distribution by post-operative time is given in Supplementary table 2.

Temporal trend of post-operative atrial fibrillation

Prevalence of POAF changed with time since surgery. The non-linear logistic mixed-effects model yielded 2 distinct phases for the risk of being in atrial fibrillation since valve surgery. There was a sharp early peaking phase around 2 weeks post-surgery with a peak prevalence of 13% for POAF which sharply decreased to 3% at 3 months. This was followed by a gradually increasing late phase with peak prevalence of 9% at 7 years (Figure 1a and 1b).

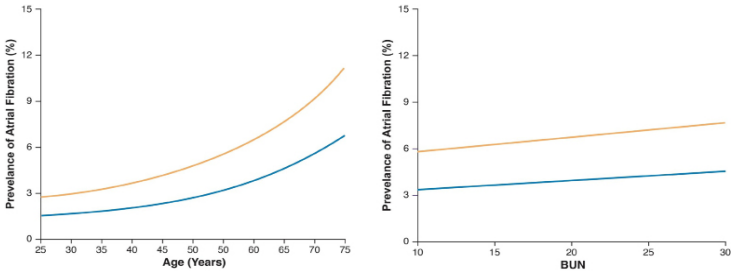


Figure 2: Nomograms for age and BUN obtained by solving the equation in table 2

2a: Predicted effect of age on risk of POAF: Solid lines are parametric estimates of prevalence of atrial fibrillation. The 1-Year prevalence of atrial fibrillation profile is shown in blue and the 5-Year prevalence of atrial fibrillation profile is shown in yellow.
2b: Predicted effect of BUN on risk of POAF: Solid lines are parametric estimates of prevalence of atrial fibrillation. The 1-Year prevalence of atrial fibrillation profile is shown in blue and the 5-Year prevalence of atrial fibrillation profile is shown in red.

Table 2: Risk factors associated with post-operative atrial fibrillation.

Factor	Estimate ± SE	P-value	Odds Ratios (95% CI)
Overall			
Older Agea	0.822±0.0350	<.0001	See Figure 2a
Surgery: Mitral Valve Replacement (more likely)	0.367±0.0616	<.0001	1.44 (1.28, 1.63)
Higher Preop TV Regurgitation Degree	0.124±0.0204	<.0001	1.13 (1.09, 1.18)
Prior Cardiac Surgery	0.277±0.0533	<.0001	1.29 (1.18, 1.46)
Early peaking phase			
Surgery: Tricuspid Valve Repair (less likely)	- 0.150±0.0691	0.0313	.86 (.75, .98)
Late increasing phase			
Higher Preop Blood Urea Nitrogen	0.333±0.0264	<.0001	See Figure 2b
History of Peripheral Arterial Disease	0.402±0.0934	<.0001	1.49 (1.24, 1.80)
History of Hypertension	0.284±0.0691	<.0001	1.33 (1.16, 1.52)

LDL cholesterol (mg/dL) 99.3±36.1 9,070 (87)
COPD: Chronic obstructive pulmonary disease
CHF: Congestive heart failure
CVA: Cerebrovascular accident
LVEDV: Left ventricle end diastolic volume
LVESV: Left ventricle end systolic volume
LVEF: Left ventricle ejection fraction
eGFR: Estimated glomerular filtration rate
HDL: High density lipoprotein
LDL: Low density lipoprotein

Risk factors associated with POAF

The statistical model yielded a set of risk factors with time-independent and dependent effects associated with POAF. Age, mitral valve replacement [OR 1.44 (1.28-1.63)], tricuspid regurgitation [OR 1.13 (1.09-1.18)] and prior cardiac surgery [OR 1.29 (1.18-1.26)] were associated with an increased risk of POAF irrespective of time since valve surgery.

In contrast, tricuspid valve repair [OR 0.86 (0.75-0.98)] was associated with a reduced risk of POAF in the early phase. Elevated blood-urea-nitrogen (BUN) levels, hypertension and peripheral artery disease were associated with an elevated risk of late-phase

POAF (Table 2). For continuous risk factors, nomograms instead of point estimates are used, and are presented in figure 2.

Risk factors associated with post-operative atrial fibrillation. Only statistically significant variables are listed in this table. The effect of risk factors listed under "overall" remained constant with time. Risk factors with time-varying effect are listed under the "early peaking phase" or "late increasing phase" as determined by the statistical model. Of note, tricuspid valve repair was associated with a decreased risk for POAF, thereby a negative precedes the point estimate.

Discussion

This single-center cohort study evaluated the temporal trend of POAF prevalence since surgery and its associated risk factors following cardiac valve surgery, either in isolation or in combination with coronary artery bypass grafting at a tertiary care center from 2003 to 2013. It identified two distinct phases in the post-operative period associated with increased risk of atrial fibrillation

Comparison with previous studies

Previous studies have been performed studying POAF and associated risk factors with varying results[4]. However, majority of these studies were done in patients undergoing primary CABG with or without concomitant valve surgery, and calculated POAF incidence which ranged from 14-47%. The peak POAF prevalence in our study was 13%, which was around 2 weeks following surgery. This is lower than the incidence rates reported in most of the previous studies. In comparison to previous studies, we excluded patients with pre-existing AF which partly explains the lower than expected prevalence in our study[4-9]. In addition, use of adjudicated ECGs alone without the use of continuous monitoring devices to define POAF also contributed to the lower prevalence in our study. Lastly, this is a single center study and differences in surgical techniques, intraoperative and post-operative care potentially influenced POAF rates.

Time-varying prevalence and risk factors

Although POAF risk with cardiac surgery has been extensively studied as mentioned before, utilization of a time-varying risk model has been infrequent[15]. POAF risk prediction utilizing conventional methods have yielded modest results signaling the need for novel risk prediction techniques[7]. POAF risk is not constant, with an early phase peaking near 2 weeks followed by a gradually increasing risk with peak near 7 years. The early post-operative AF risk is consistent with prior studies, although the peak time of POAF risk in our study is different compared to previous studies (2 weeks compared to 2 days). Differences in adjudicating POAF, surgical techniques and post-operative care might account for this difference. It is however, similar to the increased risk seen in phase II of a similarly modeled study by Melby et al[15]. In addition, our study evaluated the long-term risk of AF following surgery and noted late increase in risk after the initial post-operative period. This is also consistent with earlier studies[16-18].

Increasing age, a history of cardiac surgery as well as mitral valve replacement were time-independent risk factors for POAF. Although the mechanism underlying AF and POAF is multifactorial and incompletely understood, a combination of degenerating efficiency of myocyte electrical conduction, increased arrhythmogenicity and scarring from prior cardiac surgeries is potentially at play[3]. Preoperative tricuspid regurgitation was also a time-independent risk factor, which likely represents a surrogate marker for right atrial volume. The association of tricuspid repair in the early phase with a decrease in risk of POAF further corroborate this hypothesis, with correction of regurgitant pressure and volume load on the right atrium leading to a reduction in POAF. Late phase risk factors associated with atrial fibrillation might indicate increasing risk associated with the natural history of AF progression in general rather than POAF.

Limitations

This study has limitations. Utilization of ECGs alone for diagnosis of POAF without continuous monitoring possibly underestimated POAF prevalence. Post-operative telemetry data for patients was not available and thereby unable to be included in the model. This is a limitation of the study design because this was a retrospective study incorporating patient data spanning multiple years. As mentioned before, this likely resulted in a lower reported prevalence compared to previous studies. However, description of POAF rates following cardiac surgery was not the main objective of this study since multiple elegant studies describing these rates are already available. Our aim was to highlight and analyze the variance in POAF with time and its associated risk factors. Secondly, this was a single center study at a tertiary care hospital. These results may not be generalizable to different institutions due to inter-institutional variations in surgical techniques and post-operative care. In addition, pre and post-operative bloodwork including electrolytes and medication use, including anti-arrhythmic medications, was not available for patients undergoing surgery prior to 2007 due to a change in the EMR software and was not included in the model which could be a source of bias. Despite these shortcomings, the study cohort was sizeable, all ECGs were adjudicated by board certified cardiologists, with considerable time of follow-up post-surgery and a novel but validated statistical method to model longitudinal binary outcome was used to report the time-varying change in risk of POAF.

Conclusion

This single center, observational study validates the risk for POAF in a cohort undergoing cardiac valve surgery, either alone or in combination with other surgical procedures. In addition, it adds incremental information on the time-varying nature of POAF, emphasizing the increasing risk of AF with the passage of time after the initial reduction in POAF risk, along with associated risk factors. Patients with these risk factors could be targeted for longer follow-up. Randomized controlled trials are needed to establish superiority of longer follow-up compared to routine post-operative follow up before widespread acceptance. In addition, cost-effectiveness, frequency and duration of long-term monitoring was not addressed in this study and are questions for future research, especially in the current era of value-based practice.

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Supplementary Tables

Table 1: Yearly distribution of surgeries

Year	N = 10,461	Total %
2003	1,102	10.5
2004	1,036	9.9
2005	978	9.3
2006	913	8.7
2007	868	8.3
200	1,025	9.8
2009	1,140	10.9
2010	1,217	11.6
2011	822	7.9
2012	668	6.4
2013	692	6.6

Table 2: ECG distribution based on post-operative time

Time	Number of ECGs	Number of Patients (%)
≥24 hour	100,146	10,461(100)
≥ 2 weeks	48,338	4,962 (47.4)
≥ 1 month	43,640	4,278 (40.9)
≥ 3 months	38,319	3,641 (34.8)
≥ 6 months	35,558	3,444 (32.9)
≥ 1 year	31,814	3,161 (30.2)
≥ 1.5 years	28,823	2,913 (27.8)
≥ 2 years	26,250	2,714 (25.9)
≥ 3 years	21,993	2,428 (23.2)
≥ 5 years	14,564	1,816 (17.4)
≥ 7 years	8,569	1,161 (11.1)
≥ 8 years	6,146	893 (8.5)
≥ 9 years	4,347	667 (6.3)
≥ 10 years	2,933	468 (4.5)
≥ 11 years	1,910	330 (3.2)

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Transient Inferior Lead ST Elevation During Radiofrequency Ablation of Atrial Fibrillation

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Abstract

Radiofrequency ablation (RFA) is a commonly performed procedure for symptomatic atrial fibrillation (AF). Herein, we describe a case of transient ST elevation during the isolation of right-sided pulmonary veins. The patient was hemodynamically stable and due to the transient nature of ST-elevation, the procedure was completed successfully. Subsequently, the cardiac catheterization was performed which did not reveal any significant obstructive coronary lesion or a thrombus. In this report, we attempt to explain possible mechanisms for ST-elevation during RFA of AF.

Introduction

Radiofrequency ablation (RFA) has emerged as the most effective rhythm control strategy for atrial fibrillation (AF) [(1)]. These procedures are routinely performed in most electrophysiology laboratories. Over years these procedures have become safe with emerging new technologies. The risk of complication during atrial fibrillation ablation is less than one percent [(1)]. We describe a very rare phenomenon of transient ST elevation in inferior limb leads during pulmonary vein isolation of right sides veins.

Case Study

A 70-year-old Caucasian female, with a history of hypertension, prior stroke, chronic kidney disease and hypothyroidism who presented to our arrhythmia clinic with symptomatic atrial fibrillation and flutter refractory to medical therapy including Cardizem, Digoxin, and Flecainide. She underwent multiple synchronized cardioversions in the past. Her CHADS-VASC score was 4. Her symptoms included shortness of breath, fatigue, and dizziness. Due to persistent symptomatic atrial fibrillation refractory to medical therapy, she was offered RFA. Risks and benefits were explained, and the patient decided to proceed with RFA for AF.

The patient was brought to the electrophysiology in the fasting state. Venous access was obtained using four vascular sheaths (SL-0 x2, SR-0 X 1) and short 11 Fr ultrasound guidance.

A Carto sound mapping catheter was advanced, and a three-dimensional electro-anatomical map of the right atrium, Cavo-tricuspid isthmus, left atrium and pulmonary veins was created. Pulmonary vein anatomy was normal. The electrophysiology catheters were advanced using electroanatomic mapping guidance to the His bundle and coronary sinus. Heparin boluses were administered throughout the procedure and the ACT was maintained between 350 - 400 sec. Isolation of the veins was performed through the creation of circumferential linear ablation lesions using an irrigated ablation catheter. The Pentarray catheter was used to guide and confirm the complete isolation of all four pulmonary veins through the identification of early activation within the ostia. The isolation of each pulmonary vein was confirmed by the presence of an entrance block to each vein. During the RFA of the right superior vein anterosuperiorly, the patient developed ST elevations in the inferior leads (Figure 1-3). Ablation was stopped and a hemodynamic assessment was performed. Her blood pressure and heart rate were stable. ST segments started coming down to baseline within 3 minutes and ablation was resumed with close attention to the surface EKG throughout the procedure (Figure 3). ACT at the time of ST elevation was noted to be 360 secs. Cardioversion was performed and all veins were checked for isolation (Figure 4 and 5). Cavo tricuspid isthmus ablation for atrial flutter was performed with the demonstration of a bidirectional block. There were no further ST elevations noted and after isolation of all veins and ablation of Cavo tricuspid isthmus a coronary angiography was performed.

Coronary angiography was performed and revealed a normal left main, left anterior descending, left circumflex and right coronary

Key Words

Atrial fibrillation, Radiofrequency ablation , Cardizem

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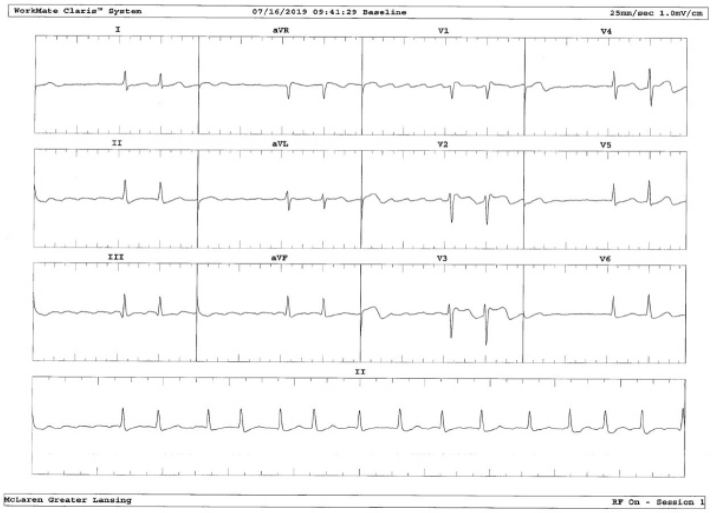

Figure 1: Baseline EKG showing atrial fibrillation without any ST deviations.

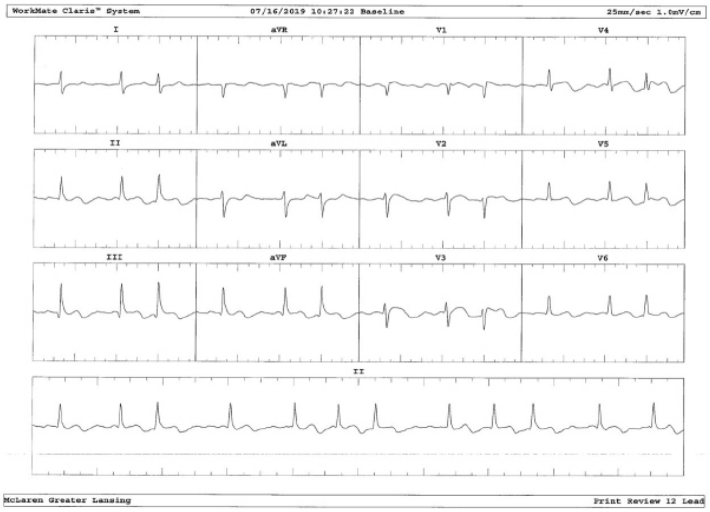

Figure 2: EKG showing ST elevation especially in inferior leads during ablation.

arteries (Figure 6 and 7) . The first obtuse marginal was noted to have a mid 50% focal lesion that was not determined to be hemodynamically significant. Anticoagulation was continued with Rivaroxaban in the post-operative period. The patient was monitored in the hospital for 24 hours without developing additional ischemic changes on telemetry or electrocardiogram. The patient was seen subsequently in follow-up in our arrhythmia clinic and has been doing well.

Discussion

AF is a common arrhythmia affecting up to 2% of the general population (1). AF commonly affects elderly patients and is associated with a lifetime risk of 26% in males and 23% in females by age 80 (1,2). RFA has emerged as the most effective rhythm control strategy for the management of AF.

Over years RFA as a rhythm-control strategy for AF has evolved as a very safe procedure with a low risk of complication rates. The potential complications of RFA include femoral vascular injury, myocardial perforation, stroke, atrio-esophageal fistula, and death. Myocardial ischemia or infarction has rarely been reported as a complication of RFA of AF ablation (1,2).

Due to the proximity of the right coronary artery to the Cavo tricuspid isthmus injury to the right coronary artery has been reported previously during ablation of Cavo tricuspid isthmus (3-7). Acute ST-elevation has been reported during transeptal puncture (8) and during slow pathway ablation for Atrioventricular reentrant tachycardia as well (9). Recently, ST-elevation has been reported during vagally mediated atrial fibrillation and a mechanism similar to

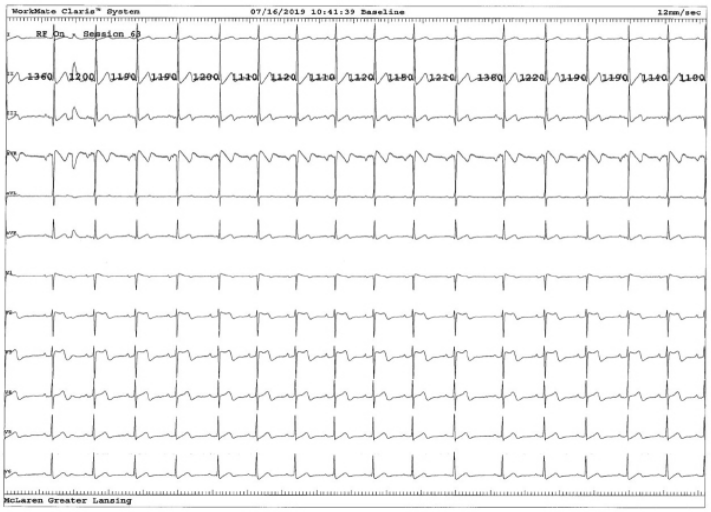

Figure 3: Post Procedure EKG showing resolution of ST deviations.

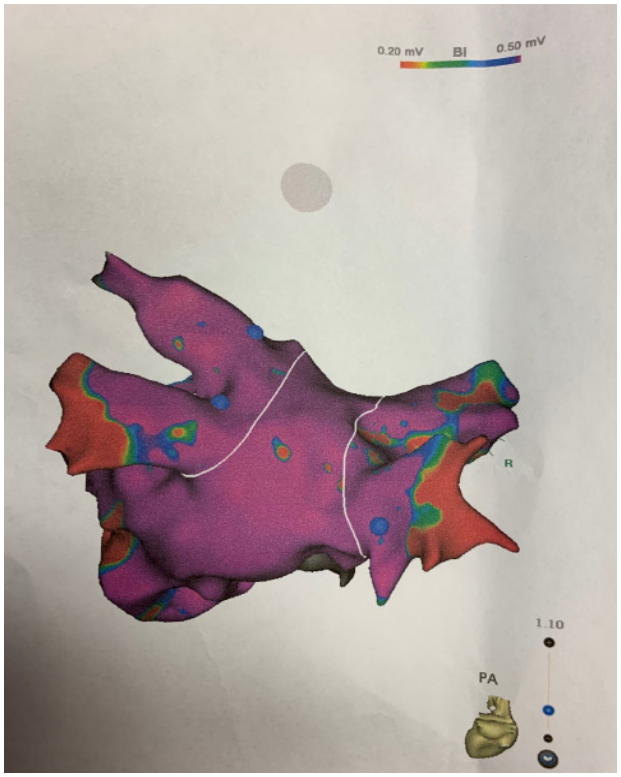

Figure 4: Pre isolation Voltage map of the veins using 3D electroanatomic mapping.

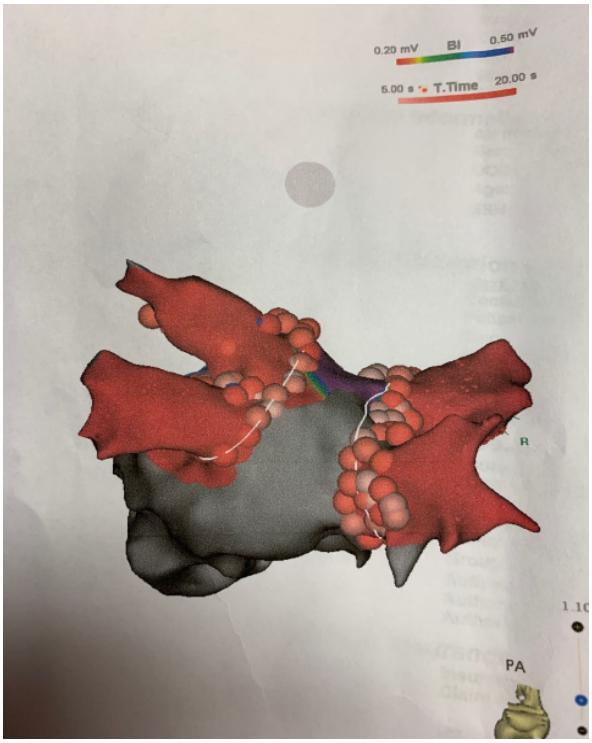

Figure 5: Post pulmonary vein isolation voltage map using 3D electroanatomic mapping showing isolation of pulmonary vein

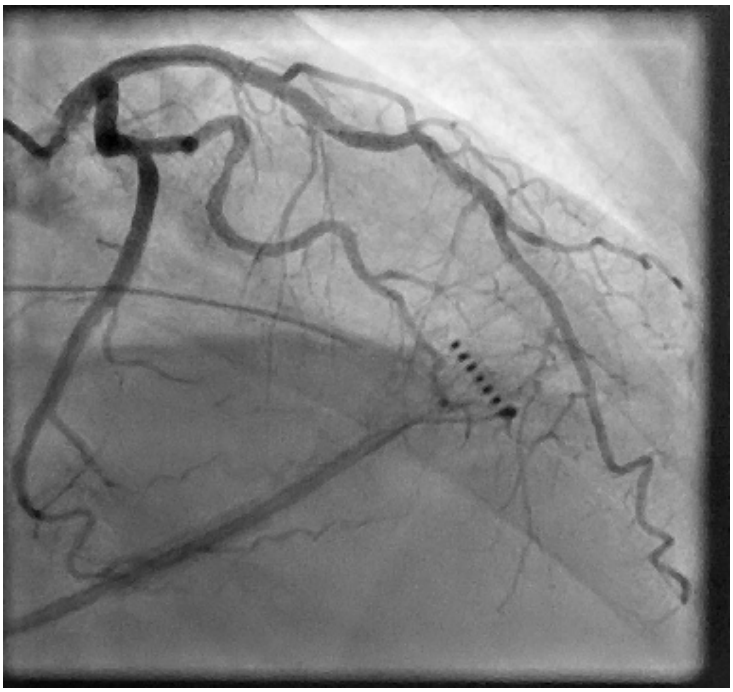

Figure 6: Cardiac Cathetrizations showing no significant left coronary artery and Left circumflex disease.

the Bazold-Jarish reflex has been implicated (10).

Although the exact mechanism of ischemic injury and resultant ST elevation during RFA has not been well elucidated the potential mechanisms include direct thermal injury, mechanical injury, thromboembolism, air embolism, and neurohumoral activation.

Direct thermal injury is possible during ablation when a target area

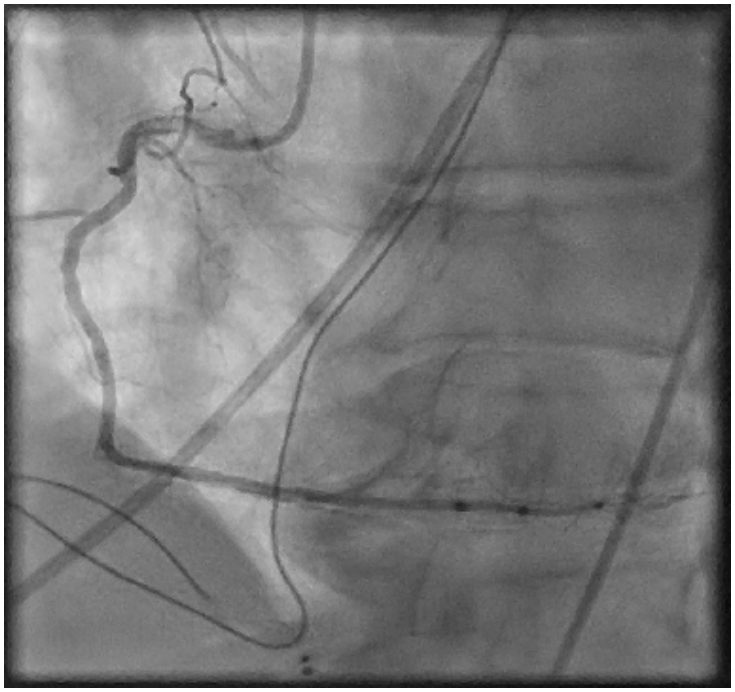

Figure 7: Cardiac Cathetrizations showing no significant right coronary artery.

is in close anatomic proximity to the coronary vascular system as has been explained during the ablation of Cavo tricuspid isthmus and slow pathway ablation for AVNRT. Mechanical stretch or pressure on the vascular system is a possibility during transeptal puncture. Other potential mechanisms including coronary embolism, air embolism or thermal injury-induced vasospasm. In our patient direct thermal injury and embolism was unlikely because the ACT was maintained between 350 – 400 secs and ablation site was not in close proximity to the arterial system.

It is also possible that the ablation could lead to local neurohumoral activation with the generation of vasospastic neurohormones that can lead to transient vasospasm and ST elevation. In our case, ST-elevation occurred while ablation was performed in the right superior vein in the anterior and superior area of the vein (RSPV). This area is usually rich in ganglionic plexus. Ablating a ganglionic plexus usually results in bradycardia and hypotension and these reflex responses are transient and subside as soon as the ablation is turned off. It is possible that the parasympathetic activation while ablating in the superior area of the RSPV could lead to transient hypoperfusion and ST-elevation through stimulation of ganglionic plexus.

We believe that the mechanism of ST-elevation could have been a reflex phenomenon rather than a direct thermal injury, as there is no major coronary artery close to the anterior superior area of the RSPV. Electrophysiologists have to be careful when encountered with such a situation especially while ablating. We should pay close attention not only to the rhythm but also to the ST segments. In our case the ST elevation was transient, and we were able to complete the procedure without any adverse outcome. However, it is crucial to monitor the patient closely for any further ST elevation. If recurrent or persistent ST elevation is noted the procedure should be aborted and an urgent

cardiac catheterization should be performed. In our patient cardiac catheterization did not show any hemodynamically significant coronary artery disease. Given the normal cardiac catheterization, an air embolism, thrombus or a direct injury to the vessel was unlikely as a mechanism for ST elevation. We believe all patients who have any ST deviation during RFA of AF should be evaluated with cardiac catheterization to rule out any possible vascular injury that would need therapeutic intervention.

Conclusion

Physicians need to be aware that ST elevation can occur during RFA of AF ablation. If transient, ablation can be continued successfully. However, if recurrent or persistent procedure should be aborted and a diagnostic cardiac catheterization should be performed urgently to rule out any possibility of an arterial injury.

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The Link Between CHA_2DS_2-VASc Score and Thromboembolic Risk in Patients Without Known Atrial Fibrillation: Are We Missing a Silent Culprit?

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Abstract

Stroke is a leading cause of morbidity and mortality. The majority of strokes are ischemic and a subset of these are due to atrial fibrillation (AF). Other etiologies include a variety of cardiovascular disorders. The CHA_2DS_2-VASc score is a validated stroke prediction tool for patients with non-valvular AF. However, it has also been shown to predict increased risk for stroke or thromboembolism in the absence of AF. Given how common subclinical AF (SCAF) is when looked for in patients with elevated CHA_2DS_2-VASc scores who are not known to have AF, (especially when implanted monitors are used), the stroke/thromboembolism risk that has been associated with CHA_2DS_2-VASc scores absent known AF may be an overestimate of the true risk due to the likely presence of SCAF in some of the subjects included. This has not yet been adequately addressed in the literature. Finally, the risk of a left atrial thromboembolic event is a consequence of the altered atrial anatomy and physiology (atrial cardiomyopathy) that may result from comorbid disorders and AF itself, or, additively from both – whether or not the AF has been already recognized clinically.

Introduction

Stroke is a leading cause of morbidity and mortality, killing up to 140,000 people in the United States every year [(1)]. Up to 90% of strokes are ischemic (vs. hemorrhagic or lacunar) with 15-20% occurring secondary to atrial fibrillation (AF). Compared to patients without AF, thromboembolic strokes due to AF are more likely to be fatal and/or debilitating. Because AF is often asymptomatic, the AF-attributable stroke risk is likely substantially underestimated [(2)]. Other etiologies of ischemic stroke include aortic and cerebrovascular atherosclerosis and non-AF related thromboembolic disease.

Non-AF risk factors for both stroke as well as atherosclerotic vascular disease include age, hypertension, hyperlipidemia, diabetes mellitus, and genetic predisposition [(3)]. Notably, many of these same clinical and anatomical factors that contribute to non-AF-related stroke or thromboembolism (TE), also underlie and predict AF as well.

Recently, clinical studies of patients with implanted pacemakers or defibrillators have shown both a substantial incidence of clinically unrecognized AF (e.g. subclinical AF (SCAF)) and an epidemiologically increased risk of both stroke and mortality when SCAF is present in such patients [(4 5)]. More recently, clinical trials using inserted cardiac monitors (ICM) in patients without known AF but with demographic and/or laboratory features common to AF, including older age, hypertension, diabetes, and heart failure have shown a high likelihood of such patients having SCAF [(6-8)]. Detection rates have been as high as 40% by 30 months of monitoring [(6)].

Thus, in an AF patient, is a TE consequent to the AF or consequent to the comorbidity underlying the AF? In parallel, in a patient with cardiovascular disease (CVD) and a TE event, but without known AF, is the event due to the CVD or is it due to as of yet unrecognized but monitor-detectable AF?

Technological advances in medicine have increased not only our ability to treat disease but also to better comprehend its pathophysiology. With these discoveries, classic cause and effect roadmaps may become muddied. AF and TE risk, including stroke, is a good example. We suggest herein the possibility that a subset of patients without known AF but with the presence of CVD may actually have SCAF that contributes to the overall likelihood of TE. In other words, stroke risk that has been associated with elevated CHA_2DS_2-VASc (congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, stroke or transient ischemic attack, vascular disease, age 65-74 years, gender) scores in the absence of AF [(10-17)] may not always be truly absent AF. Improved patient identification

Key Words

Atrial Fibrillation, Cardiovascular Disease, Subclinical Atrial Fibrillation, Thromboembolism.

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and screening strategies to detect SCAF, and treat accordingly, may reduce associated cardiovascular morbidity in this population.

Although the CHA_2DS_2-VASc score: (a) is a validated stroke prediction tool in patients with non-valvular AF; (b) is designed to identify AF patients who warrant prophylactic anticoagulation; and (c) is now the major guideline-recommended risk prediction tool in AF patients, having improved upon the original $CHADS_2$ score by refinement of low-intermediate risk AF patients [9]; a myriad of studies have demonstrated the ability of both scores to predict stroke or TE even in the absence of AF. Liu et al. published a meta-analysis and systematic review designed to evaluate the accuracy of $CHADS_2$ and CHA_2DS_2-VASc scores in non-AF populations. They pooled 6 trials and ultimately demonstrated good sensitivity. However, both scores were subject to inherent heterogeneity and poor specificity, most likely due to failure to consider stroke subtype (e.g. ischemic or hemorrhagic) [10]. A separate large study of nearly 1,800 patients with first ever ischemic strokes without known AF documented the ability of pre-stroke $CHADS_2$ and CHA_2DS_2-VASc scores to predict stroke recurrence, cardiovascular events, and 5-year mortality [11]. Further, both scores have been associated with stroke risk and other adverse cardiovascular events in non-AF patients with coronary artery disease and/or those undergoing cardiac surgery [12-14]. More recently, Nayyar et al. have shown that the risk in non-AF patients with elevated CHA_2DS_2-VASc scores may be highest if intra-atrial block is also present, which is known to be associated with an increased incidence of AF [15].

The predictive ability of these scores, despite the absence of AF, also appears to span other areas of structural heart disease. Wolsk et al. evaluated >100,000 patients admitted with heart failure in sinus rhythm and confirmed that the CHA_2DS_2-VASc score could predict TE rates within the first year of follow up, with diabetes, age, vascular disease, and prior TE independently conferring increased risk [16]. Even a retrospective analysis of a small cohort of patients with left ventricular non-compaction demonstrated higher $CHADS_2$ and CHA_2DS_2-VASc scores in patients with than without stroke or TE [17].

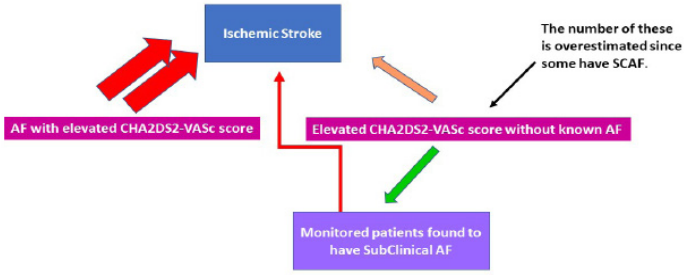

Figure 1: AF and Ischemic Stroke.

Contributors to ischemic stroke in patients with AF include AF and the associated comorbidities that constitute the CHA_2DS_2-VASc score. Note, some of those without known AF in fact have subclinical AF (see text).

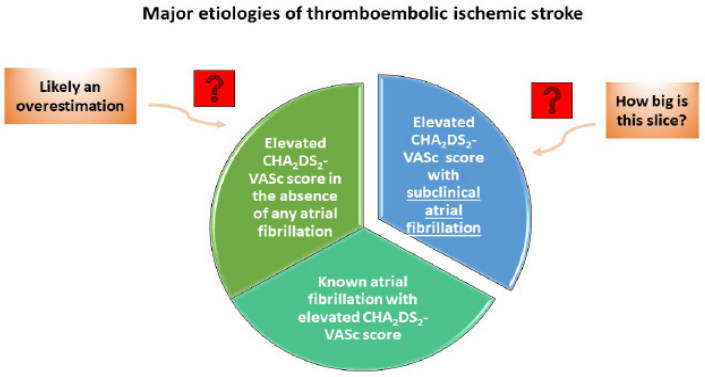

Figure 2: Major Etiologies of Ischemic Stroke

Note: Those without known AF are likely overestimated since some of these must have AF, given our current knowledge about subclinical AF (see text).

While the relationship between CHA_2DS_2-VASc score and increased stroke/TE risk may exist because many of the score's components are independent mechanisms of stroke even in the absence of an intracardiac thrombus, the ICM trials noted above suggest that SCAF is likely present in many such patients, and therefore, that some of the reported stroke/TE events in these CVD patients, unknown to have AF, may in fact be due to SCAF with AF-related thromboembolism (Figures 1 and 2). Importantly, in addition to quantifying stroke risk, the CHA_2DS_2-VASc score also correlates with the development of SCAF, especially when diabetes and/or heart failure are also present [18].

Thus, we suggest herein that some of the TE risk associated with CVD and an elevated CHA_2DS_2-VASc score may actually be related to SCAF and that the magnitude of risk reported directly consequent to or associated with comorbidities that contribute to elevated CHA_2DS_2-VASc scores in patients without known AF may overestimate their direct causative relationship. In this context, the true risk of stroke or TE is likely related to the magnitude of synergy between CVD comorbidities and AF and their combined contribution to left atrial thrombus formation (Figure 3).

The concept of "atrial cardiomyopathy" is increasingly evoked as a potential link between atrial arrhythmias and TE. Termed the "common pathological denominator of all forms of AF", the same predictors included in the CHA_2DS_2-VASc score are known to cause myopathic changes in the atria [19]. Thus, importantly, left atrial thrombus formation and cardioembolic disease are directly related to the underlying substrate of the left atrium and not solely due to AF alone. This helps to explain why patients with AF but without CVD (e.g. "lone AF") have comparably lower stroke risk [20] and that TE risk increases as CHA_2DS_2-VASc score increases. Moreover, there is often temporal discordance between the onset of AF and a TE event [21], again sugesting a role for the underlying atrial myopathy beyond simply the presence of AF. Further it is well understood that restoration of sinus rhythm does not immediately mitigate stroke risk, especially in the early post-cardioversion period [22]. To what extent the presence and type of cardiomyopathy is an independent predictor of stroke and/or to what extent AF leads to

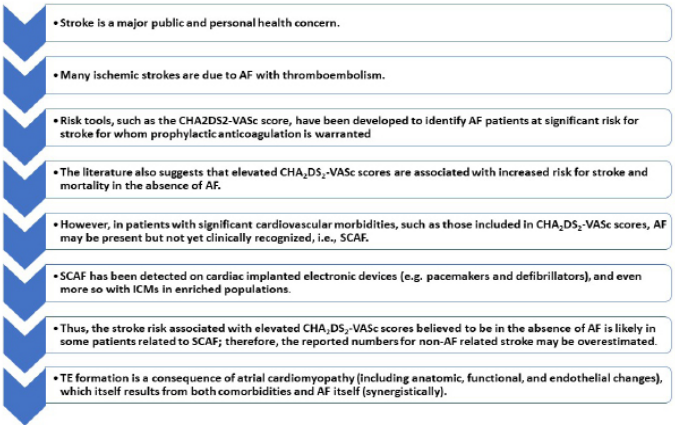

Figure 3: **Concepts regarding ischemic stroke, AF, and concomitant comorbidities.**

atrial remodeling independent of cardiovascular disease or age-related effects is unknown, but it is likely that the processes are occurring both in parallel and in series [23, 24]. Hence, to fully quantify stroke risk, one needs to consider atrial-affecting disorders and timing and burden of AF synergistically [4, 25].

That the number, type, and magnitude of associated disorders as well as AF burden can all relate to stroke risk seems inherent. But, what about the timing between AF and stroke? Why can ischemic strokes be temporally unrelated to the immediacy of AF? For example, in some studies, the last AF event prior to a stroke occurred >30 days before, while in others, such as the CRYSTAL AF study, [26] AF is first demonstrated on continuous monitoring initiated one or more years post stroke. The reasons include the fact that atrial endothelial, metabolic, anatomic, histopathologic, and contractile alterations associated with factors contributory to the atrial cardiomyopathy (as discussed above) can each contribute to the prothrombotic state and may not resolve either immediately or completely upon cessation of AF (whether paroxysmal AF, cardioverted AF, or SCAF) [21]. Thus, neither may the prothrombotic state. Moreover, if a clot forms during a period of AF, it need not embolize synchronously with the termination of AF. Conceptually, it may even be more likely to do so after some improvement of atrial contractile function following AF cessation. Thus, AF may contribute to causation but not be present at the time of thromboembolism [21]. Additionally, beyond a diseased left atrium, cardioembolic stroke can also arise from a patent foramen ovale, myopathic left ventricle, atrial myxoma or other vascular etiologies, independent of AF [27].

Not surprisingly, increasing duration of SCAF as well as comorbidity severity correlates with increasing stroke risk [8, 28-31]. Accordingly, since SCAF-associated thromboembolic risk depends not only upon AF burden but also on the type and severity of associated comorbidities, longer AF durations may result in stroke when comorbidities are less severe while lower AF burdens may result in stroke only when more severe comorbidities are present as has been clearly demonstrated by both Botto et al. [30] and by Kaplan et al. [31] The key is the presence and degree of left atrial cardiomyopathy either or both may synergistically-create.

In conclusion, AF is a major contributor to stroke risk. Such risk is reducible with appropriate use of OAC. Many markers that are predictive of ischemic stroke in patients with AF exist. [32] Yet, not all patients with AF are known to have AF. That is, SCAF may also be a factor to consider. Independent of recognized AF, stroke may be due to CVD and due to or associated with SCAF, the latter being relatively common when actually searched for. Its frequency of detection increases with population demographics and as screening goes from ECGs, to ambulatory monitoring (with a variety of devices and durations) to prolonged continuous monitoring. Thus, in those CVD patients with elevated CHA_2DS_2-VASc scores but without known AF, the TE risk that has been associated with these scores may be an overestimate of their direct risk due to the likely presence of SCAF in some and perhaps many of the subjects included. The true TE risk is likely related to atrial cardiomyopathy, that in turn is due to both AF, its burden, and CVD-related comorbidities. Given the interplay between AF, atrial cardiomyopathy, and stroke/TE risk factors, it seems most reasonable to screen for SCAF in particularly vulnerable populations for whom the initiation of oral anticoagulation (OAC) could modulate TE risk. Ongoing trials are expected to shed light on whether OAC improves outcomes in patients with SCAF [33-35]. In the meantime, the CHA_2DS_2-VASc score could be used as a surrogate to help clinicians identify candidates for SCAF screening. Even in patients without known AF, AF may be shown to play a role if it is searched for with modern technologies and an open mind.

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Jeff Healey is the director of arrhythmia services at Hamilton Health Sciences, Professor of medicine at McMaster University and the Population Health Research Institute Chair in Cardiology Research. He is also the principal investigator and chair of the Canadian Stroke Prevention Intervention Network (CSPIN), which is conducting a series of clinical trials related to atrial fibrillation and stroke prevention and will also support the development of new Canadian researchers in this field. He is the past co-chair of the Canadian Cardiovascular Society's Atrial Fibrillation Guidelines Committee and past chair of the Cardiac Care Network of Ontario's Heart Rhythm Working group.

Dr. Amr Salah Omar, MBBch, Msc, PhD, MD, MBA

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Dr. Denis Terekhov

I work as chief of emergency at the Cardiovascular Institute of Buenos Aires, Argentina. My area of interest in research is chest pain, biomarkers and acute coronary syndromes.

Dr. Damian Redfearn , MD

Dr Damian Redfearn was recruited to Queen's University in Kingston, Ontario in 2006 and was appointed Director of the Heart Rhythm Service in 2007. He has overseen the growth of the electrophysiology program at Kingston General Hospital with the addition of complex ablation and the delivery of a full spectrum of electrophysiology services and procedures to the south eastern Ontario region. Dr Redfearn is a clinician scientist with a special interest in applied computer science holds several peer reviewed research grants to investigate the mechanisms of atrial fibrillation and ventricular arrhythmia through advanced signal processing.

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Dr. Laish-Farkash is an electrophysiologist at Rambam Medical Campus in Haifa and a lecturer at Ben-Gurion University of the Negev in Israel. A graduate of Tel Aviv University, she completed a residency in internal medicine and Cardiology at Sheba Medical Center in Israel and fellowship in Electrophysiology at Sunnybrook Health Science Center, University of Toronto, ON, Canada. She has a PhD degree in basic electrophysiology from the Sackler Faculty of Medicine, Tel-Aviv University in Israel.

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