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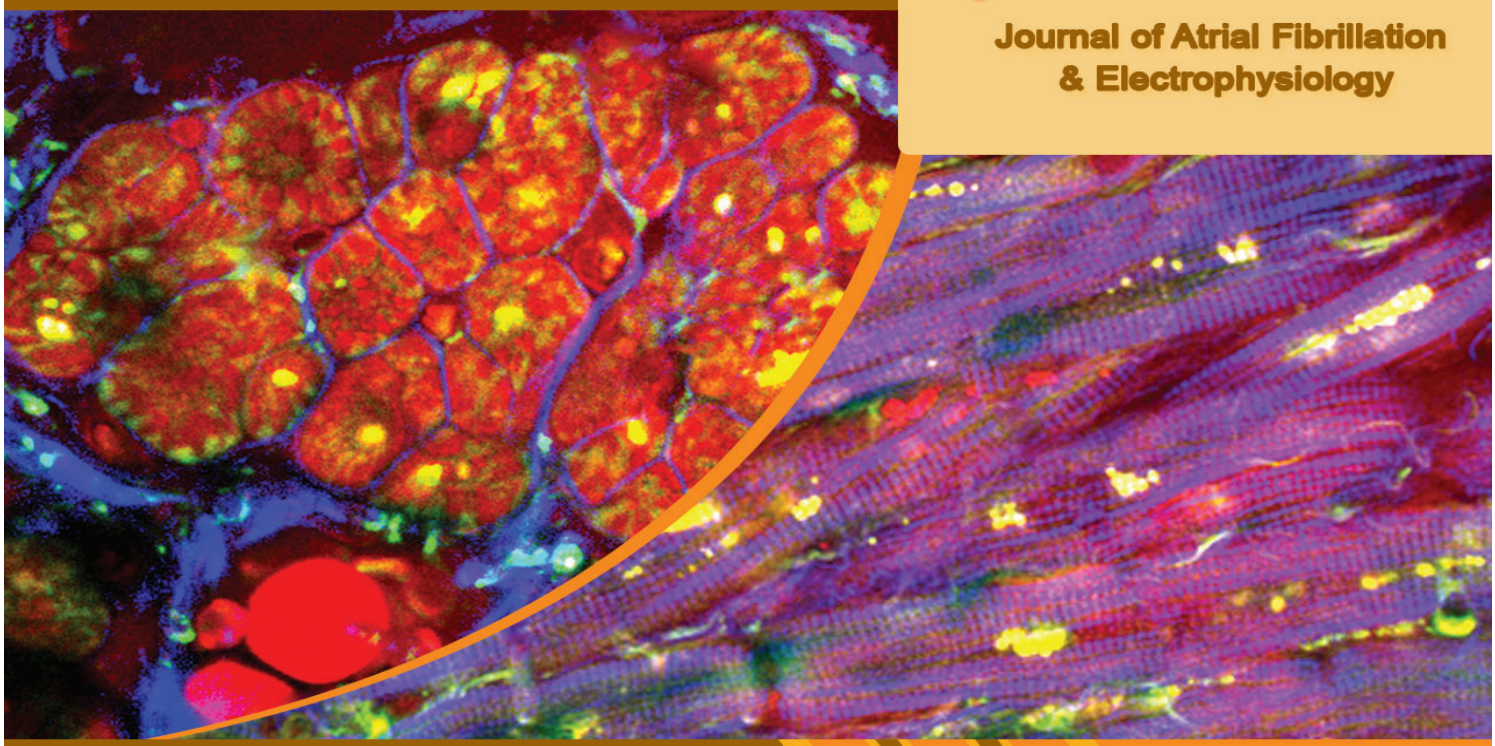

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Original Research

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Assessment of Epicardial Ganglia Pulsed Electric Fields Ablation with Botulinum Toxin

Ammar M. Killu[1], Alan M. Sugrue[1], Niyada Naksuk[2], Jason Tri[1], Brad Bolon[3], Suraj Kapa[1], Samuel J. Asirvatham[1]

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Abstract

Introduction: Pulsed-electric field (PEF) ablation induces cell membrane pore formation and permits cellular drug uptake. Botulinum toxin-A (Botox) has been shown to reduce the rate of atrial fibrillation when injected directly into intracardiac ganglia. We sought to evaluate the electrophysiological (EP) effect of percutaneous epicardial PEF and Botox delivery.

Methods: We performed 12 acute canine studies involving 4 PEF cycles (1000V, 100μs, 10pulses) either alone (control, N=6) or with 100units Botox (treatment, N=6). Botox administration was via specialized catheters permitting simultaneous PEF . Ganglia in oblique and transverse sinuses, periaortic and vein of Marshall region were targeted. Changes in EP parameters were determined.

Results: Baseline heart rate (HR) was 103±6bpm and 128±13bpm in control and treatment groups, respectively (P=0.01). Following therapy, HR decreased by 4±24bpm in the control (P=0.7) and increased by 24±21bpm in the treatment group (P=0.04). In controls, right atrial (RA) effective refractory period (ERP) (87±25 pre vs 145±33ms post) and left atrial (LA) ERP (100±24 pre vs 158±77ms post) increased by 58±34ms (P=0.01) and 58±64ms (P=0.08), respectively. In treated dogs, RA (102±13 pre vs 177±66ms post) and LA ERP (102±21 pre vs 227±81ms post) increased by 75±67 ms (P=0.04) and 125±84ms (P=0.02). There was a trend towards greater HR (P=0.06) and QTc (P=0.07) change in treated dogs though sample size was small and there were significant baseline differences.

Conclusion: Percutaneous epicardial PEF results in acute EP changes which seem accentuated when combined with Botox, possibly suggestive of additive effect on ganglia; however, this approach warrants further evaluation.

Introduction

Atrial fibrillation (AF) is the most common arrhythmia, found in over 2.5 million individuals in the United States alone with a projected increase in prevalence suggest that it will affect over 5 million individuals by the year 2050[1].

Catheter ablation, namely pulmonary vein isolation (PVI), is the mainstay of therapy for AF currently, though results remain suboptimal with a high rate of recurrence despite use of antiarrhythmic drug therapy. It is known that autonomic neural activity is important in the pathogenesis of AF and that ganglionated plexi (networks of cardiac autonomic ganglia and nerves located on the epicardial surface) occur predominantly in pericardial fat pads[2]. While a significant number of epicardial ganglia may be targeted during conventional PVI, several clinical studies assessing specifically the impact of autonomic modulation in AF have shown promising results[2]. Further, studies targeting cardiac ganglia with neurotoxins such as botulinum toxin (Botox) have been shown to reduce the susceptibility of AF[3-5].

Recently, pulsed-electric field (PEF) ablation has demonstrated increasingly promising results in management of AF[6,7]. Furthermore, PEF has been used to enhance drug delivery to cells of interest[8]. Given the reported effect of Botox and PEF individually on the activity of epicardial ganglia, we sought to determine if intrapericardial delivery of Botox at the time of peri-ganglionic PEF had additive effects on the structure and function of atrial myocardium.

Key Words

Atrial Fibrillation, Epicardial, Ganglia, Electroporation, Botox

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Methods

Animals

The protocol was approved in advance by the Mayo Clinic Institutional Animal Care and Use Committee in accordance with U.S. federal regulations and the Guide for the Care and Use of Laboratory Animals, 8th edition. The study was performed on 12 mongrel canines.

Animals were housed individually in pens.

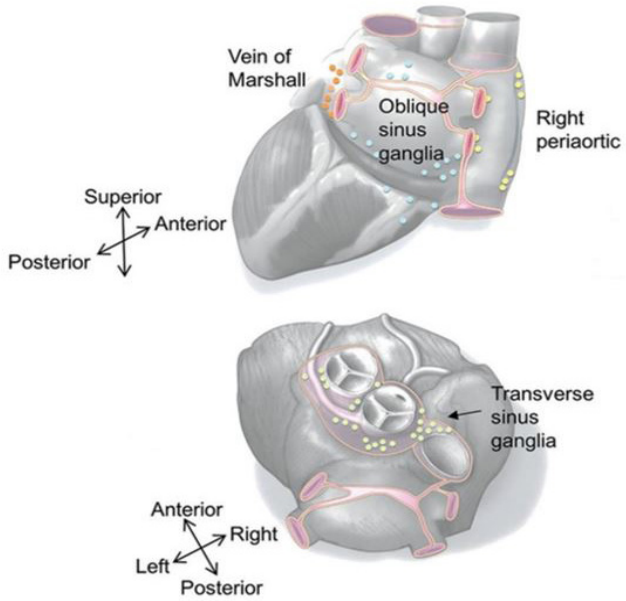

Figure 1: **Anatomical representation of cardiac ganglia sites targeted. The oblique sinus was targeted with the 6-electrode "glove" catheter; the other regions were targeted with the 4-electrode "finger" catheter.**

Electrophysiological Testing

Dogs were anesthetized with intravenous (IV) ketamine (10 mg/kg) and diazepam (0.5 mg/kg) prior to endotracheal intubation. Following this, they were maintained on isoflurane (1%) during ventilation for the duration of the study. Standard ECG leads were placed for continuous ECG monitoring. Vascular access was obtained via the percutaneous modified Seldinger technique. 12-Fr and 8-Fr sheaths were placed in the right and left external jugular veins for intracardiac echocardiography (ICE) and placement of a multipolar(10-pole) coronary sinus catheter. An 8-Fr femoral artery sheath was used for continuous blood pressure recording. Two 8-Fr femoral vein sheaths were placed for right atrial and right ventricular recordings/stimulation, respectively. Epicardial access was obtained using a Tuohy epidural needle under fluoroscopic guidance. Following pericardial puncture, a 0.032" wire was advanced through the needle over which the steerable sheath was advanced into the pericardial space. Following pericardial sheath placement, IV heparin (bolus dose 100 U/kg) was administered, with additional slow infusion at 30 U/kg/hr to minimize endocardial catheter related thrombus formation.

Intracardiac conduction intervals were recorded for baseline, and repeated at the end of the study, so that each animal could serve as its own control. Electrocardiographic and electrogram recordings were made using the Prucka system (General Electric, Milwaukee, WI, USA). Atrial extra-stimulation from the right atrium and proximal coronary sinus was performed to determine the right atrium (RA) and left atrium (LA) effective refractory period (ERP), respectively. The basic cycle length of the drivetrain was 500ms, or 10ms shorter than the baseline intrinsic heart rate if the baseline heart rate was faster than this; the extrastimulus (S2) was introduced at decrements of 10ms until atrial ERP.

Ablation

We used the anatomical description of the ganglionated plexi (GP) targets as previously described[2] to target the ablation treatments. Fluoroscopic and ICE imaging guidance as well as electrogram recordings were used to locate the respective epicardial gangliawithin the oblique sinus, transverse sinus, and periaortic region (Figure 1). Each region was treated twice at an interval of 3 min according to the PEF protocol outlined below.

The pulsed electric field (PEF) was delivered using two prototypical ablation catheters that allow injection of irrigants in the pericardial space (Figure 2) [9]. A 9-Fr deflectable multi-array "glove" (two-pronged) catheter was designed with six electrodes (3.3-mm electrode, 2-mm spacing) in two rows and irrigation ports located in the center of each electrode for ablation in the oblique sinus. Each "arm" of the catheter was built upon a nitinol frame to support the electrodes. The posterior surface of the electrode arms was covered by a polyester fabric to provide insulation of adjacent non-cardiac structures while delivering energy in a unidirectional fashion to the GP. A second 9-Fr quadripolar ablation catheter (3.2-mm electrodes with 3-mm spacing) was built in the shape of a "finger" (single-prong) in order to achieve maneuverability in smaller areas. Each electrode had an irrigation port through which an irrigant was infused during PEF. In this study, we used botulinum toxin-A (Botox®; Allergan, Ireland. PEF was delivered via the NanoKnife System (Angiodynamics, Latham, NY). PEF delivery was uniform (1000V/100μs x 10 pulses, 1Hz) and unipolar between the electrodes in contact with the atrial tissue and the ablation patch. Control animals (N =6) received PEF alone. Treated animals (Group B, N = 6) received 100U of botulinum toxin-A, which was delivered via the electrode ports at the time of ganglia PEF delivery. Contact between the ablation catheter and region of interest was confirmed by the presence of a near-field atrial electrogram and myocardial capture during pacing. A radio-opaque marker on the insulated side and the radio-opacity of the electrodes were used to confirm positioning of the electrodes on the myocardium using fluoroscopy. After the last PEF treatment, repeat electrophysiological testing was performed using same protocol outline above.

Histopathologic Evaluation

Following completion of the procedure, dogs were maintained at a surgical plane of anesthesia and humanely euthanized by induction of ventricular fibrillation. The heart, lungs, and esophagus were excised

Table 1: **Changes in baseline parameters between the control group and Botox treatment group.**

	Control group			Botox group		
Parameter	**Pre**	**Post**	**P-value**	**Pre**	**Post**	**P-value**
HR, bpm	128±13	124±12	0.70	103±14	127±20	0.04
SBP, mmHg	107±9	94±12	0.09	106±16	96±7	0.13
DBP, mmHg	71±6	58±9	0.02	65±13	54±4	0.15
MAP, mmHg	83±7	71±10	0.07	79±12	72±5	0.18
QTc, ms	354±30	363±20	0.46	313±30	366±32	0.03
ERP, ms						
RA	87±25	145±33	0.01	102±13	177±66	0.08
LA	100±24	158±77	0.08	102±21	227±81	0.02
Dispersion	13±20	13±71	1.00	0±30	50±70	0.12

Abbreviations: bpm, beats per minute; DBP, diastolic blood pressure; HR, heart rate; LA, left atrium; MAP, mean arterial pressure; ms, milliseconds; mmHg, millimeters of mercury; QTc, correct QT interval; RA, right atrium; SBP, systolic blood pressure.

enbloc. Harvested organs were examined for macroscopic (gross) lesions, after which hearts and esophagi of treated dogs were prepared for histopathological examination. Hearts were fixed while intact by immersion in 10 or more volumes of neutral buffered 10% formalin (pH 7.4), containing approximately 1% methanol as a stabilizing agent, at room temperature for at least 48 hrs. Multiple tissue blocks were acquired from each heart (oblique and transverse sinuses, oblique vein [of Marshall], aorta, pulmonary vein), both bracketing the ablation sites and at distant points to provide non-treated (no Botox or PEF) control tissue, which were interpreted by a pathologist (B.B). The esophageal wall that was located nearest the PEF sites was isolated. Each sample was placed in its own cassette and processed routinely into paraffin. Five-µm-thick sections were obtained for each block and stained with hematoxylin and eosin (H&E) to evaluate general architecture of the tissue. Serial sections of selected blocks were stained with the following stains: anti-cleaved caspase 3 (to detect apoptotic myocardial cells); Masson's trichrome or picrosirius red (to delineate fibrous connective tissue); or tyrosinase (to reveal cardiac ganglia and nerves).

Statistical Analysis

Continuous and categorical variables were summarized as mean values (± standard deviation) and percentages, respectively, and compared between groups using the paired t-test and Fischer's exact test, respectively. A two-sided P-value <0.05 was considered to be statistically significant. All statistical analyses were performed using JMP7 (14.1.0; SAS Institute, Cary, NC, USA).

Results

Baseline Electrophysiological Characteristics

There was no difference in mean weights between groups (28.7±2.3kg in control vs 29.0±1.3kg in Botox-treated dogs).Percutaneous pericardial access was successful in all canines without acute complications. Baseline and electrophysiological changes in parameters between the control and treated groups are shown in Table 1. At baseline, the heart rate (HR) and QTc interval were significantly lower in the treated group relative to the control group (103±14vs 128±13 bpm [P=0.01] and 313±28 ms vs 354±30 ms [P=0.03], respectively). Otherwise, there was no difference (P-value >0.05 for all) in terms of mean blood pressure (106/64 vs 107/71 mmHg) or baselineRAand LA ERP (101 vs 92 ms and 101 vs 100 ms).

Electrophysiological Changes after Ablation

Following ablation therapy in the control (PEF only) group, the mean heart rate decreased by 4 bpm (128±13 bpm vs 124±12 bpm, P=0.7, Figure 3A), and the mean QTc interval increased by 9 ms (354±30 ms vs 363±20 ms, P=0.46,Figure 3B). Systolic (107±9 vs 94±12 mmHg, P=0.09) and diastolic (71±6 vs 58±9 mmHg, P=0.02) blood pressures both decreased by 13 mmHg. In the treated (PEF + Botox) group, the mean heart rate increased by 24 bpm(103±14 bpm vs 127±20 bpm, P=0.04,Figure 3A), and the mean QTc interval increased by 52ms(313±28 vs 366±32ms, P=0.03, Figure 3B). Systolic (106±16 vs 96±7 mmHg, P=0.13) and diastolic (65±13 vs 54±4 mmHg, P=0.15) blood pressures decreased by 10 mmHg and 11 mmHg, respectively. There was no significant change in mean arterial pressure (MAP) between baseline and follow-up measurements in either group, though there was a trend towards lower MAP following treatment in the control group (mean drop 12 mmHg, P=0.07).

In the control group, the average S2 coupling interval for RA ERP (87±25 pre vs 145±33 ms post, Figure 3C) and LA ERP (100±24 pre vs 158±77 ms post,Figure 3D) increased by 58±34 ms (P=0.01) and 58±64 ms (P=0.08), respectively. Meanwhile in the Botox-treated group the average S2 coupling interval for RA ERP (102±13 pre vs 177±66 ms post,Figure 3C) and LA ERP (102±21 pre vs 227±81 ms post,Figure 3D) increased by 75±67 ms (P=0.04) and 125±84 ms (P=0.02).

Clinical and Electrophysiological DifferencesBetween Groups

The absolute and relative changes in HR following therapy were greater in the Botox-treated group compared to the control group (24±21 vs -4±24 bpm [P=0.06] and 23.8±22.3vs-1.4±18.1% [P=0.06], respectively), but did not meet statistical significance. The absolute and relative changes in QTc were greater in the Botox-treated group (53±44 vs 9±27 ms, [P=0.07] and 17.9±16.7 vs 2.9±7.3 ms, [P=0.07], respectively), but also did not meet statistical significance.

There were no significant differencesin the absolute or relative RA ERP (58±34 vs 75±67 ms [P=0.17] and 76±60 vs 76±68 % [P=0.8], respectively) and LA ERP (58±64 vs 125±84 ms [P=0.15] and 57±56 vs 113±88 % [P=0.1], respectively) between the control and Botox groups, respectively. The control group had no change in the dispersion of ERP (LA ERP – RA ERP) which was 13±20 ms pre and 13±71 post(P=1); however, the Botox-treated group had an increase in dispersion of ERP from 0±30 ms pre to 50±70 ms post (P=0.12). The change in dispersion of ERP following treatment was numerically greater in the Botox group though did not meet statistical significant (P=0.25).

Complications

Pericardial access was successfully obtained without complication in all dogs. The rate of sustained AF occurrence during PEF was lower in the Botoxgroup (8% vs 19%) but was not statistically significant (P=0.30). Continuous ECG monitoring did not show evidence of coronary artery injury. No ventricular arrhythmias were noted, and no ventricular fibrillation occurred in any animal.

Histopathological Findings

In PEF treated dogs, there was no macroscopic or microscopic evidence of damage to the esophagus or adjacent myocardium. Similarly,

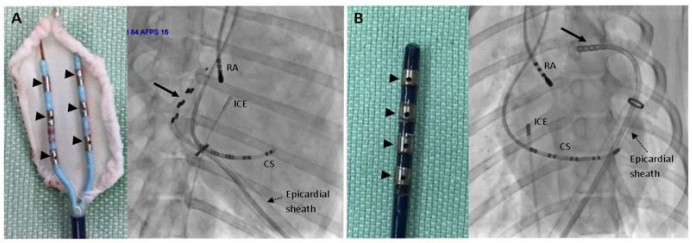

Figure 2: Prototype catheters and fluoroscopic images demonstrating catheter positioning. A, two-pronged, 6-electrode "glove" catheter intended for PEF delivery within the oblique sinus. B, deflectable one-prong, 4-electrode "finger" catheter intended for PEF delivery within the transverse sinus (as demonstrated), periaortic region, and oblique vein (of Marshall) region. Irrigation pores are noted in both catheters (black arrowheads) that permit drug delivery during PEF.

Abbreviations: CS, coronary sinus catheter; ICE, intracardiac ultrasound catheter; RA, right atrial catheter.

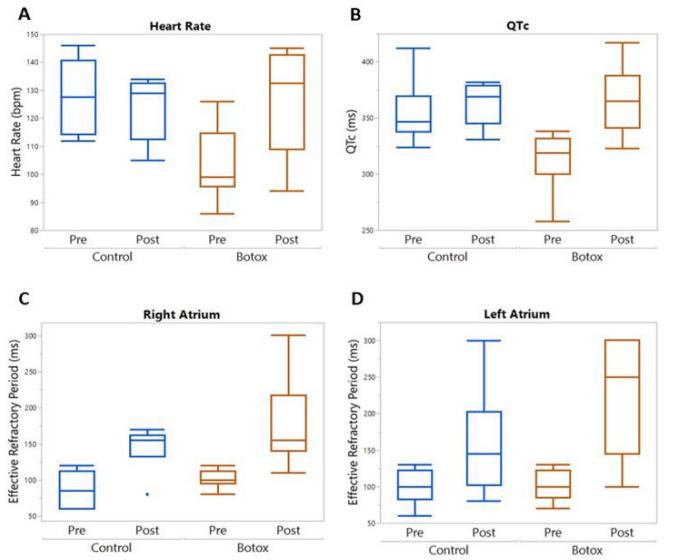

Figure 3: **Comparison between the control (PEF only) group and treated (PEF + Botox) group across a range of electrophysiological parameters.**

in PEF + Botox treated dogs, no microscopic evidence of injury was seen in the myocardium, great arteries, coronary arteries, and esophagus on gross examination. Three treated dogs had no microscopic lesions in these same tissues, while three had acute myocardial hemorrhage in some portions of the heart. In one dog, hemorrhage was limited to the anterior walls of the left and right ventricles and also the left ventricular apex and was of minimal or occasionally mid degree. In the other two affected dogs, minimal hemorrhage occurred mostly in the epicardium and rarely the superficial myocardium associated with the oblique (N = 2) and transverse (N = 1) sinuses; these hemorrhages occasionally were accompanied by focal, minimal infiltration by neutrophils. These changes were considered to be predictable effects of the access/ ablation method, and were considered to be sufficiently minor that they were interpreted as nonadverse. Cardiac fibrosis was not apparent at any site. Ganglionated plexi (epicardial ganglia and nerves) expressed tyrosinase widely in all dogs. The stained neural tissues were intact.

Discussion

The autonomic nervous system has long been recognized to play an important role in cardiac arrhythmogenesis. Targeted therapy of the extrinsic[10, 11] and intrinsic[2, 4, 12, 13] autonomic ganglia that impact cardiac function have suggested that modulation of baseline autonomic signaling can improve outcomes in arrhythmia management.Prior animal studies have shown that reduced susceptibility to AF can be gained by targeting cardiac ganglia with a neurotoxin. For example, Oh et. al demonstrated temporary suppression of vagal nerve-mediated AF with Botoxinjection of the sinoatrial and atrioventricular epicardial fat pads through a thoracotomy incision[4]. Similarly, Pokushalov et. al expanded on this by showing Botox injection into the human epicardial fat pads prevented recurrences of atrial tachyarrhythmia in the post-operative period in patients undergoing coronary artery bypass grafting (CABG)[5]. Both of these studies required a surgical approach to target the epicardial ganglia.

Ideally, clinical application of autonomic ganglia modification on the heart surface can be accomplished with less invasive means. We have previously demonstrated the ability to ablate the epicardial autonomic ganglia using PEF with the same tools percutaneously[9, 14]. In theory, PEF has several advantages over existing ablation techniques in that it has the ability to deplete ganglionated plexi without the consequences of thermal injury, thereby providing better preservation of collateral cardiac structures. This ability to limit collateral damage would be especially important if percutaneous ganglia modification was attempted with radiofrequency or cryothermal techniques which could result in injury to the esophagus, coronary vessels and phrenic nerve given their juxtaposition to the epicardial ganglia. In our current study, we aimed to leverage the perceived safety and efficacy benefits of PEF and combine them with the reported benefits of neuromodulation by using a potent neurotoxin (botulinum toxin-A) as a potential means of increasing the degree of ablation. Unlike nerves, ganglionated plexi are more susceptible to PEF. This is due to the fact that neurons have a fatty myelin sheath surrounding the nerve which absorbs much of the voltage change, thereby sparing the nerve from injury[15]. PEF has been leveraged in the treatment of tumors, whereby the local electric field induced by PEF causes membrane pore formation, thus allowing cellular drug entry[16]. Our acute animal study demonstrates that PEF delivery using our prototypical catheters is feasible and is associated with appreciable changes in the electrophysiological milieu. Furthermore, though the data did not meet statistical significance due to the small animal numbers and occasional outlier values, the electrophysiological effects produced by PEF were enhanced in the presence of Botox co-administration.

While we were able to demonstrate changes on an electrophysiological scale in terms of atrial tissue ERP, no statistically significant difference between those who were administered Botox in concert with PEF was seen compared to those who did not receive Botox. However, there were several numerical differences including a greater change heart rate and ERP in the Botox treatment group. The lack of statistical significance may be related to the small sample size or the acute nature of the study whereby effects may be expected to be seen on a longer timescale. Indeed, in the study by Pokushalov et. al[5], benefits were seen only after a few days, and that was with direct injection of the ganglia at the time of surgery. Similarly, in the animal study by Oh, change in the ERP was demonstrated 1 week after therapy[4]. Both groups had an increase in ERP following therapy with a greater change in the Botox treatment group, though this was not significant. Regardless the increase in ERP after PEF and Botox delivery has important implications as a short ERP is a well-recognized factor that predisposed to AF[17-19]. Lengthening of the ERP can result in reduction and extinction of re-entrant wavelets that promote atrial fibrillation. The increase in ERP may have an antiarrhythmic effect, as has been demonstrated with antiarrhythmic drugs such as dofetilide[20]. Dofetilide and Botox, though the latter is temporary, cause a reduction in the dispersion of ERP. Meanwhile, we saw the opposite in the treatment group which could be proarrhythmic; the increase in dispersion could be reflective of enhanced vagal effects from preferential sympathetic fiber ablation though this is hypothetical[20].

Though we did not demonstrate significant differences in the current work, we feel that the demonstration of greater electrophysiological improvement when PEF and Botox were given concurrently

warrants further study of this technique. Epicardial ablation for the management of atrial arrhythmias is likely to gain prominence given the recognition of the importance of endocardial-epicardial dissociation in the maintenance of arrhythmia[21]. As such, it would be desirable to have an effective concomitant method of neuromodulation that can be performed in this manner without the need for surgical intervention. Furthermore, though we used Botox in our study, it is conceivable that other targeted therapy could be delivered in this fashion to treat other disorders, such as cardiac malignancies and intractable pericarditis.

Study Limitations

The small sample size may mask benefits that may occur from our treatment approach. We did not check the inducibility of AF pre and post therapy using standardized protocols, but rather assessed atrial tissue ERP. Similarly while we did not determine long-term outcomes, we have previously assessed the effect of epicardial PEF without Botox in the medium-term[14]. Though we infused Botox during PEF, we could not determine whether there was any uptake of Botox into the ganglia; as such, lack of benefit may be due to a failure of toxin uptake rather than the ineffectiveness of combined therapy. Botox treatment alone with sham PEF would have added further insight but unfortunately resources were limited to the study methodology performed. Duration of effect is unable to be determined from this acute study. Furthermore, the degree of PEF may also impact outcomes; specifically, Botox delivery with irreversible PEF may not have additive effects due to the proclivity of neural tissue to expire when targeted by irreversible PEF[22]. However, some degree of axonal reinnervation may be expected such that the concomitant use of a neurotoxin has some merit[23]. The effect on heart rate observed is difficult to interpret as there was a statistically significant difference in the baseline measurements and thus the result may be due to regression to the mean. Further evaluation is warranted.

Conclusion

Percutaneous epicardial PEF to autonomic ganglia within the oblique sinus, transverse sinus and oblique vein (of Marshall) results in changes in electrophysiological parameters including increased refractoriness. The effects appear to be accentuated when combined with Botox delivery, possibly suggestive of an additive effect on epicardial ganglia; however, this remains undetermined and the approach warrants further evaluation.

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Persistent Carina Conduction after Wide Area Circumferential Ablation is Associated with Inadequate Lesion Creation During Pulmonary Vein Isolation

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Abstract

Background: Ablation at the intervenous carina is often required for pulmonary vein isolation (PVI) after wide-area circumferential ablation (WACA). This might be a marker of lower lesion quality of WACA and influence the outcome of the procedure.

Methods: We reviewed PVI cases done after the introduction of the Ablation Index (AI), but before specific target values were implemented. In six segments around ipsilateral PVs mean and minimum contact force (CF), impedance drop (IPD) and AI were determined and correlated with the need for carina ablation.

Results: Twenty-five patients (age: 65±10 years),2960 ablation lesions and 9428 parametric data were included. Ablation at the carina was required for PVI after 12/25 (48%)left WACA and 16/25 (64%) right WACA (p=0.39). The average and minimum AI, the minimum CF and average IPD were lower in the WACA lines where carina ablation was needed, compared to those resulting in "en bloc" PVI (p≤0.02).The most consistent association was found between lesion quality in the anterior segments of left PVs and the requirement of left carina ablation. While there was no recurrence in the 7/25 (28%) patients with both left and right "enbloc" PVI by WACA, 1/8 (12.5%) of those with one and 7/10 (70%) of those with both carinas ablated experienced recurrent arrhythmia within one year (p<0.01).

Conclusions: Failure to isolate the PVs without carina ablation is associated with lower quality of the WACA line, especially at the left anterior ridge. This compromises the effectiveness of PVI.

Introduction

Pulmonary vein isolation (PVI) is the cornerstone of catheter ablation of atrial fibrillation (AF)[1]. During point-by-point radiofrequency (RF) ablation PVI is attempted "en bloc", encircling ipsilateral PVs by left and right, wide area circumferential ablation (WACA) [2]. However, RF delivery between two ipsilateral veins, at the intervenous carina may be needed to achieve isolation in a considerable number of PV pairs[3,4]. This may be the result of peculiar anatomy, but can also be caused by ineffective lesions in the WACA line sparing epicardial tissue[5,6,7]. This latter may also increase the recurrence rate after PVI. Recent developments in technology have led to improved RF lesion delivery (by contact-force (CF) sensing) and provided a means to better characterize lesion quality (by the Ablation Index)[8]. Improvement in the quality of the WACA line likely contributes to diminishing rates of "epicardial connections" necessitating carina ablation for PVI reported in the literature over the years[5,6,7]. To confirm this, we examined a special population of patients undergoing PVI in whom lesion quality could be characterized retrospectively but was not used to guide RF delivery, resulting in a wide variation of lesions. Our aim was to explore the association between the need for ablation at the carina for PVI, lesion quality of the WACA line and the outcome of the procedure. We hypothesized that "en bloc" PVI, without the need for carina ablation might be a marker of better lesion quality of WACA and result in more favorable outcome.

Key Words

Atrial Fibrillation, Box Isolation

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Methods

We selected consecutive patients undergoing their first PVI for AF at a time when the Ablation Index (AI) was measured during the procedures, but specific target values were not established, resulting in greater variation of AI of individual lesions. Exclusion criteria were: presence of a common PV trunk (lack of a carina) and any gap in the WACA line (interlesion distance > 6 mm anywhere along the line).

The ablation strategy was to create antral WACA lines around

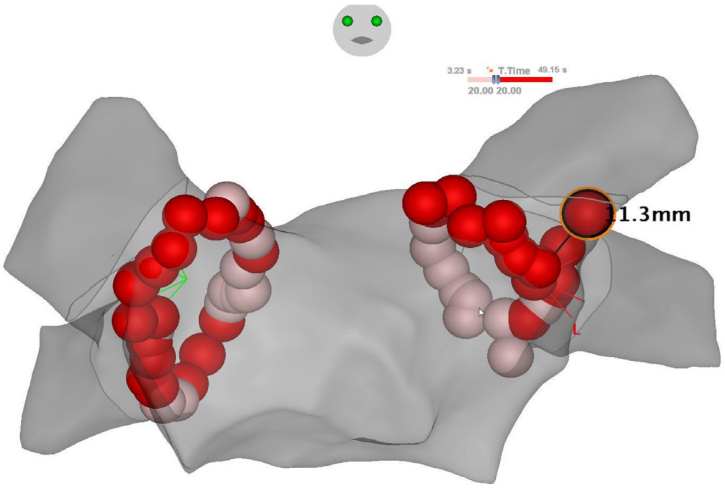

Figure 1: Three dimensional reconstruction of the pulmonary veins (PVs) and posterior left atrium seen from an anteroposterior view. Ablation tags around ipsilateral PVs are colored according to ablation time (red: ≥ 20 s, white <20 s). Ablation was also performed inside the left WACA ring, at the anterior PV carina, with the innermost tag being 11.3 mm inside the WACA ring.

ipsilateral PVs guided by electroanatomical mapping (CARTO, Biosense Webster, Irvine, CA), CF sensing (target value: 5-10 gram) and intracardiac echocardiography (ICE). Whenever PVI could not be achieved by RF delivery along the WACA line, ablation at the intervenous carina was undertaken until both PVs became electrically isolated. The RF energy was delivered in a point-by-point fashion using a 3.5 mm open irrigated-tip catheter with CF sensing (Thermo Cool Smart Touch, Biosense Webster) and power setting of 25-35 W. Power was reduced on the posterior wall, in the vicinity of the esophagus as seen on ICE. Automated ablation tag marking (Visi Tag) was used, set to the following annotation criteria: catheter stability range of motion≤ 3 mm, duration ≥ 3 s, force over time: ≥2 g over ≥25% and tag diameter 3 mm. The Ablation Index (AI) - a recently introduced marker of lesion depth that incorporates CF, ablation time, and power in a weighted formula - was available to the operator, but no specific targets were set.

The CARTO maps were reviewed retrospectively by an investigator blinded to clinical data. Any ablation tag at the intervenous carina region > 6 mm inside the WACA line delivered after completion of WACA was regarded as evidence for carina ablation (Figure 1.). Both left and right WACA lines were divided into six segments and the average and minimum CF, AI and impedance drop (IPD) determined in each segment. The perimeters of WACA lines were measured using proprietary tools of the CARTO software.

Patients were followed in the outpatient clinic at 3, 6 and 12 months after the procedure. Asymptomatic patients underwent 7-day Holter monitoring between 6 and 12 months post procedure, while any symptoms prompted event monitoring using transtelephonic ECG. Documented atrial arrhythmia ≥ 30 seconds in duration, after an 8-week blanking period was counted as a recurrence.

Statistics

Continuous variables are presented as mean ± standard deviation and compared using the independent samples t-test. Categorical variables are presented as percentages and compared by Fisher's exact test. A p-value < 0.05 was considered statistically significant.

Results

Twenty-five patients were studied, their clinical profiles are summarized in Table 1. The 50 WACA lines included 2960 ablation lesions, of which 9428 parametric data were analyzed. After 28 of 50 (56%) WACA PVI was not achieved and ablation at the intervenous carina was necessary. These included 12/25 (48%) left and 16/25 (64%) right WACA (p=0.39).

The average and minimum ablation index, the minimum CF and average IPD were lower in the WACA lines after which carina ablation was needed, compared to the ones resulting in "en bloc" PVI (353 ±40 vs. 387±40, p<0.01, 243±46 vs. 282±39, p<0.01, 2.6±0.9 vs. 3.2±0.9 grams, p=0.02, 8.4±3.1 vs. 11.1±3.3 Ohms, p<0.01, respectively).

When analyzing the left sided WACA: the average and minimum AI were lower in those requiring carina ablation for PVI (339±42 vs. 378±35, p=0.02 and 229±48 vs. 283±41, p=0.01, respectively). There was no difference however in overall average or minimum CF and IPD (p≥0.2). The six-segment analysis showed the most consistent association between parameters of lesion quality and the need for left carina ablation in the anterior segments of left PVs. Average and minimum AI, as well as minimum CF in these segments showed a strong association with the requirement of carina ablation for PVI (Table 2.). When anteriorly the superior and inferior segments were averaged, all parameters of lesion quality showed lower values in patients with left carina ablation (mean CF: 5.6±1.5 vs 7.4±2.6 grams, minimum CF: 3.4±1.1 vs. 5.2±2.2 grams, mean IPD: 8.8±4.3 vs. 13.3±4.4 Ohms, minimum IPD: 4.0±3.5 vs. 9.8±4.7 Ohms, mean AI: 409±42 vs. 357±59, minimum AI: 302.8±95.4 vs. 377.7±63.2, p<0.05 for all).

Regarding the right sided WACA those without "en bloc" PVI tended to show lower average AI, IPD and minimum CF (365±37 vs. 400±45, p=0.05 and 7.8±2.2 vs. 11.4±3.62 Ohms, p=0.01 and 2.6±0.7 vs. 3.2±0.5 grams, p=0.04, respectively). Segmental analysis did not identify a particular region with consistently lower values in those with carina ablation (Table 2.).

Left and/or right carina ablation was required for complete PVI in 18/25 (72%) patients. There was no difference in sex, BSA, echocardiographic parameters or total RF time between these patients

Table 1: Baseline parameters of patients. LAD=left atrial diameter, EDD= end - diastolic diameter, EF=ejection fraction

Age (years)	65±10
Women (%)	32
BSA (m2)	1.96±0.22
Persistent AF (%)	36
LAD (mm)	45±6.6
EDD (mm)	52±3.6
EF (%)	63±8.3

Table 2: Ablation parameters of left and right WACA resulting in "en bloc" PVI vs. need for carina ablation. AI=Ablation Index, CF=contact force, IPD=impedance drop

	Left WACA			Right WACA		
	"En block" PVI	Carina ablation	p-value	"En block" PVI	Carina ablation	p-value
Perimeter (mm)	103±19	106±18	0.71	126±15	135±19	0.28
Overall avg. AI	378±35	339±42	0.02	400±45	365±37	0.05
Minimum AI	283±41	229±48	0.01	282±39	253±43	0.12
Overall avg. CF (g)	6.7±2.1	6.0±2.1	0.39	9.1±1.1	8.5±2.1	0.41
Minimum CF (g)	3.1±1.2	2.5±1.0	0.17	3.2±0.5	2.6±0.7	0.04
Overall avg. IPD (Ohms)	10.9±3.2	9.39	0.28	11.4±3.62	7.8±2.2	0.01
Minimum IPD (Ohms)	3.6±3.5	2.5±2.7	0.42	2.7±2.1	1.5±1.5	0.13
Avg. AI						
roof	406±37	362±47	0.02	416±59	380±48	0.11
sup ant	418±44	369±66	0.04	429±54	396±46	0.12
sup post	353±36	328±33	0.09	413±57	354±46	0.01
inf ant	400±44	345±66	0.02	420±60	393±49	0.22
inf post	333±35	304±28	0.03	338±40	321±26	0.22
inf	359±43	324±39	0.04	376±40	343±28	0.02
Min. AI						
roof	325±63	279±71	0.1	364±66	321±77	0.17
sup ant	378±63	303±95	0.03	381±68	356±57	0.34
sup post	337±39	304±35	0.04	369±70	321±58	0.08
inf ant	348±67	269±67	0.01	387±72	365±41	0.34
inf post	321±38	282±42	0.02	291±39	272±44	0.3
inf	306±43	268±55	0.06	336±40	289±39	0.01
Avg. CF						
roof	7.9±2.1	7.7±2.4	0.81	10.9±2.5	9.1±3.3	0.18
sup ant	7.4±2.6	5.6±1.5	0.04	11.2±2.5	10.4±3.5	0.53
sup post	6.2±2.2	6.4±2.6	0.85	8.3±2.4	7.4±4.4	0.6
inf ant	7.3±3.3	5.1±1.9	0.06	9±3.1	9.7±3.7	0.66
inf post	5.1±1.4	6.2±3.9	0.34	6.6±1.7	5.9±1.7	0.34
inf	6.5±2.8	5.1±2.9	0.22	8.6±1.8	8.3±3.5	0.8
Min. CF						
roof	4.6±1.8	3.4±1.7	0.09	5.9±2.6	4±2	0.05
sup ant	5.2±2.2	3.4±1.1	0.02	7.2±2.9	5.9±3.4	0.35
sup post	5.2±2.2	4.5±2	0.42	5.1±1.8	4.5±2.5	0.53
inf ant	5.6±2.3	3.3±1.7	0.01	5.7±2.1	5.4±2.6	0.72
inf post	3.9±1.3	4.9±3.9	0.34	4.5±1.6	3.6±1.5	0.14
inf	3.8±1.3	3.1±1.5	0.23	3.5±1	3.8±2	0.66
Avg. IPD						
roof	12.1±3.9	10.7± 3.9	0.34	13.7±4.8	8.5±2.9	0.01
sup ant	11.5± 3.4	10.7±3.1	0.55	13.8±3.6	10±2.5	0.01
sup post	8.9± 2.8	8.4±5.5	0.79	9.5±5.2	5.9±2.2	0.7
inf ant	13.3±4.4	8.8±4.4	0.02	12.4±4.3	9±2.5	0.02
inf post	8.9±3.6	8.1±5.1	0.65	8±3.7	5.7±2.1	0.12
inf	10.5±4.6	8.9±4.7	0.4	10.7±4.2	7.7±3.2	0.06
Min. IPD						
roof	5.9±3.7	4.1±3.2	0.21	6.8±5.3	3.8±3.3	0.09
sup ant	7.1±4.5	6.9±3	0.93	7.9±4	6±2.8	0.16
sup post	6.7±3.2	5.3±3.2	0.29	6.5±3.5	2.6±1.6	0.01
inf ant	9.8±4.7	4±3.5	0.01	8.5±3.9	5.6±2	0.02
inf post	6.5±3.4	5.3±3.7	0.4	4.1±3	2.9±2.1	0.26
inf	6.1±3.5	5.4±3.7	0.66	5.2±2	4.1±3.5	0.41

and those with bilateral "en bloc" PVI (p≥0.13).

While there was no recurrence in the seven patients with both left and right "en bloc" PVI by WACA, 1/8 (12.5%) of those with one and 7/10 (70%) of those with both carinas ablated experienced recurrent arrhythmia within one year (p<0.01). There was no difference in any other parameter between patients with or without recurrence, including percentage of persistent AF, sex, BSA, echocardiographic measurements and average AI of left or right WACA (p>0.1).

All 8 patients with recurrence underwent a repeat procedure. The one with only unilateral right carina ablation at the index procedure had reconnection of right PVs, the other 7 with bilateral carina ablation had reconnection of left in 2 (28.5%), right in 3 (43%) and both left and right PVs in 2 (28.5%) cases, respectively.

Discussion

The main findings of this study are:

1. The need for carina ablation to achieve PVI is related to the quality of the original WACA: several markers of lesion quality are lower in WACA lines without "en bloc" PVI
2. The most consistent relationship between poor lesion quality and failure of "en bloc" PVI is observed at the anterior segments of left PVs, ie. the PV-left atrial appendage (LAA) ridge.
3. The requirement of carina ablation is associated with reduced effectiveness of PVI

Ablation between ipsilateral PVs, at the intervenous carina can be required to achieve PVI after creating a WACA line in up to 50 % of the cases[3,4]. Although recent advances in technology likely decreased this percentage, it is nevertheless still reported in some contemporary series in more than 10% of cases[6,9].

The intervenous carina has long been recognized as the most common site to retain conduction after WACA[3,4]. This has been attributed to its unique anatomical structure and thickness[4]. Cabrera et al. described crossing myocardial fibers in the intervenous carina, connecting the posterior wall of the superior PV with the anterior wall of the inferior PV or vice versa, in most hearts[10]. Early activation at the PV carina can be the result of sparing these - frequently epicardially located –crossing fibers along the insufficient WACA line. This may explain the frequent occurrence of carinal breakthrough after incomplete WACA.

However, recently it has been recognized that ablation at the anterior carina of the left PVs can lead to isolation even when the carina is not the earliest entrance site of activation[6,9]. The postulated explanation of this finding is activation through the vein of Marshall (VOM), running in the left PV-LAA ridge. Our results corroborate this assumption by showing that left PV carina ablation was less frequently required when sufficiently deep lesions were delivered along the left PV-LAA ridge, likely eliminating VOM conduction.

Non-transmural ablation along the WACA line not only results in the requirement of carina ablation to achieve PVI, but also leaves some – likely epicardial - part of the PV antrum unablated. This may explain the observed higher recurrence rate in these patients. The unfavorable impact of residual carina conduction after circumferential ablation

on outcome was also shown in the international Minimax Study. In this randomized trial routine carinal ablation did not affect outcome, but the need for carina ablation in the group originally assigned to circumferential PVI-only was associated with an increased rate of recurrences[11].

Therefore, while carina ablation per se is not detrimental to the outcome of PVI, not being able to produce "en bloc" isolation of ipsilateral PVs is.

Technological improvements in RF lesion creation, including standardized lesion delivery based on the AI and higher power, short duration ablation have resulted in high rates of "en bloc" PVI, likely improving current success rates[12].

Limitations

Patient recruitment was limited to a period in the beginning of our experience with the use of the AI when standardized target values were not defined. Therefore, some of the ablation lesions may have been suboptimal to current standards. This period provided the opportunity to study the effect of differences in lesion quality on PVI effectiveness. Later, more standardized WACA resulted in less variation in lesion quality and less need for carina ablation. Limiting the study to procedures during this transitional period underlies the relatively low number of patients. However, a large number of ablation points were included and thousands of parametric data were analyzed.

Conclusions

Failure to isolate the PVs without carinal ablation is related to lower lesion quality of the WACA line, especially at the left PV-LAA ridge. It is likely the result of epicardial sparing by the not sufficiently deep lesions in the WACA ring. This compromises the therapeutic effectiveness of the procedure. The results suggest that in case of incomplete PVI by WACA reinforcement of the original ring rather than carinal ablation may be more effective.

Conflict of Interest

Dávid Tasnádi is an employee of Biosense Webster, Inc. The others have no conflicts of interests to disclose.

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Predictors of Increased Length of Stay of Patients Undergoing Catheter Ablation of Atrial Fibrillation

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Abstract

Background: To evaluate predictors ofincreased length-of-stay (LOS) following catheter ablation (CA) of atrial fibrillation (AF)in order to extrapolate high-risk populations for same-day-discharge (SDD).

Methods: We conducted a retrospective analysis of 200 patients undergoing AF CA from July 2017-June 2018 at a tertiary academic medical center.

Results: Among 200 patients, 11.5% (n = 23) had LOS > 1 day (Group A) while 88.5% had an overnight stay (n = 177, Group B). Group A patients had more persistent AF (50.0% vs. 25.1%, p = 0.017), diabetes mellitus (52.2% vs. 16.4%, p < 0.001), loop diuretic use (60.9% vs. 23.7%, p < 0.001), and warfarin use (26.1% vs. 10.7%, p = 0.037), as well as higher mean CHA2DS2VASc scores (3.91± 1.35vs. 2.65 ± 1.54, p < 0.001) and longer mean procedure times (341 minutes vs. 270 minutes, p = 0.005) requiring more intraprocedural furosemide(51.4 mg vs. 27.6 mg, p = 0.031).30 day heart failure hospitalizations (17.4% vs. 1.13%, p < 0.001), access site complications, (13.0% vs. 1.70%, p < 0.003) and recurrent atrial arrhythmias both pre- and post-discharge (pre: 17.4% vs. 0%, p < 0.001; post: 47.8% vs. 19.8%, p < 0.001) were also more prevalent in Group A. Multivariate modeling demonstrated that diabetes mellitus, warfarin use, and longer procedure times were predictors of increased LOS.

Conclusion: This study identified predictors of increased LOS following AF CA in a pre-SDD, pre-COVID cohort and explored how these factors could influence discharge planning for high-risk populations.

Introduction

Catheter ablation (CA) has emerged as an effective treatment for atrial fibrillation (AF) in symptomatic and drug-refractory patients, showing superiority over antiarrhythmic medication as first-line and second-line therapy for paroxysmal and persistent AF[1-4]. Recent clinical trial data has also demonstrated a possible mortality benefit to CA of AF over medical therapy in heart failure patients[5-8]. Due to this promising data, CA procedures are anticipated to increase in the next decade.

Concomitantly, there is burgeoning interest in optimizing the periprocedural management of AF CA and other catheter-based procedures with a focus on same day discharge (SDD)[9-19].This need has heightened during the COVID-19 pandemic due to strained hospital capacity and resources. Several recently published studies have reported on the excellent safety and efficacy of SDD, yet they demonstrated that a significant number of patients did not meet criteria for it due to intraprocedural complications, prolonged post-procedural recovery, logistical issues, or lack of comfort[13-19]. Additionally, there may have been some physician bias in choosing patients with fewer comorbidities, lack of systolic heart failure, and paroxysmal atrial fibrillation for SDD [11-16]. Overall, standardized selection criteria for SDD are lacking but must be carefully devised if there is to be widespread implementation of SDD protocols. The selection criteria must identify appropriate, low-risk candidates for SDD and distinguish them from higher risk patients that would benefit from longer hospital stays for monitoring. As such, theobjective of this study was to ascertain factors that correlate with longer hospital length of stay (LOS) for patients undergoing AF CA, which could be taken into account when forming SDD selection

Key Words

Catheter Ablation, Atrial Fibrillation, Length Of Stay, Procedure Time, Warfarin

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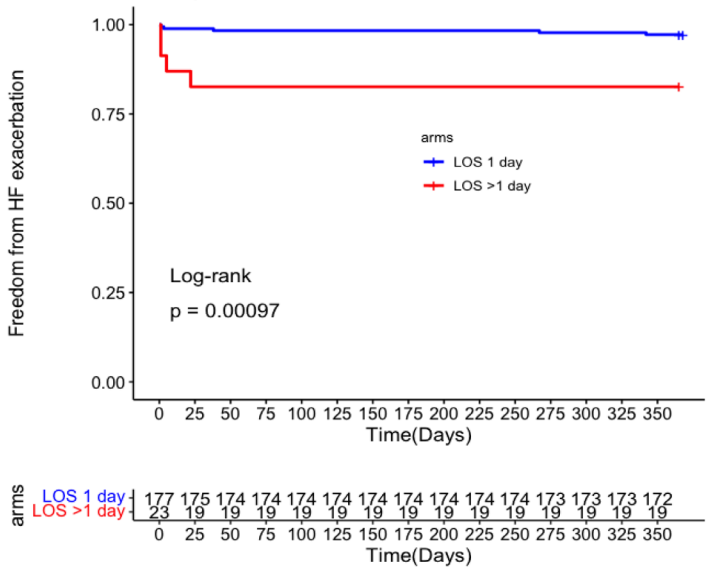

Figure 1: **Kaplan-Meier curve of freedom from heart failure exacerbation**

Freedom from heart failure (HF) exacerbation following CA of AFin aone year follow-up, comparing patients with overnight stay (LOS 1 day, blue) vs. increased length of stay (LOS > 1 day, red)

criteria. This cohort of patients all underwent at least overnight stay (LOS = 1 day), which was the standard of care at the time, or had prolonged hospital stays (LOS > 1 day).

Methods

This was a single center, retrospective cohort study of 200 consecutive patients who underwent AF CA between July 2017 and June 2018 at a major tertiary referral center in central Virginia (University of Virginia Health System, Charlottesville, Virginia). Both index and repeat AF ablation procedures utilizing both radiofrequency and cryoballoon strategies were included in adults older than 18 years old. The study was approved by the institutional ethics review board at the University of Virginia.

Detailed chart review was done to characterize baseline patient characteristics as well asprocedural and post-procedural outcomes. Diuretic administration (reported as furosemide equivalent dosage) was considered post-procedural if it occurred within 24 hours of the official procedure end reported in the Anesthesiology record. Access site complications were defined as any complication resulting from puncture of the femoral vasculature, such as groin site oozing or hemorrhage, hematomas, pseudoaneurysms, arteriovenous fistulas, and retroperitoneal bleeds. Major bleeds were defined as hemodynamically significant bleeds potentially requiring transfusions, while minor bleeds were defined as all persistent bleeds without the aforementioned qualities. Clinical hypervolemic state was defined as evidence of mild volume overload based on physical exam findings (e.g., trace to 1+ bilateral lower extremity edema) but without an increased oxygen requirement compared to baseline, significant pulmonary edema on CXR, or symptoms characteristic of a heart failure (HF) exacerbation (e.g., orthopnea, paroxysmal nocturnal dyspnea, decreased exercise tolerance). At the time of the studied AF ablation procedures, for uncomplicated patients, it was routine to discharge following a single overnight stay for recovery and monitoring (LOS = 1 day). SDD protocols were not yet adopted for this procedure in the health system.

Statistical Analysis

Categorical data are represented by numbers and percentages while continuous data are represented by mean ± standard deviation. Mann Whitney U tests were used to compare both categorical and continuous variables. A Kaplan-Meier curve was constructed to determine the probability of heart failure exacerbations up to one year following CA. A multivariable logistic regression model was constructed to identify baseline and procedure-related predictors of increased inpatient LOS (LOS > 1 day). Adjusted odds ratios were calculated for each of the potential predictors. All tests were reported as significant if $p < 0.05$, and all confidence limits were two-sided. The analysis was conducted in SPSS, version 27 (IBM, Armonk, New York) and SAS, version 9.4 (SAS Institute, Cary, North Carolina).

Results

Study population

A total of 200 patients who underwent CA of AF were examined over the study period. Patients who had a LOS > 1 day (Group A, n = 23) were compared against patients who had the standard of care, single overnight stay (Group B, n = 177). The mean LOS was 1.44 ± 1.83 days. A comparison of the major demographic and echocardiographic characteristics are shown in Table 1.

In this sample, the mean ages were similar (64.9 years and 64.8 years for Groups A and B, p = 0.772). Sex differences were not significant between the two groups. There were more patients with persistent AF in Group A (50.0% vs. 25.1%, p = 0.015), while there more patients with paroxysmal AF in Group B (22.7% vs. 49.7%, p = 0.017).

Overall, patients in Group A compared to Group B were more likely to have all the assessed comorbidities, though a significantly higher percentage of Group A patients had diabetes mellitus specifically (52.2% vs. 16.4%, p < 0.001). Accordingly, mean CHA_2DS_2VASc scores were higher in Group A patients (3.91 ± 1.35 vs. 2.65 ± 1.54, p< 0.001).

Baseline loop diuretic use was significantly higher in Group A patients (60.9% vs. 23.7%, p < 0.001), but use of other medications forHF (ACE inhibitor, ARB, aldosterone antagonist) were similar. Although overall rates of anticoagulation were similar for both groups (91.3% for Group A vs. 93.8% for Group B), Group A patients had higher rates of warfarin use (26.1% vs. 10.7%, p = 0.037) while Group B patients had higher rates of direct oral anticoagulant use (83.1% vs. 65.2%, p = 0.041).

The mean ejection fractions (EF) of patients in Group A and Group B were similar (44.7± 15.8and 50.3± 11.5 respectively, p = 0.167). There were no differences between the groups in the percentages of patients above or below an ejection fraction threshold of 50%. There were also nodifferences in other echocardiographic parameters such as left atrial diameter or left atrial volume index.

Procedural and diuretic characteristics

Key procedural and diuretic characteristics are featured in Table 2. 11 patients underwent cryoballoon ablation, all members of Group B. 189 patients underwent radiofrequency ablation. Nearly all patients

	LOS > 1 day (n = 23)	LOS = 1 day (n = 177)	P-value
Sex			
Male	10 (43.5%)	113 (63.8%)	p = 0.060
Female	13 (56.5%)	64 (36.2%)	
Age (mean ± SD)	64.9 ± 12.0	64.8 ± 10.7	p = 0.772
Atrial fibrillation/flutter			
Paroxysmal AF	5 (22.7%)	87 (49.7%)	p = 0.017*
Persistent AF	11 (50.0%)	44 (25.1%)	p = 0.015*
Typical AFL	1 (4.55%)	2 (1.14%)	p = 0.220
Atypical AFL	0 (0%)	4 (2.29%)	p = 0.475
AF Unspecified	5 (22.7%)	38 (21.7%)	p = 0.914
Comorbidities			
Congestive heart failure	10 (43.5%)	55 (31.1%)	p = 0.233
BNP (within 30 days of ablation)	116 ± 32.1 (n = 3)	605 ± 1160 (n = 7)	p = 0.267
Hypertension	20 (87.0%)	123 (69.5%)	p = 0.082
Diabetes mellitus	12 (52.2%)	29 (16.4%)	p < 0.001***
Stroke/TIA	3 (13.1%)	11 (6.21%)	p = 0.228
Kidney function (GFR)	74.7 ± 22.7	73.9 ± 18.9	p = 0.893
Medications			
ACE	7 (30.4%)	41 (23.2%)	p = 0.444
ARB	7 (30.4%)	39 (22.0%)	p = 0.369
Aldosterone antagonist	3 (13.0%)	12 (6.78%)	p = 0.285
Loop diuretic	14 (60.9%)	42 (23.7%)	p < 0.001***
Thiazide	4 (17.4%)	33 (18.6%)	p = 0.885
Warfarin	6 (26.1%)	19 (10.7%)	p = 0.037*
DOAC	15 (65.2%)	147 (83.1%)	p = 0.041*
ASA	9 (39.1%)	59 (33.3%)	p = 0.582
Digoxin	1 (4.35%)	4 (2.26%)	p = 0.547
Ejection fraction (mean % ± SD)	44.7 ± 15.8	50.3 ± 11.5	p = 0.167
EF < 50%	8 (44.4%)	40 (27.4%)	p = 0.135
EF 50%	10 (55.6%)	106 (72.6%)	
Left atrial diameter (mean ± SD), cm	4.73 ± 1.16	4.14 ± 0.67	p = 0.089
Left atrial volume index (mean ± SD), mL/m²	29.8 ± 11.0	38.4 ± 14.2	p = 0.128
CHA_2DS_2-VASc (mean ± SD)	3.91 ± 1.35	2.65 ± 1.54	p < 0.001***

Table 1: **Baseline Patient Characteristics Prior to Atrial Fibrillation Ablation.**

Key demographic and echocardiographic characteristics of patients undergoing catheter ablation of atrial fibrillation, separated by patients with prolonged length of stay (LOS > 1 day, Group A) and patients with standard, overnight stay (LOS = 1 day, Group B).*p < 0.05; **p < 0.01; ***p < 0.001

Abbreviations: ACE = Angiotensin converting enzyme inhibitor; AF = atrial fibrillation; AFL = atrial flutter; ARB = angiotensin II receptor blocker; ASA = aspirin; BNP = brain natriuretic peptide; DOAC = direct oral anticoagulant; EF = ejection fraction; HF = heart failure; GFR = glomerular filtration rate

had Foley catheters placed, which allowed for accurate volume measurements (100% in Group A vs. 98.3% in Group B, p = 0.530). Patients in Group A had longer procedure times than patients in Group B (341 ± 117 minutes vs. 270 ± 91.7 minutes, p = 0.005) that were not explained by longer fluoroscopy times, and they also had higher amounts of procedural fluid intake (2792 ±1268 mL vs. 2292 ± 870 mL, p = 0.086) and intraprocedural diuretic (51.4 ± 25.4 mg vs. 27.6 ± 16.1mg, p = 0.031). However, net volumes following the procedure were not significantly different, with the vast majority of patients in both groups being net positive. Subsequent IV and PO postprocedural diuretic administration(IV: 33.9 ± 22.5for Group A and 30.0 ±30.2 for Group B, p = 0.218; PO: 40.0 ± 14.1 for Group A and 37.4 ± 17.4 for Group B, p = 0.600) given up to 24 hours following the procedure was also not significantly different between the two groups.

Post-proceduralfollow-up

Table 3 shows a comparison of the major post-procedural outcomes between the two groups. Many in-hospital (prior to discharge) and out-of-hospital (after discharge) complications were observed at higher rates in members of Group A. Three in each group developed access site complications (13.0% vs. 1.70%, p = 0.003), but one patient in Group A had a major bleed while none did in Group B (4.35% vs. 0%, p = 0.006). Directly after the procedure, some patients in both groups developed signs of hypervolemia on physical exam without signs of overt HF exacerbation (17.4% in Group A vs. 6.21% in Group B, p = 0.056). However, within 30 days of the procedure, there were four heart failure hospitalizations and two emergency department visits in Group A, as well as two hospitalizations and one emergency department visit in Group B (Hospitalizations: 17.4% vs. 1.13%, p < 0.001; ED visits: 8.70% vs. 0.565%). One member of Group A also suffered a transient ischemic attack immediately following the procedure. Additionally, several patients in Group A experienced atrial arrhythmia recurrence immediately after the procedure (17.4% vs. 0%, p < 0.001). Recurrence also occurred several months following the AF ablation procedure, requiring cardioversions or repeat AF ablation (47.8% vs. 19.8%, p = 0.007).

c	LOS > 1 day (n = 23)	LOS = 1 day (n = 177)	P-value
Procedural characteristics			
Procedure duration (min)	341 ± 117	270 ± 91.7	p = 0.005**
Fluoroscopy duration (min)	23.5 ± 33.8	16.5 ± 26.3	p = 0.563
Contrast use in cryoablation procedures (mL)	2792 ± 1268	33.1 ± 26.9 2292 ± 870	p = 0.086
Intake (mean ± SD), mL	1046 ± 1134	809 ± 704	p = 0.919
Output (mean ± SD), mL	1746 ± 920	1480 ± 725	p = 0.134
Net (mean ± SD), mL	21 (95.5%)	174 (98.9%)	p = 0.218
Net positive	1 (4.55%)	2 (1.14%)	
Net negative	23 (100%)	174 (98.3%)	p = 0.530
Foley catheter			
Diuretic administration			
Postprocedural diuretic			
IV (mean ± SD), mg	33.9 ± 22.5 (n = 18)	30.0 ± 30.2 (n = 120)	p = 0.218
PO (mean ± SD), mg	40.0 ± 14.1 (n = 5)	37.4 ± 17.4 (n = 23)	p = 0.600

Table 2: **Procedural and Diuretic Characteristics of Atrial Fibrillation Ablation**

Key procedural and diuretic characteristics of patients who underwent catheter ablation of atrial fibrillation, separated by patients with prolonged length of stay (LOS > 1 day, Group A) and patients with standard, overnight stay (LOS = 1 day, Group B). *p < 0.05; **p < 0.01; ***p < 0.001

Freedom from heart failure exacerbations

HF exacerbations were noted over one year follow-up in these patients. Group A was found to be at higher risk for HF periprocedurally (HR 4.5, 95% CI (1-20), p = 0.04, Figure 1).

Predictors of increased length of stay

As illustrated in Table 4, in a multivariable analysis, increased inpatient LOS correlated with the presence of diabetes mellitus (ORadj 3.465, 95% confidence interval (CI) (1.090-11.016), p = 0.035), increased procedure time (ORadj 1.006, 95% CI (1.001-1.012), p = 0.019), and pre-procedure use of warfarin (ORadj 3.445, 95% CI (1.036-11.458), p = 0.044). Loop diuretic use, persistent AF, and CHA_2DS_2VASc score were not predictive ofincreased LOS.

Discussion

This was a retrospective, single center study comparing the baseline characteristics and outcomes of 200 consecutive patients who underwent CA of AF in the pre-COVID, pre-SDD era. We found the following: 1) Group A patients were more likely at baseline to have persistent AF and a higher overall burden of comorbidities, 2) Group A patients had longer procedure times leading to more intraprocedural volume intake and intraprocedural diuretic, and 3) Group A patients had increased rates of complications such as major bleeds, access site bleeds, arrhythmia recurrence, and 30-day HF exacerbations. Multivariable logistic regression analysis showed that longer procedure durations, pre-procedure warfarin use, and diabetes are predictive of increased inpatient LOS.

Most published SDD protocols have indirectly accounted for procedure length by avoiding late procedure start times or end times, since later endings would preclude sufficient time for bed rest or hemostasis [13-16]. However, procedure duration may also be important to note due to its positive correlation with intraprocedural volume intake[20]. In this study, over 2L of fluid intake on average was recorded for both groups of patients during the procedure, but patients in Group A received at least 500 ml of additional fluid (>2.7L in Group A and >2.2L in Group B). In patients with left ventricular systolic dysfunction (mean EF 44.7 in Group A and 50.3 in Group B), such large volumes could conceivably lead to signs of fluid overload and decompensated heart failure. In further examining HF exacerbations, in Group A, there were a total of 4 exacerbations (17.4% of cohort, 2 out of 4 managed prior to discharge), and another 4 patients who were clinically hypervolemic. There were 2 exacerbations in Group B (1 prior to discharge). Since there is increasing evidence for benefit of CA in heart failure patients, it is imperative to identify this cohort of patients who need longer stays due to high risk of precipitating an exacerbation (26% of patients in Group A) [5-8]. Notably, there may be a delay in the time to HF exacerbation. Other studies have noted that exacerbations occur within 3 days of the procedure [21-22], while in this study, 5 out of 6 exacerbations occurred within 5 days. Group A did receive higher average doses of intraprocedural diuretic (51.4 mg vs. 21.6 mg)but did not receive higher doses of PO or IV postprocedural diuretic within 24 hours compared to Group B patients. Whether administration at this time could have affected HF exacerbations and hospital stays remains to be known. Overall, we would recommend that providers be more vigilant in monitoring for volume overload and administer more aggressive post procedural diuresis within 24 hours with active patient engagement, particularly in patients with long procedure times of 5 hours or beyond.

Access site complications and major bleeds were also higher in Group A, with warfarin pre-procedure anticoagulation emerging as a significant predictor of LOS. Out of the warfarin-related bleeds, there was one major bleed, a retroperitoneal hematoma resulting in hypotension requiring pressors and massive transfusion, which in turn precipitated a HF exacerbation. This patient was on warfarin for primary stroke prevention and had a supratherapeutic INR of 4.1 at the time of her retroperitoneal bleed. Two other minor bleeds at femoral access sites also occurred due to supratherapeutic INR levels (3.6 and 4.3). Out of these 3 bleeding events, 2 required longer LOS (67%). In comparison, there were 4 total bleeding events with DOAC use (no major bleeds), but only 1 required longer LOS (25%). Although the sample sizes are small, these observations point to a possible association of warfarin with more significant post-ablation bleeding events due to fluctuating INR levels, leading to longer hospitalizations. Notably, patients on warfarin did not receive antibiotics up to 15 days pre-procedure, though antibiotics have been tied to increased risk of

	LOS > 1 day (n = 23)	LOS = 1 day (n = 177)	P-value
In-hospital (prior to discharge) complications			
Pericardial effusions	0 (0%)	0 (0%)	
Major bleeds	1 (4.35%)	0 (0%)	p = 0.006**
Minor bleeds	2 (8.70%)	4 (2.26%)	p = 0.090
Access site complications	3 (13.0%)	3 (1.70%)	p = 0.003**
Clinical hypervolemic state	4 (17.4%)	11 (6.21%)	p = 0.056
Out-of-hospital (after discharge) complications			
HF hospitalizations within 30 days[a]	4 (17.4%) [a]	2 (1.13%) [a]	p < 0.001***
HF ER visits within 30 days	2 (8.70%)	1 (0.565%)	p = 0.003**
Stroke/TIA within 30 days	1 (4.35%)	0 (0%)	p = 0.006**
MI within 30 days	0 (0%)	0 (0%)	
Atrial arrhythmia requiring DC cardioversion	4 (17.4%)	0 (0%)	p < 0.001***
Atrial arrhythmia recurrence (3 months – 1 year)	11 (47.8%)	35 (19.8%)	p = 0.003**

Table 3: **Post-procedural Outcomes of Atrial Fibrillation Ablation.**

Key post-procedural outcomes of patients who underwent catheter ablation of atrial fibrillation, separated by patients with prolonged length of stay (LOS > 1 day, Group A) and patients with standard, overnight stay (LOS = 1 day, Group B). *p < 0.05; **p < 0.01; ***p < 0.001; a ½ of the HF hospitalizations in both groups occurred within the hospital.
Abbreviations: MI = myocardial infarction; TIA = transient ischemic attack

significant bleeding events with concurrent warfarin use[23]. Additionally, patients in this cohort were continued on uninterrupted warfarin prior to the ablation, an approach that has been shown in prior studies to reduce minor bleeding complications[24-25]. Vascular closure devices (VCDs) were not used in this time frame and ultrasound guided access was obtained per operator discretion, so it remains to be known whether these measures could have reduced access site bleeding in particular for warfarin patients.

While there is an overall lack of data about who should be prioritized for SDD, both prospective and retrospective cohort trials demonstrate similar characteristics of patients who successfully underwent SDD. SDD patients tended to be younger with lower BMIs and CHA_2DS_2VASc scores and underwent earlier ablations [12-16]. Chu et al.also demonstrated that LVEF less than or equal to 35% and a significantly dilated left atrium were associated with delayed discharge, while Rajendra et al. excluded patients with systolic heart failure and prior history of bleedingfor SDD [16-17]. For patients who failed SDD, several studies have reported access site bleeding/hematomas as some of the most common complicationsseen in these patients [9-14], with one study attributing their SDD success to augmented use of vascular closure devices, or VCDs[9]. Altogether, the literature substantiates the findings uncovered in our study. Longer procedure durations can cause later end times and volume overload that would preclude SDD. We would caution providers to avoid SDD for procedure durations longer than 5.5 hours (the median procedure duration of Group A), especially in patients with baseline left ventricular systolic dysfunction. These patients should be prioritized for overnight stay with intensive post-operative monitoring and diuresis. Additionally, providers should consider ultrasound guided vascular access or closure devices for patients being continued on warfarin for peri-procedural anticoagulation [26], as well as close INR monitoring. Certain comorbidities such as diabetes may also predispose patients to complications, though the mechanism is likely multifactorial. Patients without these factors may be able to undergo SDD safely within 4-6 hours of the procedure. To optimize workflow, shorter procedures where the patient has no other contraindications to SDD should be planned for the morning hours so as to avoid late end times that keep patients in the hospital [16]. Novel ablation strategies, such as cryoballoon ablation, may be associated with decreased procedure times that could increase the likelihood of

Variables	Adjusted Odds Ratio	95% CI	*P*-value
Procedure duration	1.01	1.00 - 1.01	**0.019***
Diabetes mellitus	3.47	1.09 - 11.0	**0.035***
Loop diuretic use	2.53	0.864 - 7.42	0.090
Persistent atrial fibrillation	1.24	0.42 - 3.67	0.699
CHA_2DS_2VASc score	1.20	0.81 - 1.77	0.362
Warfarin use	3.45	1.04 - 11.5	**0.044***

Table 4: **Multivariable predictors of prolonged length of stay (LOS >1 day)**

*p < 0.05

successful same-day discharge [27].

Limitations

This study was a single center, retrospective analysis with unequal group matching, such that certain characteristics may have been overrepresented by chance in Group A. However, variables such as longer procedure times and persistent AF that were prevalent in Group A have already been validated in the literature as being associated with longer stays. Second, a true SDD protocol could not be studied since SDD was not adopted at our institution at the time.Admittedly, it is unknown whether some of the patients who were discharged after overnight stay would have been appropriate for SDD, or whether patients with prolonged stay would have been definitively excluded from SDD. We acknowledge that a prospective study of SDD in a sufficiently large population is the most ideal method for evaluating the validity of selection criteria. However, we still believe there is merit to analyzing retrospective data that could shed light on factors that have resulted in longer lengths of stay, which could provide necessary background for constructing a viable SDD protocol.

Conclusions

This study identified predictors of inpatient LOS> 1 day following AF CA that could guide selection criteria for SDD. Our study suggests that long procedure duration, high bleeding risk from fluctuating INR levels, and certain comorbidities such as diabetes mellitus should be considered for at least overnight stay for close monitoring of volume status and bleeding complications. Patients with short procedures, low bleeding risk, and overall fewer cardiovascular comorbidities may be able to undergo SDD safely.

Declarations

Conflicts of Interest/Competing Interests: The authors have no conflicts of interest to disclose.

Authors' contributions

Sahitya Allam and Evan Harmon collected the data; Sahitya Allam, Nishaki Mehta, and Sula Mazimba analyzed the data; Sahitya Allam prepared the manuscript; Sahitya Allam and Nishaki Mehta revised the manuscript.

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Newly Identified Cardiomyopathy Often Presents with Advanced, Global Cardiac Remodeling When Associated with Atrial Fibrillation

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Abstract

Background: AF concurrent with cardiomyopathy is associated with increased morbidity and mortality. There is limited research comparing the extent of cardiac remodeling present in patients with new-onset cardiomyopathy (CM) associated with atrial fibrillation (AF) (AF-CM group) to that present in patients with new-onset CM without any concomitant or antecedent dysrhythmia (CM group). This study aimed to evaluate the extent of baseline cardiac remodeling present in patients with new-onset CM with and without AF. This review does not attempt to address the gap in knowledge of the mechanisms or the temporal relationship of AF-associated remodeling in patients with CM and AF.

Hypothesis: AF has effects on the heart at structural, functional, and electrophysiological levels. Thus, we hypothesized that AF-CM will have more pan-myocardial chamber remodeling compared to isolated CM.

Methods: Patients with a left ventricular ejection fraction ≤40% without a prior history of CM were identified from our healthcare system's electronic medical records for the period of January 1, 2012 to September 30, 2016. Those with an antecedent or concomitant diagnosis of AF comprised the AF-CM group, and those with no prior dysrhythmia comprised the CM group. The AF-CM group (n=196) was compared with the CM group (n=197). The groups were controlled for left ventricular ejection fraction.

Results: Patients in the AF-CM group had more left atrial, right atrial, and right ventricular remodeling, more advanced right ventricular systolic dysfunction, and increased severity of both tricuspid and mitral regurgitation at presentation than the CM group.

Conclusions: Patients with newly – identified CM with AF had greater global cardiac remodeling at presentation than those with CM not associated with AF.

Key Words

Atrial Fibrillation; New-Onset Cardiomyopathy; Cardiac Remodeling

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Introduction

This study evaluated the morphological and physiological differences between new-onset cardiomyopathy (CM) with and without atrial fibrillation (AF). The distinction between the CM groups is whether there was concomitant or antecedent AF (AF-CM group) or no history of dysrhythmia (CM group). There is scant literature comparing the degree of cardiac remodeling present at baseline between these two

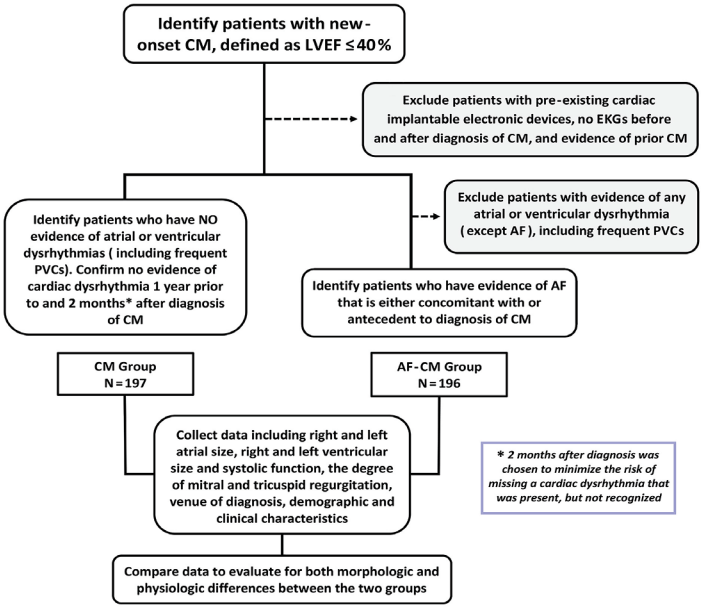

Figure 1: **Study design.**

AF, atrial fibrillation; CM, cardiomyopathy; LVEF, left ventricular ejection fraction; PVC, premature ventricular contraction;

groups that are commonly encountered in clinical practice.

Methods

The Advocate Aurora Health Institutional Review Board approved this study, which was conducted in accordance with the Declaration of Helsinki.

Study Population and Data Collection

We identified patients with new-onset CM, defined as an LVEF ≤40% and no prior history of low EF, from January 1, 2012 to September 30, 2016 through retrospective review of data from electronic medical records (EPIC, Verona, WI). Both inpatients and outpatients were included in the study. Patients with any pre-existing evidence of CM based on office notes and/or cardiac imaging were excluded. Patients with a pre-existing cardiovascular implantable electronic device or with a history of any other dysrhythmia, including frequent premature ventricular contractions,were excluded, as were patients with an unreadable or poor-quality echocardiogram, mortality during inpatient admission, or congenital heart disease. Patients were divided into two groups: the AF-CM group encompassed those with an antecedent or concomitant diagnosis of AF and the CM group comprised those with no history of preceding dysrhythmia. Patients in the CM group had not had any atrial or ventricular dysrhythmia in the one year preceding or the consecutive two months following the diagnosis of CM. Echocardiographic data were collected from the echocardiographic reports. Information about the treatment these patients received both as an inpatient and outpatient and outcome data also were collected. An almost equal number of patients were included for each 5% difference in LVEF. An equal number of patients were collected for LVEF <20% (Figure 1). The demographic and clinical characteristics of these patients are listed in Table 1.

Statistical Methods

All categorical and continuous variables were described using appropriate descriptive statistics. For example, all categorical variables, such as sex, race, tobacco and alcohol use, hypertension, history of percutaneous coronary intervention, hyperlipidemia, coronary artery disease, diabetes mellitus, mortality, and categories of LVEF, were described as frequencies and percentages, and, wherever appropriate, chi-square and/or Fisher's exact test were used to compare the AF-CM and CM groups. All continuous variables, such as age, body mass index, LVEF, and LV diastolic diameter, were described as mean±standard deviation, and the mean values of these variables for the two groups were compared using t test for independent samples. An alpha of 0.05 was used for all statistical tests, and all statistical analysis was done using SAS 9.4, SAS Institute, Cary, NC.

Table 1: **Demographic and clinical characteristics.**

Characteristic	AF-CM group (n=196)	CM group (n=197)	Pvalue
Age, years	73.51±12.14	64.18±15.98	<0.001
Body mass index	31.5±8.2	29.8±7.7	0.04
Sex, male	124 (63.3)	97 (49.2)	0.01
Race			<0.001
White	190 (96.9)	151 (76.7)	
Black/African American	4 (2.0)	39 (19.8)	
Others	2 (1.0)	7 (3.5)	
Tobacco use	119 (60.7)	132 (67.0)	0.19
Alcohol use	24 (12.2)	71 (36.0)	<0.001
Hypertension	138 (70.4)	105 (53.3)	<0.001
History of PCI	36 (18.4)	38 (19.3)	0.82
Hyperlipidemia	115 (58.7)	81 (41.1)	<0.001
Coronary artery disease	66 (33.7)	41 (20.8)	<0.01
Diabetes mellitus	59 (30.1)	57 (28.9)	0.80
History of drug abuse	4 (2.1)	15 (7.6)	0.01
Outpatient diagnosis	70 (35.7)	20 (10.2)	<0.001
Presenting symptoms			<0.001
Congestive heart failure	128 (65.3)	82 (41.6)	
Myocardial infarction	0 (0.0)	46 (23.3)	
Others/unknown	68 (34.7)	69 (35.0)	
Mortality	62 (31.6)	44 (22.3)	0.04
Palpitations on presentation	23 (11.7)	3 (1.5)	<0.001
LVEF on diagnosis			0.99
6-40%	43 (21.9)	42 (21.3)	
31-35%	40 (20.4)	43 (21.8)	
26-30%	45 (23.0)	43 (21.8)	
21-25%	33 (16.8)	33 (16.8)	
≤20%	35 (17.9)	36 (18.3)	

Data presented as n (%) or mean±standard deviation.
AF, atrial fibrillation; CM, cardiomyopathy; LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention.

Table 2: Echocardiographic characteristics.

Echocardiographic characteristic	Total (n=393)	AF-CM group (n=196)	CM group (n=197)	P value
LVEF	393, 29.38±7.73	196, 29.54±7.68	197, 29.21±7.81	0.67
LV diastolic diameter (mm)	381, 5.32±0.82	193, 5.19±0.79	188, 5.45±0.84	0.0024
LV size				0.0059
Normal/mild	302 (81.2)	163 (86.7)	139 (75.5)	
Moderate/severe	70 (18.8)	25 (13.3)	45 (24.5)	
RV size				<0.001
Normal/mild	320 (83.1)	145 (75.5)	175 (90.7)	
Moderate/severe	65 (16.9)	47 (24.5)	18 (9.3)	
RV function				<0.001
Normal/mild	298 (77.2)	132 (68.8)	166 (85.6)	
Moderate/severe	88 (22.8)	60 (31.2)	28 (14.4)	
LA size				<0.001
Normal/mild	127 (41.9)	35 (24.6)	92 (57.1)	
Moderate/severe	176 (58.1)	107 (75.4)	69 (42.9)	
LA volume index	334, 45.1±18.4	164, 51.9±19.5	170, 38.5±14.5	<0.001
RA size				<0.001
Normal/mild	239 (62.1)	77 (40.1)	162 (83.9)	
Moderate/severe	146 (37.9)	115 (59.9)	31 (16.1)	
Mitral regurgitation				0.001
Normal/mild	211 (58.9)	92 (50.6)	119 (67.6)	
Moderate/severe	147 (41.1)	90 (49.4)	57 (32.4)	
Tricuspid regurgitation				<0.001
Normal/mild	225 (63.7%)	93 (51.4%)	132 (76.7%)	
Moderate/severe	128 (36.3%)	88 (48.6%)	40 (23.3%)	

Data presented as n, mean±standard deviation or n (%).
AF-CM, cardiomyopathy with atrial fibrillation; CM, cardiomyopathy without dysrhythmia; LA, left atrial; LV, left ventricular; LVEF, left ventricular ejection fraction; RA, right atrial; RV, right ventricular.

Results

(Figure 2, Table 2)

Left Ventricle

Both the AF-CM group and CM group were controlled for presenting LVEF. Despite having heart failure with reduced EF, LV dimensions were within normal limits for most patients in both groups. LV cavity size was slightly larger in the isolated CM group, with a median value of 54.5 mm vs. 51.9 mm in the AF-CM group (P=0.0024). The LV was the only cardiac chamber that showed greater remodeling at baseline in the isolated CM group.

Right Ventricle

Most patients in the CM group (134/193, 69.43%) had a normal right ventricular (RV) size at presentation, whereas a majority of patients in the AF-CM group (112/192, 58.33%; P<0.001) had an enlarged RV at the time of the initial diagnosis of CM. Almost a quarter of patients in the AF-CM group had moderate-to-severe RV enlargement on the initial echocardiogram, whereas < 10% of patients had a similar degree of enlargement in the CM group. RV systolic dysfunction was much more prevalent in the AF-CM group. Moderate-to-severe RV dysfunction was more than twice as prevalent in the AF-CM group (60/192, 31.2%) at presentation than in the CM group (28/194, 14.4%; P<0.0001) (Figure S1).

Left Atrium

Greater left atrial (LA) enlargement was seen in the AF-CM group; mean LA volume index was severely enlarged in the AF-CM group (51.93 mL /m^2) vs only mildly enlarged (38.52 mL /m^2) in the CM group. A majority of patients (92/161, 57.1%) in the CM group had a normal or slightly enlarged LA, whereas only a small number of patients in the AF-CM group (35/142, 24.6%, P<0.0001) had similar LA size. More than three-quarters of patients in the AF-CM group (107/142, 75.4%) had moderate-to-severe LA enlargement at presentation. The percentage of patients with severe LA enlargement in the AF-CM group was almost twice (65.6%) that of the isolated CM group (34.4%, P<0.0001)(Figure S1).

Right Atrium

Right atrial (RA) remodeling was even more pronounced at baseline in the AF-CM group than the CM group. A majority of patients had a normal RA size in the isolated CM group (112/193, 58%), whereas less than one-third of that number (33/192, 17.18%) had a normal RA size in the AF-CM group (P<0.0001). Moderate-to-severe RA enlargement was prevalent in the AF-CM group (115/192, 59.9%) but was relatively uncommon in the CM group (31/193, 16.1%) (Figure S1).

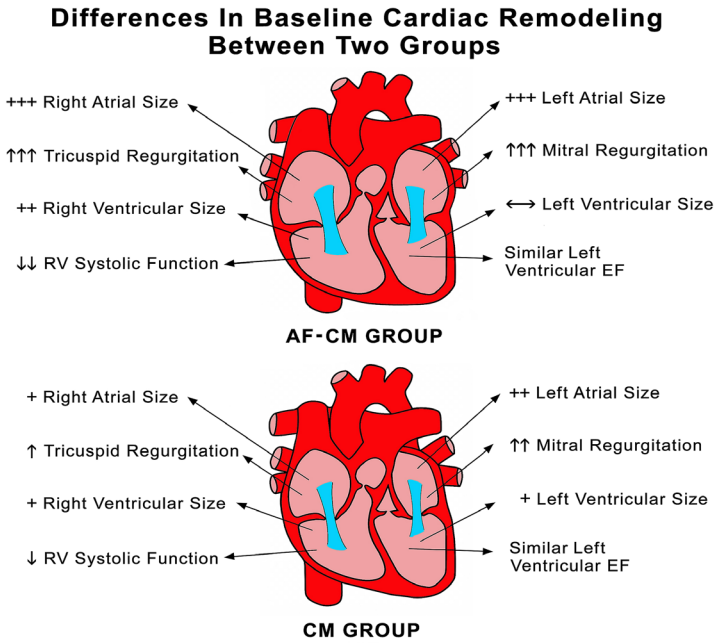

Figure 2: Differences in baseline cardiac remodeling between two groups.

↑ Mild, ↑↑ Moderate, ↑↑↑ Severe Valvular Regurgitation
↓ Mild, ↓↓ Moderately Decreased RV Systolic Dysfunction
↔ LV Size Within Normal Limits
+ Mild, ++Moderate, +++ Severely Enlarged

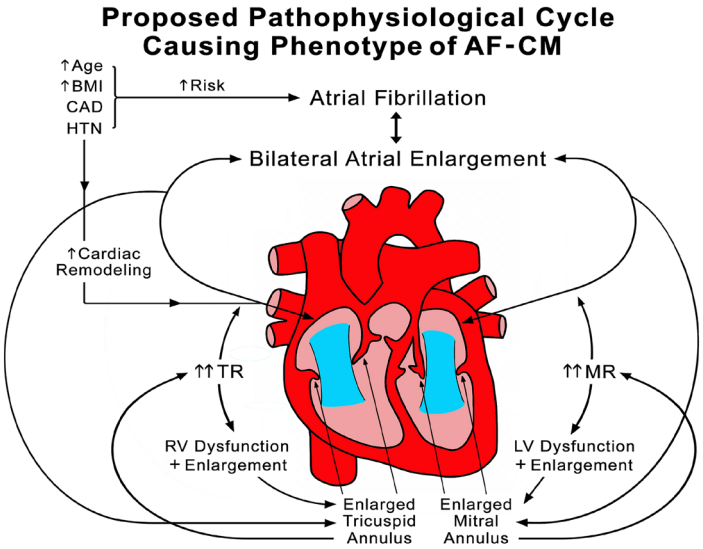

Figure 3: **Proposed pathophysiological mechanism causing phenotype of AF-CM.**

BMI, body mass index; CAD, coronary artery disease; HTN, hypertension; MR, mitral regurgitation; TR, tricuspid regurgitation.

Greater Prevalence, Severity of Valvular Regurgitation in AF-CM Group

A majority of patients in the isolated CM group were reported to have either no or mild mitral regurgitation (119/176, 67.6%), whereas almost half the patients in the AF-CM group (90/182, 49.4%; P=0.0010) had either moderate or severe mitral regurgitation. The difference in tricuspid regurgitation was even more marked. There was either no or just mild tricuspid regurgitation in the CM group for most patients (132/172, 76.7%), with less than a quarter (40/172, 23.3%) reported as having moderate-to-severe tricuspid regurgitation. On the other hand, more than twice that percentage of patients (88/181, 48.6%) in the AF-CM group were reported to have moderate-to-severe tricuspid regurgitation at presentation (P<0.0001) (Figure S2).

AF- CM Group More Likely to Present in the Outpatient Setting

Despite having markedly more advanced global cardiac remodeling at presentation, the AF-CM group patients were more likely to present and be diagnosed as outpatients. AF symptoms were much more likely to be atypical (tiredness, fatigue, weight gain) rather than typical (palpitations) in this group.

Mortality in the AF- CM Group

The mortality rate in the AF-CM group was considerably higher than in the isolated CM group (Table 1). This was despite the CM group having a more acute presentation and greater elevation in traditional cardiac biomarkers. The Kaplan-Meier survival curves for the two groups diverged further apart throughout the time follow-up data were collected.

Discussion

Left Ventricular Size

Mean LV size was within normal parameters in both groups, though the dimensions were slightly larger in the isolated CM group. There were more patients with moderate-to-severe enlargement in the CM group than the AF-CM group (Figure S1). This may indicate that an LV myopathic process likely caused isolated LV dysfunction in the CM group and a global pan-myocardial maladaptive process occurred in the AF-CM group that affected all chambers of the heart, rather than just the LV. The only chamber that was more remodeled in the CM group was the LV, pointing toward the underlying pathophysiological process having been more localized to the LV in the CM group.

Comparing Biatrial Remodeling in AF-CM and CM Groups

There was notably more LA and RA remodeling present at baseline in the AF-CM group than the CM group. A larger LA portends an increased risk for development of AF[1,2]. AF can also lead to enlargement of both the LA and RA[3]. The triggers for AF have been localized to the LA in a majority of patients[4], but it is interesting to note that the difference in RA enlargement was greater in the AF-CM group. A large percentage of patients (83.9%) in the CM group had a normal or mildly enlarged RA, whereas a majority of patients (59.9%) in the AF-CM group had moderate-to-severe enlargement of the RA (Figure S1). The more pronounced RA enlargement may be explained by:

1) RV enlargement/dysfunction and tricuspid regurgitation, both of which were more prevalent and severe in the AF-CM group, could have resulted in more advanced remodeling of the RA [5].

2) Significant LA enlargement has been shown to occur in patients with heart failure with reduced EF [6]. As isolated CM appears to be more of a localized LV myopathic process with increased LV remodeling present at baseline, it could have led to more adverse hemodynamic effects and remodeling of the LA in the CM group. This, in turn, could have resulted in a smaller relative difference in the size of the LA and a larger relative difference in the size of the RA between the two groups.

However, AF is known to cause both RA and LA enlargement[3]. Biatrial enlargement could have caused both tricuspid and mitral annular dilation and functional tricuspid and mitral valve regurgitation, setting up a mutually reinforcing vicious remodeling effect with further enlargement of both atria, perpetuation of AF, and development of further ventricular remodeling and dysfunction (Figure 3). In addition, risk factors like hypertension and coronary artery disease, which were more prevalent in the AF-CM group, are also known to cause cardiac remodeling [7,8]. But it does appear that the process of global, advanced remodeling transpired slowly though inexorably, maybe over months or even years, for the following reasons:

1) This degree of cardiac remodeling is unlikely to occur over hours or days even in the presence of serious underlying pathology.

2) Most of the patients in the AF-CM group presented with subacute or atypical symptoms, which is suggestive of the fact that the homeostatic mechanisms in these individuals had time to adapt to the profound structural and functional changes occurring in the heart.

Right Ventricular Remodeling and Dysfunction

The degree and extent of RV enlargement and dysfunction was even

greater in the AF-CM group. The exact pathophysiologic mechanisms for this are unknown. Possible reasons may include:

1) AF leads to RA enlargement, which in turn can cause tricuspid annular dilation and functional tricuspid regurgitation[5,9];the increased load due to tricuspid regurgitation can lead to RV enlargement and dysfunction (Figure 3).

2) The underlying pathophysiologic factors that increase the risk for development of AF, like obstructive sleep apnea[10], have also been implicated to cause RV dilation and dysfunction[11].

3) Isolated CM being a more LV-centric disease process preferentially involves the LV, with other chambers eventually getting involved due to LV dysfunction, whereas AF-CM, being a more systemic disease process, more uniformly affects all chambers, and thus the RV is in a more advanced disease state at presentation.

The answer remains perplexing. This review does not attempt to address the gap in knowledge of the mechanisms or the temporal relationship of AF-associated remodeling in patients with CM and AF. Nonetheless, significantly more advanced right-sided chamber involvement appears to be a characteristic phenotypical feature of AF-CM (Figures 2, S2).

Presence of Coronary Artery Disease and Biventricular Dysfunction

Based on previous studies, biventricular dysfunction is more likely to be associated with nonischemic CM, whereas isolated LV dysfunction with wall motion abnormalities is more commonly encountered in patients with coronary artery disease or ischemic CM[12,13]. In this study, the AF-CM group, despite having a higher prevalence of coronary artery disease (Table 2), had more biventricular cardiac dysfunction. It is important to understand that the presence of coronary artery disease does not determine the cause of the CM.

Patients with biventricular remodeling/enlargement have also been found to be more symptomatic at presentation[14], but even though the AF-CM group patients had more marked biventricular dysfunction, they were less acutely symptomatic than the CM group patients. This again points toward the fact that this phenotype of CM likely develops more gradually, leading to a subacute and atypical presentation despite the presence of significantly more biventricular dysfunction. The subacute presentation, though, did not provide any protection against a worse prognosis: Patients in the AF-CM group had a higher mortality rate on follow-up. This increased mortality in the AF-CM group is likely multifactorial and raises the question of the impact of AF on mortality in this group. This needs further investigation.

Differences in Valvular Regurgitation Between Groups

Tricuspid Regurgitation

The presence and severity of tricuspid regurgitation was greater in the AF-CM group, with almost twice the number having moderate-to-severe tricuspid regurgitation compared to the isolated CM group (Figures 2, 3). Postulated explanations include:

1) The relative difference in RA enlargement was even more marked between the two groups than LA enlargement. This may have led to relatively greater tricuspid annular dilation and functional tricuspid regurgitation [5,9].

2) Factors like obstructive sleep apnea and obesity probably caused more baseline RV enlargement, tricuspid annular dilation, and tricuspid regurgitation.

3) Arrhythmia-induced and arrhythmia-mediated CMs do cause profound changes in cellular and extracellular matrix in the entire heart[15].This can cause more pan-myocardial chamber remodeling, rather than isolated LV remodeling, in AF-CM, leading to more severe tricuspid regurgitation.

Mitral Regurgitation

The prevalence of moderate-to-severe mitral regurgitation was also greater in the AF-CM group (49.4% vs 32.4%). There is increasing recognition that AF may be an etiological factor for mitral regurgitation[16]. The difference between the two groups was less for mitral regurgitation than for tricuspid regurgitation. This may be owing to the heterogeneous remodeling of left-sided chambers seen in the two groups. While the right-sided chambers were uniformly more enlarged in the AF-CM group (Figure S1), the same was not seen in the left-sided chambers (Figure S1). The LA was significantly more remodeled in the AF-CM group, whereas the LV was slightly larger in the CM group. Both LA and LV dilation probably lead to functional mitral regurgitation[17]. The fact that these factors were contradictory in these two groups may have led to a smaller relative difference in the degree of significant mitral regurgitation between them.

Generally, more severe valvular regurgitation is associated with a more symptomatic presentation[18-20]. However, patients in the AF-CM group, despite having worse valvular regurgitation, had a more subacute presentation than those in the CM group, which again points toward a slow but unremitting pathophysiologic process set in motion in the AF-CM group.

Ubiquitous and Advanced Cardiac Remodeling at Presentation in AF-CM Group: Distinct Phenotype of CM?

Even though a lot of research into arrhythmia-mediated CM has focused on the LV, the process of remodeling in AF-CM appears to be systemic and pan-cardiac. There are multiple mechanisms by which dysrhythmias have been proposed to cause CM, which involve complex and pervasive changes at the structural, functional, molecular, and electrophysiological levels[15,21]. These changes affect the entire heart and not just the LV, and thus a more pan-myocardial pathology at presentation would be expected; this is what was found in the current study. An individual can also be predisposed to AF owing to a variety of risk factors, including older age, increased body mass index, and history of hypertension, among others[22]. All these factors were more common in the AF-CM group, and it is possible that these factors independently caused some of the cardiac remodeling seen in this phenotype (Figure 3). The temporal changes in cardiac chamber remodeling are in need of further exploration in both groups. Regardless of the temporal association of AF in the development of this disease, the AF-CM group phenotype appears to be quite distinct from the CM group.

Limitations

This is a retrospective study with all the limitations inherent in that type of study, including incomplete or inaccurate data and the possibility of selection bias. Echocardiographic reports were utilized for

assessing LVEF; these can sometimes be challenging to read, especially in patients with atrial dysrhythmias. One of the reasons a cut-off of 40% was selected was to minimize the probability of patients with a normal EF being included in the study. Additionally, the two defined groups are heterogeneous and may have variable phenotypic expression causing the distinctions between the two groups to be less precise.

Each patient chart was thoroughly evaluated by a research coordinator to identify a group of new-onset CM patients with a concomitant or antecedent diagnosis of AF (AF-CM group); the CM group patients were also carefully assessed to rule out contribution of any dysrhythmias to CM. Nonetheless, it is possible that some CM group patients had AF that was undiagnosed or not captured in medical documentation or electrocardiographic, telemetry, or rhythm strip evaluation. In addition, "new-onset" AF-CM and CM may have been identified late in the clinical course with variable degree of remodeling.

We excluded patients with a cardiovascular implantable electronic device because a significant percentage of them have structural heart disease, and also, pacing can confound patient characteristics and outcomes. Thus, we obtained as uncontaminated a sample as possible so that patients with AF-CM and CM without any dysrhythmias could be compared.

There were some missing data in reports; e.g., some reports did not have LA or RA size listed. But the amount of missing data was small, and a majority of data points were available in the reports.

Echocardiograms were read by different readers, had varying quality, and were performed on different echocardiography machines. Additionally, quantitative assessments of cardiac chambers and valvular regurgitation were not available. The temporal duration of AF at the time of diagnosis is often unknown, and, therefore, the degree of cardiac chamber remodeling is variable. Also, we were unable to address whether AF was the sole driver of the CM or a marker of an advanced CM.

Nonetheless, there was consistency in the broad narrative across all those studies and readers. Moreover, the likelihood of researcher bias in those echocardiography readers would be non-existent as they were not trying to accomplish a particular research goal but were reading the studies in service of clinical decision-making in the real world.

Conclusions

AF-CM and isolated CM groups are frequently encountered in clinical practice. To our knowledge, this is the first study to evaluate the differences in structural and functional cardiac remodeling at presentation in patients with new-onset CM with and without AF. Despite having significantly greater cardiac remodeling at baseline, a majority of patients in the AF-CM group presented with atypical symptoms of AF and had less acutely perceptible congestive heart failure symptoms, yet had an inferior prognosis. The underlying pathophysiologic mechanisms for the development of AF-CM may be a complex interplay of comorbid conditions, AF itself, and the gradual progression of cardiac remodeling. This may set up a vicious, self-perpetuating path physiological cycle (Figure 3) that is relentless in its progression, leading to the development of a distinct phenotype of CM (Figure 2). Further studies to explore the distinctive characteristics, underlying pathophysiological mechanisms, temporal evolution of cardiac chamber remodeling, and appropriate treatment pathways for the AF-CM group will shed more light on this 21st-century "epidemic of cardiovascular disease."

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Safety and Efficacy of Direct Acting Oral Anticoagulants Compared with Warfarin in Patients with Atrial Fibrillation and Liver Cirrhosis

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Abstract

Warfarin was considered as the anticoagulation agent of choice for patients with liver cirrhosis and atrial fibrillation (AF) before the emergence of direct acting oral anticoagulants (DOACs). Given their superior efficacy, safety, predictable effect, and fewer drug interactions, the latter has revolutionized stroke prevention in AF, but much of this data excluded patients with liver cirrhosis.

The aim of this study was to compare the efficacy and safety of DOACs to warfarin in this unique patient population.

This is a retrospective longitudinal study of patients with liver cirrhosis and atrial fibrillation on anticoagulation who were either admitted to our hospital or seen at our outpatient clinic, between January 1, 2016-January 1, 2020. Outcomes included intracranial hemorrhage, gastrointestinal bleeding, cerebrovascular insult, deep venous thrombosis/pulmonary embolism (DVT/PE), and all-cause mortality amongst these two groups.

Warfarin had an increased incidence of GI bleeding when compared to DOACs (37.03% vs 20.45%, $p < 0.005$) but when the differences in sex distribution and duration of follow up were accounted for, there was no statistically significant difference. There was a trend towards difference in all-cause mortality, but it failed to reach statistical significance (40.74% for 27.27% for DOACs, $p=0.069$). Subgroup analysis revealed that female sex was associated with an increased incidence of GI bleeding in those treated with warfarin (48.38% vs 23.33%, $p<0.05$). One unexpected finding was that lower HAS-BLED scores did not correlate with a low incidence of GI bleeding in women, whereas it reliably predicted bleeding risk in males.

Our study did not show any significant difference in the safety and efficacy of DOACs as compared to warfarin when used for anticoagulation in patients with atrial fibrillation and concurrent liver cirrhosis.

Introduction

Atrial fibrillation-related stroke can be prevented by anticoagulation, however, anticoagulation for atrial fibrillation (AF) in patients with concomitant liver cirrhosis presents a challenge. These patients are likely to be at an increased risk for both thrombosis and bleeding, complicating the use of anticoagulants[1,2,3]. Direct oral anticoagulants (DOAC) have revolutionized stroke prevention in AF patients because of their superior efficacy, safety, fewer drug interactions, and predictable effect without the requirement of frequent monitoring, as compared to warfarin. Since major trials demonstrating DOAC efficacy excluded patients with advanced liver disease, concerns regarding their safety in this patient population have been raised; especially because most DOACs are predominantly metabolized in the liver and have high plasma protein binding, potentially increasing free drug levels in conditions of hypoalbuminemia such as liver cirrhosis. Hence, there is no specific recommendation in AF guidelines regarding anticoagulation agent of choice in patients with liver cirrhosis. With this study, we aimed to identify if DOACs were comparable to warfarin in their safety and efficacy in AF patients with liver cirrhosis.

Key Words

DOAC, Warfarin, Atrial Fibrillation, Liver cirrhosis, HAS-BLED.

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Methods

This is a retrospective longitudinal study using data from patients either admitted to our hospital or seen at our outpatient clinic between January 1, 2016-January 1, 2020, who had a diagnosis of liver cirrhosis and were on anticoagulation for AF. We used ICD-10 codes I 148, K

70.3, K 70.2,K 71.1, K 74.60,K 74.69,K 74.3,K 74.4,K 75.81 andK 71.7 to identify patients with AF and liver cirrhosis and then excluded the patients who were not on anticoagulation. We were able to identify 142 patients who satisfied our inclusion criteria, among which 88 were on DOACs (apixaban, rivaroxaban and dabigatran) and 54 on Warfarin. Of note, these patients might have been on anticoagulation even prior to 2016, but to be included they must have had either an inpatient or outpatient encounter at our hospital between the aforementioned time. The patients were followed up until their last visit in our healthcare system and the median duration of follow up was calculated.

Study Outcomes

Intracranial hemorrhage, gastrointestinal bleeding, cerebrovascular insult, deep venous thrombosis/pulmonary embolism (DVT/PE) and all-cause mortality were recorded based on chart review during the period of follow up. The outcomes were compared among those on DOACs and those on warfarin.

Statistical Analysis

The statistical analysis methods used were student t test for the parametric data and chi square (or Fisher's exact test for extremely low numbers) for non-parametric data. Mann-Whitney Rank Sum test was used for ordinal data (CHA_2DS_2-VASc or HAS-BLED scores) or parametric data that failed the normalcy test. SigmaStat 3.5 software was used.

Results

Table 1 compares the baseline characteristics amongst the patients who received DOACs and those who received Warfarin. It demonstrates that the characteristics of the two groups were quite similar in most aspects. However, there were three significant differences amongst the two groups. First, the patients that received Warfarin had a decreased risk of developing major bleeding as determined by the lower HAS-BLED score (60.3% of those in the Warfarin group had HAS BLED scores< 2vs 29.5% in the DOACs group, p <0.001). Second, while the Warfarin group comprised of similar proportions of males and females, the DOAC group was composed predominantly of male subjects (42.5% males in Warfarin group vs 65.9% in DOAC group, p<0.01). Third, the median duration of follow up was 30 months in the Warfarin group and 24 months in the DOACs group (Interquartile range (IQR) of 23-73 months for Warfarin vs IQRof 12-36 months for DOACs,p<0.001). We noted that several patients in the Warfarin group had longer period of follow up (outliers) and we used Mann Whitney Rank Sum test for their analysis. The outcomes of our study are shown in Table 2.

Our results demonstrated that the Warfarin group had an increased incidence of GI bleeding when compared to the DOAC group (37.03% vs 20.45%, p <0.005), but when the differences in sex distribution and duration of follow up amongst the two groups were accounted for, there was no statistically significant difference in GI bleeding amongst the two groups. Also, there was a trend towards difference in all-cause mortality, but it failed to reach statistical significance (40.74% for Warfarin vs 27.27% for DOACs, p=0.069).

Subgroup analysis revealed that female gender was associated with an increased incidence of GI bleeding especially in those treated with Warfarin (48.38% vs 23.33%, p<0.05). Table 3 shows the GI bleeding incidence amongst males and females in the two groups. One peculiar finding of our study was that lower HAS-BLED scores did not correlate with a low incidence of GI bleeding in women, wherein most of the female GI bleeders were found to have a low risk HAS-BLED score (<2) whereas in males higher HAS-BLED score correlated with occurrence of GI bleeding.

Discussion

The liver produces both procoagulant factors (such as factor II, V, VII, IX, X and XI) and anticoagulant factors (such as antithrombin, proteins C and S) in the human body. Liver cirrhosis is well known to disrupt the delicate balance between these factors thereby increasing both the development of thrombosis and bleeding in patients with liver cirrhosis[4, 5]. Atrial fibrillation is the most common arrhythmia and is associated with risk of cardioembolic stroke. Risk stratification scores such as CHA_2DS_2-VASc score help identify AF patients who benefit from anticoagulation for prevention of stroke andincorporates attributes such as congestive heart failure, hypertension, age, diabetes, stroke/transient ischemic attack, vascular disease, and sex[6]. On the other hand, long term anticoagulation therapy for stroke prevention increases bleeding risk, thereby, necessitating the use of bleeding risk stratification scores such as the HAS-BLED score, which incorporates stroke, hypertension, labile international normalized ratio (INR), bleeding history or predisposition to bleeding, abnormal renal/liver function, age and drugs/alcohol use [7, 8].

It is evident from the above discussion that concomitance of liver cirrhosis and AF in patients causes a unique interaction between thromboembolic and bleeding risk. The existing evidence of the benefits of oral anticoagulation for stroke prevention in cirrhotic AF patients is unclear. Studies have showed that patients with AF and liver cirrhosis had a higher risk of both stroke and intracranial hemorrhage compared to AF patients without cirrhosis[1, 9]. One study also demonstrated that warfarin use was associated with a lower risk of stroke in these patients[1].

Table 1: Patient characteristics

Underlying conditions	Warfarin (n=54)	DOACs (n=88)	Significance
Age	69.46 ±1.55	69.67±1.25	NS
BMI	32.41 ±1.27	31.63±0.92	NS
Male Gender %(n)	42.59 (23)	65.90 (58)	p<0.01
Caucasian Race % (n)	85.18 (46)	88.37(76)	NS
Hypertension%(n)	20.37 (11)	21.59 (19)	NS
Diabetes Mellitus %(n)	48.14(26)	52.27 (46)	NS
Chronic Kidney Disease* % (n)	55.55(30)	59.09 (52)	NS
Congestive Heart Failure %(n)	29.62(16)	43.18(38)	NS
Coronary Artery Disease %(n)	61.53(32)	62.50 (55)	NS
CHA_2DS_2-VASc (less or equal to 2)%(n)	23.07 (12)	27.27(24)	NS
HAS-BLED (less or equal to 2)**	60.37(32)	29.54 (26)	p<0.001
Follow up (median months, range 25%-75%)^	48 (23-73)	21 (12-36)	p<0.001

*estimated GFR <60ml/min.

**In direct comparison of the two groups the median HAS-BLED of the patients that received warfarin was 2, lower than that observed in the DOACs receiving group (p<0.001)

^ In view of several patients with longer follow up in the warfarin group (outliers) we used the Mann-Whitney Rank Sum test.

Table 2: Outcomes amongst the two anticoagulation groups

Outcomes%(n)	Warfarin (n=54)	DOACs (n=88)	Significance
Intracranial bleeding	5.5 (3)	2.27 (2)	NS
GI bleeding	37.03 (20)	20.45 (18)	p<0.05
DVT/PE	0	5.68 (5)	NS
Stroke	3.70 (2)	5.68(5)	NS
All Cause Death	40.74 (22)	27.27 (24)	p=0.069

DOACs have a superior efficacy, safety, predictable effect, and fewer interactions when compared with warfarin and have revolutionized stroke prevention in AF, but much of this data excluded patients with liver cirrhosis[10]. Hence, there is a scarcity of data regarding use of DOACs in liver cirrhosis with AF and mostly restricted to small retrospective clinical studies [11,12]. One study showed that DOACSs have effectiveness similar to warfarin and a better safety profile in Asian population with AF and liver cirrhosis[2]. Our study aimed to compare the safety and efficacy of DOACs with warfarin in this unique patient population.

Our results indicated that there was a higher incidence of GI bleeding in the warfarin group, even though the warfarin group had a lower HAS-BLED score. We considered two factors which contributed to these findings. One was the difference in the duration of follow up, with longer duration in the warfarin group than DOAC group, giving those on warfarin an increased opportunity to bleed. On limiting the duration of follow up to three years for both the groups, there was no statistically significant difference in the occurrences of GI bleed. Hence the apparent difference results from a difference in the length of follow up rather than the specific therapy used.

We then evaluated the males and females in the two groups separately to see if gender played a role in our observed difference among the warfarin and DOAC group. In our retrospective study, females appeared to be more susceptible to develop GI bleeds than their male counterparts (36.06% Vs 19.75%, $p<0.05$), especially when treated with warfarin (48.38% Vs 21.73%, $p<0.05$). The reason for this remains unclear as no study so far has found any significant association between gender and bleeding. Although a few studies have reported female gender to be of borderline significance as an independent risk factor for bleeding[13].

We further evaluated HAS-BLED scores among the genders. In our study HAS-BLED score reliably predicted high risk of bleeding in males (81.25% of the males who developed GI bleed had high risk HAS-BLED scores), but for the females, only a minority of those who had a GI bleed had high HAS-BLED scores($p<0.01$), thereby, raising questions on the validity of HAS-BLED score in females. The cause for this remains unclear since validation studies for HAS-BLED score have included substantial female population and have not demonstrated results like ours[14].

Table 3: GI bleeding relative to gender and anticoagulation

Gender	Warfarin	DOACS	Significance
Male%	21.73	18.96	NS
Female%	48.38	23.33	p<0.05
Significance	p<0.05	NS	

As mentioned above, our study raises concerns on the accuracy of HAS-BLED scores in female subjects, but it remains to be seen if HAS-BLED scores are inaccurate for entire female population or only in females with liver cirrhosis. It would be interesting to study HAS-BLED scores in females with cirrhosis. With that being said, it is crucial to note that the HAS-BLED score was recognized as a novel score to assess 1 year risk of major bleeding in patients with AF based on the data from The Euro Heart Survey which did not collect data pertaining to liver cirrhosis in their study population[8]. The major HAS-BLED score validation study which was based on the cohort from the "stroke prevention using an oral thrombin inhibitor in atrial fibrillation trial" (SPORTIF- AF) trial also did not study the effect of abnormal liver function as an independent risk factor for major bleeding[14]. Thereby, raising questions on the applicability of HAS-BLED score in patients with cirrhosis, particularly females with cirrhosis.

Our study has a few limitations. First, we did not include laboratory data for prognostic scores of liver cirrhosis, such as Child–Pugh scores, nor did we differentiate between the different causal factors for liver cirrhosis[15]. It is unclear if advanced stage liver cirrhosis has a higher risk for thrombosis or bleeding in AF patients. Second, we did not study the effect of DOAC dose adjustments separately. The most important limitation of our study is that it is a retrospective longitudinal study. Hence, prospective studies with double blind randomized selection of patients are needed to confirm our findings and assess the validity of HAS-BLED score.

Conclusions

Our study did not show any statistically significant difference in the safety and efficacy of DOACs as compared to warfarin when used for anticoagulation in patients with AF and liver cirrhosis.

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Relationship Between Left Atrial Myopathy and Atrial Fibrillation in Adults with Coarctation of Aorta

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Abstract

Background: Although patients with coarctation of aorta (COA) have clinical risk factors for atrial fibrillation (AF), there are limited data about AF prevalence, and role of left atrial (LA) indices for risk stratification in this population. We hypothesized that LA indices (LA reservoir strain and LA volume index) were associated with AF, and would identify patients at risk for AF progression.

Methods: We analyzed electrocardiograms/Holters, and echocardiograms of adult COA patients at Mayo Clinic (2000-2018).

Results: Of 776 patients, 726(94%), 46(5.9%) and 4(0.5%) had no history of AF, paroxysmal AF, and persistent AF respectively; yielding AF prevalence of 6.4%. LA reservoir strain (AUC 0.782 [0.751-0.808]) had more robust association with AF as compared to LA volume index (AUC difference -0.115, p<0.001).

Among 726 patients without prior AF, 25(3.4%) had new-onset AF during follow-up. LA reservoir strain <25% and LA volume index >34 ml/m^2 were independent predictors of new-onset AF (HR 1.81 [1.15-3.85], and HR 1.41 [1.03-4.78], respectively). Of 46 patients with paroxysmal AF, 22(48%) had recurrent AF, and LA reservoir strain <25% was an independent predictor of recurrent AF (HR 1.94[1.41-4.17]). LV pressure overload and stiffness indices were associated with progressive LA dysfunction and new-onset AF.

Conclusions: Collectively, these data suggest that LA strain can potentially be used for AF risk stratification. Further studies are required to determine whether LA strain can proactively identify patients that will respond favorably to different antiarrhythmic therapies, and whether interventions to reduce LV pressure overload will improve LA function and reduce AF progression.

Introduction

Atrial fibrillation (AF) is the most common sustained atrial arrhythmia in patients with acquired cardiovascular disease, and it is associated with heart failure, stroke and mortality.[1] Although the etiology of AF is multifactorial, left atrial (LA) inflammation and remodeling provides substrate for initiation of AF, and in turn, AF leads to more LA remodeling thereby creating a vicious cycle.[2] Because of the central role of LA remodeling in the pathogenesis of AF, echocardiographic assessment of LA structure and function is now routinely used for risk stratification and prognostication of AF in patients with acquired cardiovascular disease.[3,4]

AF is also becoming increasingly common in adults with congenital heart disease, and it is now the most common atrial arrhythmia is patients older than 50 years of age.[5,6] The prevalence varies depending on the type of congenital heart lesion, and tends to be higher in lesions involving the left heart.[5,6] Coarctation of aorta (COA) is characterized by chronic left ventricular (LV) pressure overload, cardiomyocyte hypertrophy and fibrosis, and increased myocardial stiffness.[7] These hemodynamic changes lead to high LA filling pressures and LA remodeling, thus creating the perfect milieu for AF in this population.[8-10] However, there are limited data about the prevalence of AF, pathophysiologic interactions between LA remodeling and AF, and clinical indices for AF risk stratification in this population.[10] While such data already exist from studies conducted in older patients with acquired cardiovascular disease,[2,3,11,12] it is unknown how well these data can be extrapolated to the COA population because of significant differences in demographic and clinical characteristics. Since risk factors for AF such as LV diastolic dysfunction, hypertension and coronary artery disease, and substrates for AF such as LA remodeling are common in the COA population,[8,10,13,14] there is a need to delineate the prevalence of AF and the mechanistic interactions between LA remodeling and AF, as the initial step towards developing robust risk stratification models for improved clinical outcomes in this population. We hypothesized that LA remodeling (changes in LA volume and

Key Words

Coarctation Of Aorta;Atrial Fibrillation; Left Atrial Dysfunction.

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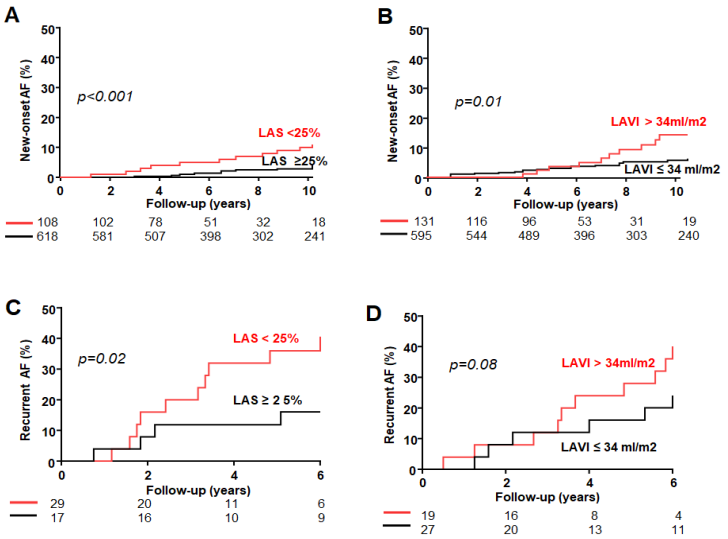

Figure 1: **Kaplan-Meier curves comparing the cumulative incidence of new-onset atrial fibrillation (AF) based on left atrial (LA) remodeling indices.**

Patients with LAdysfunction defined as left atrial reservoir strain (LAS) <25% and those with LA enlargement defined as LA volume index >34 ml/m², had higher incidence of new-onset AF and recurrent AF as compared to those with normal LA function and LA volume respectively.

function in response to hemodynamic stress) is associated with AF, and that increasing severity of LA remodeling will identify patients at higher risk for AF progression.

Methods

Study Population and Design

This is a retrospective study of adults (age ≥18 years) with COA that underwent 12-lead electrocardiogram and transthoracic echocardiogram between January 1, 2000 and December 31, 2018. Patients were identified from the Mayo Adult Congenital Heart Disease (MACHD) registry. We excluded patients with: (1) inadequate images to assess LA size and function; (2) significant mitral valve disease defined as a native mitral valve mean gradient >3 mmHg or >mild mitral regurgitation, severe mitral annular calcification based on qualitative assessment, or mitral valve prosthesis. The Mayo Clinic Institutional Review Board approved the study.

The study objectives were to determine whether LA remodeling (changes in LA volume and function in response to hemodynamic stress) at baseline echocardiogram was associated with: (1)AF prevalence at the time of initial presentation, and (2) AF progression defined as new-onset AF in patients without prior history of AF or recurrent AF in patients with prior history of AF.

A subgroup analysis was performed to determine whether temporal deterioration in LA indices (calculated as values at baseline echocardiogram minus values at follow-up echocardiogram) was associated with new-onset AF (independent of baseline LA indices). This subgroup of analysis was conducted in patients that had no history of AF at baseline echocardiogram, and had a subsequent echocardiogram performed at least 36 months from the baseline echocardiogram without any incident AF or interventions between echocardiograms.

Assessment of Atrial Rhythm

All electrocardiograms were manually reviewed by a staff cardiologist (A.C.E.) and verified by an electrophysiologist (A.J.D.) and used for cohort classification. Using the first echocardiogram, we divided the patients into 3 groups based on contemporary guidelines.[15] (1) No AF group: patients that were in sinus rhythm and without prior history of AF; (2) Paroxysmal AF group: patients that were in sinus rhythm at the time of baseline electrocardiogram but had prior history of AF or patients that were in AF but had spontaneous and chemical/electrical cardioversion to sinus rhythm within 7 days; (3) Persistent AF group: patients with AF lasting >7 days.

Electronic health records were reviewed to determine the type of antiarrhythmic therapy received. Antiarrhythmic drugs were classified using the Vaughan-Williams classification.[16] All electrocardiograms and Holter monitors performed during follow-up were reviewed to determine AF progression.

Table 1: **Baseline Characteristics (n=776)**

	No AF (n=726)	Paroxysmal AF (n=46)	Persistent AF (n=4)	p	p*
Age, years	31 (20-44)	48 (27-66)	50 (38-63)	<0.001	<0.001
Male	420 (58%)	28 (61%)	2 (50%)	0.7	0.9
Body mass index, kg/m²	26±6	27±7	27±4	0.1	0.07
Associated lesions					
Bicuspid aortic valve	449 (62%)	29 (63%)	2 (50%)	0.8	0.9
Isolated COA*	599 (83%)	32 (72%)	2 (50%)	0.001	0.02
Subaortic stenosis	70 (10%)	2 (4%)	1 (25%)	0.09	0.1
Aortic valve disease*	109 (15%)	13 (28%)	2 (50%)	0.01	0.02
Repaired VSD	18 (3%)	2 (4%)	—		0.9
Comorbidities					
Hypertension	389 (54%)	27 (59%)	3 (75%)	0.1	0.6
Coronary artery disease	42 (6%)	9 (19%)	1 (25%)	<0.001	<0.001
Hyperlipidemia	140 (19%)	13 (28%)	2 (50%)	0.08	0.2
Diabetes	31 (4%)	4 (9%)	1 (25%)	0.1	0.2
AAD therapy					
Class I	—	2 (4%)	—	—	—
Class II	199 (27%)	24 (51%)	3 (75%)	<0.001	0.0005
Class III	—	5 (11%)	3 (75%)	—	—
Class IV	80 (11%)	18 (38%)	2 (50%)	<0.001	<0.001
Laboratory data					
Hemoglobin, g/dl	13.7±2.2	13.4±.1.6	12.9±1.4	0.6	0.8
GFR, ml/min/1.73m²	97±19	87±16	81±11	<0.001	0.02
NT-proBNP, pg/ml	159 (53-359)	383 (211-722)	422 (276-654)	0.005	0.01

AAD: Antiarrhythmic drug; AF: Atrial fibrillation; VSD: Ventricular septal defect; GFR: Glomerular filtration rate; Aortic valve disease defined as aortic velocity >2m/s and/or ≥mild aortic regurgitation; Isolated COA* denotes absence of other left heart obstructive lesions such as aortic or subaortic stenosis.
p denotes comparison across all 3 groups while p* denotes comparison between the No AF group and the Paroxysmal AF group

Table 2: Echocardiography (n=776)

	No AF (n=726)	Paroxysmal AF (n=46)	Persistent AF (n=4)	p	p*
LA structure and function					
LA reservoir strain, %	39±8	26±10	21±7	<0.001	<0.001
LA conduit strain, %	25±6	14±7 [n=43]#	—	—	0.002
LA booster strain, %	15±5	12±6 [n=43]#	—	—	0.09
LA volume index, ml/m²	26±9	36±13	44±11	<0.001	<0.001
Other indices of diastolic function					
Mitral E velocity, m/s	1.1±0.3	1.1±0.3	1.2±0.2	0.9	0.9
Mitral deceleration time, ms	189±43	185±38	167±33	0.3	0.6
Septal e' velocity, cm/s	9±3	7±3	6±2	0.005	0.03
Lateral e' velocity, cm/s	13±3	9±2	7±2	<0.001	<0.001
Averaged e'	11±3	8±3	7±2	0.007	0.006
Septal E/e	11±4	14±5	16±3	<0.001	0.01
Lateral E/e	8±2	10±2	13±2	0.006	0.02
Averaged E/e'	9±3	12±3	15±2	<0.001	<0.001
Tricuspid regurgitation velocity, m/s	2.5±0.3	2.7±0.5	2.9±0.6	0.008	0.1
Other echo Indices					
LV end-diastolic volume index, ml/m²	58±12	57±9	58±8	0.6	0.7
LV end-systolic volume index, ml/m²	20±9	22±10	23±7	0.3	0.1
LV ejection fraction, %	64±7	59±11	56±7	0.006	0.03
LV global longitudinal strain, %	22±12	19±12	16±3	<0.001	<0.011
LV mass index, g/m²	91±18	118±21	106±15	0.03	<0.001
LV diastolic stiffness constant (β)	6.61±0.54	6.82±0.49	7.03±0.31	0.02	0.007
Valvuloarterial impedance, mmHg/ml*m²	3.0±0.4	3.6±0.7	3.5±1.2	0.3	0.003
Eal, mmHg/ml*m²	2.8±0.7	3.3±0.8	3.1±0.5	0.009	<0.001
≥ Moderate aortic regurgitation	50 (7%)	4 (9%)	1 (25%)	0.2	0.9
Aortic valve peak velocity, m/s	1.8 (1.5-2.5)	1.9 (1.4-2.7)	2.1 (1.8-2.4)	0.2	0.6
COA peak velocity, m/s	2.4 (1.7-2.8)	2.5 (2.0-2.9)	2.2 (1.8-2.6)	0.5	0.7
COA mean gradient, mmHg	13 (9-19)	12 (5-20)	11 (8-14)	0.7	0.8

COA: Coarctation of aorta; LA: left atrium; LV: Left ventricle; E: Mitral early diastolic velocity; e': Mitral annular tissue Doppler early velocity; AF: Atrial fibrillation; Eal: Effective arterial elastance
Of the 46 patients in the Paroxysmal AF group, 3 patients were in AF at the time of echocardiogram and hence LA conduit and booster strain were not measured in these 3 patients. [n=43]# show that values were based on the 43 patients that were in sinus rhythm at the time of echocardiogram.
p denotes comparison across all 3 groups while p* denotes comparison between the No AF group and the paroxysmal AF group

Assessment of LA Structure and Function

LA function was assessed using LA strain imaging which has 3 different components 3. (1) LA reservoir strain which is dependent on LA compliance modulated by LV systolic function through descent of the base of the LV; (2) LA conduit strain which is dependent on LV relaxation and chamber stiffness, and (3). LA booster strain which is dependent on intrinsic LA contractility and LV end-diastolic compliance. We chose LA reservoir strain as the primary metric of LA function based on previous data demonstrating superiority of LA reserve strain for prognostication as compared to LA conduit and booster strain.[17] LA dysfunction was defined as LA reservoir strain values greater than 2 standard deviation from normative values which corresponds to a cut-off point of <25%.[10,18] LA structural remodeling was assessed using LA volume index measured by biplane Simpson's method, and LA enlargement was defined as LA volume index >34ml/m2.[19] These assessmentswere based on offline analyses of echocardiographic images by two experienced sonographers (JW and KT).

The procedural details for speckle tracking strain imaging in our laboratory have been described.[20] In brief, images were obtained using Vivid E9 and E95 (General Electric Co, Fairfield, Connecticut) with M5S and M5Sc-D transducers (1.5-4.6 MHz) at frame rate of 40 to 80 Hz,and these images were exported (DICOM) and then analyzed offline using TomTec (TomTec Imaging Systems, Unterschleissheim, Germany). LA reservoir strain, LA conduit strain, and LA booster strain were assessed using the QRS as the fiduciary point as shown in Supplementary Figure 1. LV diastolic stiffness was estimated using LV diastolic stiffness constant(β), and LV afterload was estimated using effective arterial elastance index andvalvuloaorterial impedance.[7,21,22]

Statistical Analysis

Between-group comparisons were performed using unpaired t-test, Wilcoxon test, Analysis of Variance, and Fisher's exact test as appropriate. Considering that only 4 patients had persistent AF at baseline, we excluded these patients from all subsequent analyses. Logistic regression was used to assess the relationship between LAindices (LA reservoir strain and LV volume index) and AF (modeled as a binary outcome: sinus rhythm vs paroxysmal AF), and the ability of the different LA indices to detect AF was compared using the area under the curve (AUC) for the different models. Time-to-event analyses were performed using Cox regression and Kaplan Meier method. All models were adjusted for current age, age at time of COA repair, sex, left ventricular global longitudinal strain, native COA (modeled as native COA vs repaired COA), and isolated COA (modeled as isolated COA vs associated left heart obstructive lesions). The single conditional imputation method was used to correct for missing data.[23] All statistical analyses were performed with JMP software (version 14.1; SAS Institute Inc, Cary NC), a $p<0.05$ was considered statistically significant.

Results

Baseline Characteristics (n=776)

A total of 776 patients met the study inclusion criteria, and of these patients, 603 (78%) had COA repair prior to age 18 years (median age 7 [0.3-13] years), 102 (13%) had COA repair after age 18 years (median age at time of repair was 33 [19-46] years), and 71 (9%) presented with native COA. Among the 705 patients with prior COA repair, the COA repair techniques were resection and end-to-end anastomosis (n=282, 40%), subclavian flap repair (n=106, 15%), patch aortoplasty (n=117, 17%), interposition graft repair (n=113, 16%), extra-anatomic bypass (n=52, 7%), balloon aortic dilation (n=16, 3%), and stent implantation (n=19, 3%).

The overall AF prevalence was 6.4% (50/776), with 726 (94%), 46 (5.9%) and 4 (0.5%) being classified into the No AF, Paroxysmal AF and Persistent AF groups respectively. As compared to the No AF group, the Paroxysmal AF group and Persistent AF group were older, had higher prevalence of coronary artery disease and renal dysfunction, and were more likely to have associated left heart obstructive lesions, Table 1. AF prevalence differed by age group: 2.5% (13/512) among patients ≤40 years vs 10.3% (20/194) among patients 41-60 years vs 24% (17/70) among patients >60 years (p<0.001).

LA Structure and Function (n=776)

Compared to the No AF group, the Paroxysmal AF and Persistent AF groups had lower LA reservoir strain and higher LA volume index(Table 2). Similarly, the Paroxysmal AF and Persistent AF groups also had higher LV diastolic stiffness and filling pressures, more LV systolic dysfunctionand hypertrophy, and higher LV afterload (Table 2). There was good intraobserver, interobserver and test-retest reproducibility for all LA function indices based on analysis of 20 randomly selected patients(Supplementary Table 1).

LA reservoir strain, LA conduit strain, LA booster strain, and LA volume index were associated with AF at the time of presentation. Using LA reservoir strain as the reference, LA conduit strain (AUC difference -0.023, p=0.02), LA booster strain (AUC difference -0.035, p=0.007), and LA volume index (AUC difference -0.115, p<0.001) had less robust discriminatory ability for AF (Table 3). Of the 772 patients (No AF and Paroxysmal AF groups), 135 (18%) had LA dysfunction while 150 (19%) had LA enlargement. There was an interaction between LA reservoir strain and LA enlargement defined as LA volume index >34 ml/m2(p<0.001) such that the AUC for LA reservoir strain to predict AF among patients with LA enlargement was 0.866, as compared to those without LA enlargement where the AUC was only 0.712 (p interaction=0.008).

LA Dysfunction and New-onset AF (n=726)

The 726 patients in the No AF group were followed for 79 (34-109) months, and during this period, 2,858 electrocardiograms (average of 4 electrocardiograms per patient) and 166 Holter monitors (average of 0.2 Holter monitors per patient) were performed. Of the 726 patients, 25 (3.4%) patients developed new-onset AF (all paroxysmal AF), all 25 cases were confirmed by an electrophysiologist prior to therapy. Supplementary Figure 1 shows the different antiarrhythmic therapies received by these patients. The 5- and 10-year cumulative incidence of new-onset AF was significantly higher in patients with LA dysfunction vs normal LA function(5.8% vs 0.4%and 13% vs 4.2%, log-rank p<0.001), and in patients with LA enlargement vs normal LA volume(4.3% vs 1.3% and 11% vs 6.8%, p=0.01), Figure1. LA dysfunction (hazard ratio [HR] 1.81 [1.15-3.85], p<0.001) and LA enlargement (HR 1.41 [1.03-4.78], p=0.008) were independent predictors of new-onset AF (Supplementary Table 2A).

The median age at the time of new-onset AF was 38 (26-57) years, and the CHA_2DS_2-VASc scores were as follows: CHA_2DS_2-VASc score of 0 (n=9), 1 (n=13) and 2 (n=3). Of the 25 patients, 9 (36%) patients received warfarin, 6 (24%) patients received direct oral anticoagulants, and 10 (40%) patients were on antiplatelet therapy only. Four of the 25 patients (16%) had ischemic stroke during follow-up. Of the 4 patients, 3 patients (CHA_2DS_2-VASc score of 1[n=2] and CHA_2DS_2-VASc score of 0 [n=1]) were receiving antiplatelet therapy at the time of stroke while one patient (CHA_2DS_2-VASc score of 1) was on warfarin and had subtherapeutic INR at the time of stroke. All 4 patients had LA dysfunction.

LA Dysfunction and Recurrent AF (n=46)

Of the 46 patients in the Paroxysmal AF group, the median age at the time of first episode of AF was 44 (23-61) years. Table 1 shows thedifferent classes of antiarrhythmic drugs used by the patients at the time of baseline electrocardiogram. These 46 patients were followed for 84 (51-133) months, and underwent 388 electrocardiograms (average of 9 electrocardiograms per patient) and 138 Holter monitors (average of 3 Holter monitors per patient). Of the 46 patients, 22 (48%) had recurrent AF, and all 22 cases were confirmed by an electrophysiologist prior to therapy. Supplementary Figure 2 shows the different antiarrhythmic therapies at baseline and during follow-up. The 5-year cumulative risk of recurrent AF was significantly higher in patients with LA dysfunction vs normal LA function (42% vs 19%, p=0.02), but not between patients with LA enlargement vs normal LA volume (38% vs 26%,p=0.08), Figure 1. LA dysfunction (but not LA enlargement) was an independent predictor of recurrent AF after multivariate adjustment (HR 1.94 [1.41-4.17], p<0.001), Supplementary Table 2B.

The CHA_2DS_2-VASc scores at the time of baseline electrocardiogram wereas follows: CHA_2DS_2-VASc score of 0 (n=24), 1 (n=18) and 2 (n=4). Twelve patients were on warfarin (8 of them also had mechanical aortic valve prostheses), 4 patients were on direct oral anticoagulants, and 17 patients were on antiplatelet therapy. Of the 46 patients, 2 (4%) had history of ischemic stroke prior to the beginning of the study period, while another 5 (11%) had ischemic stroke during follow-up. Two of the 5 cases of stroke occurred in patients with mechanical aortic valve prostheses, of which one had subtherapeutic INR. The other 3 cases occurred in patients on aspirin, and their CHA_2DS_2-VASc score at the time of ischemic stroke was 1. Three of the 5 patients had LA dysfunction.

Determinants and Implications of Progressive LA Dysfunction (n=611)

A pre-specified subgroup analysis was performed in the 611 (84%) of the 726 patients that had additional LA function assessment performed

Table 3: Multivariate Logistic Regression Models Showing Relation between LA Indices and AF at Baseline

	AUC (95%CI)	p	AUC comparison	p
Model 1				
LA reservoir strain	0.782 (0.751-0.808)	<0.001	reference	–
Model 2				
LA conduit strain	0.759 (0.722-0.802)	<0.001	-0.023 (-0.029 to -0.006)	0.02
Model 3				
LA booster strain	0.747 (0.698-0.795)	<0.001	-0.035 (-0.053 to -0.013)	0.007
Model 4				
LA volume index	0.669 (0.644-0.681)	<0.001	-0.115 (-0.078 to -0.131)	<0.001

LA: Left atrium; AUC: Area under the curve; CI: confidence interval; AF: Atrial fibrillation

Each model was adjusted for current age, age at time of COA repair, sex, left ventricular global longitudinal strain, native COA (modeled as native COA vs repaired COA), Isolated COA (modeled as isolated COA vs associated left heart obstructive lesions)

Table 4: Multivariate Linear Regression Models Showing Determinants of Progressive LA dysfunction (ΔLA reservoir strain)

Determinants of LA reservoir strain	Beta ± SE	p
Current age, per years	-0.11±0.04	<0.001
Male sex	—	—
Body mass index, per kg/m²	—	—
Age at COA repair, per years	—	—
Transcatheter COA repair	—	—
Isolated COA*	—	—
Arterial elastance index, per mmHg/ml*m²	-0.26±0.19	<0.001
LV diastolic stiffness constant (β), per unit	-1.64±0.22	<0.001
LV mass index, per 10 g/m²	-1.2±0.06	0.002

COA: coarctation of aorta; LV: left ventricle; LA: left atrium; SE: standard error; Isolated COA (model as isolated COA vs associated left heart obstructive lesions)
Note that valvuloarterial impedance and arterial elastance were both significant predictors of ΔLA reservoir strain. However we did not include the 2 variables in the same model because of collinearity.
—: denotes non-significant beta estimates and p values.

during follow-up. The mean interval between the baseline and follow-up assessments was 41±4months, and the temporal change in LA reservoir strain (ΔLA reservoir strain) was 2.2 (1.3 -2.9) % while the temporal change in LA volume index (ΔLA volume index) was +4.8 (-1.2 to +9.4) ml/m2. Of these 611 patients, 22 (3.6%) patients developed new-onset AF during follow-up. Temporal decline is LA reservoir strain (ΔLA reservoir strain) was independently associated with new-onset AF after adjustment for baseline LA reservoir strain (HR 1.08 [1.03-1.14] per unit change, p=0.004). Temporal change in LA volume was not associated with new-onset AF.

Of these 611 patients, 559 (91%) and 52 (9%) had normal LA function and LA dysfunction respectively at the time of baseline echocardiogram. Of the 559 patients with normal LA function at baseline, 21(3.8%) developed LA dysfunction, while all the 52 patients with LA dysfunction at baseline continued to have LA dysfunction at follow-up echocardiogram. Using the time of the follow-up echocardiogram as 'time zero', the 5-year cumulative incidence of AF was significantly different across the 3 groups (Figure 2).

Exploratory analysis was performed to identify the determinants of temporal decline in LA function in the subgroup of patients with normal LA function at baseline (n=559). In this subgroup, the temporal change in LA function(ΔLA reservoir strain) was 2.3 (1.7 -2.8)%, and was associated with older age, LV mass index, LV diastolic stiffness, and arterial afterload (both arterial elastance and valvuloarterial impedance), Table 4. These data suggest that patients with LV pressure overload resulting in increased LV hypertrophy and stiffness were at a higher risk for developing progressive LA dysfunction, and new-onset AF.

Discussion

Patients with COA have clinical risk factors and substrates for AF. However, there are limited data about the prevalence, pathophysiologic interaction between LA remodeling and AF, and clinical indices for risk stratification for AF in this population. The current study addressed some of these knowledge gaps.

Atrial Fibrillation

The AF prevalence in our cohort was 6.4%, and it ranged from 2.5% in patients younger 40 years of age to 24% in patients older than 60 years of age. These estimates are significantly higher than the 2% prevalence of AF in the general population, but comparable to the 22% prevalence in older patients with heart failure with preserved ejection fraction.[1,2] This relatively high age-adjusted prevalence of AF observed in our COA cohort may be related to the high burden of risk factors such as hypertension, coronary artery disease, arterial stiffening and LV diastolic dysfunction that have been described in this population.[8,13,14,24]Although AF has been reported in COA patients,10there are no systematic analyses of the disease burden of AF in the COA population, and hence the novelty of our results.

Left Atrial Dysfunction

We observed LA enlargement and LA dysfunction in 18% and 19% of our cohort respectively, and a progressive deterioration in LA function during a relatively short follow-up period especially in the patients LV pressure overload and increased LV diastolic stiffness. In a cross-sectional study of 56 adult COA patients using speckle tracking echocardiography, Labombarda et al10reported LA dysfunction (defined as LA reservoir strain less negative that 25%) in 41% of the patients, and that atrial arrhythmias and ischemic stroke were more common in patients with LA dysfunction. In another study utilizing cardiac magnetic resonance imaging for the assessment of LA function in 51 COA patients, Voges et al[25] showed that LA dysfunctioncan occur even in the absence of hemodynamically significant re-coarctation, and was associated with aortic stiffness. While these studies provide important insight about LA dysfunction in patients with repaired COA, the small sample size and the cross-sectional study design limits the prognostic inferences that can be drawn from these studies. Building on the existing literature, the current study showed that LA strain analysis can identify patients at risk for new-onset and recurrent AF, and hence can be used for risk stratification.

Clinical Implications and Future Directions

The above results open new horizons for further investigations in three important areas. First, there is a need to determine whether LA strain indices can potentially be used to identify patients that will respond favorably to different antiarrhythmic therapies.

Second, the temporal relationship between LV pressure overload and stiffness, progressive LA dysfunction and new-onset AF in the current study provides mechanistic insight into the pathogenesis of AF in this population. Building on these data, further studies are needed to determine whether interventions that reduce LV after load and stiffness will improve LA function and reduce AF progression. Such potential intervention may include intensification of antihypertensive therapy with lower systolic blood pressure target, and lower threshold for re-intervention for recurrent COA.

Third, we observed ischemic stroke in 16% and 11% of patients with new-onset and recurrent AF respectively even though these patients had CHA_2DS_2-VASc score of 1 or less at the time of stroke. More importantly, most of these cases of ischemic strok eoccurred in

patients with LA dysfunction. Historically, COA has been associated with an increased risk of stroke,[26] and hence it is unclear whether the use of CHA_2DS_2-VASc scores underestimates the risk of stroke in this population. We cannot confidently draws inferences regarding the interaction between LA dysfunction, AF, anticoagulation, COA intervention type, and subsequent risk of stroke based on our data because confounders. There is a need for more rigorous studies to determine whether CHA_2DS_2-VASc score accurately reflects stroke risk in COA patients, whether the integration of LA strain indices will improve risk stratification.

Limitations

We did not control for the confounding effect of antiarrhythmic therapies and structural interventions on the incidence of new-onset and recurrent AF during follow-up, thus limiting the strength of our results. Because of the retrospective study design, there were no set protocols for rhythm monitoring, and thus we could have underestimated the cumulative incidence of AF. Additionally, the current study did not provide data regarding the relative efficacy of the different antiarrhythmic therapies for prevention of AF progression

Conclusions

Patients with COA have a high prevalence of AF relative to their age, and a high cumulative incidence of new-onset and recurrent AF during follow-up. LA dysfunction was associated with the AF prevalence at the time of initial presentation, as well as incident AF during follow-up. LV pressure overload and stiffness are risk factors for progressive LA dysfunction and new-onset AF. Collectively, these findings suggest that LA strain analysis can potentially be used for AF risk stratification in COA patients, and also provides the scientific premise for further studies to determine whether interventions to reduce LV pressure overload and stiffness will result in improvement of LA function and reduce the risk of AF.

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Wide Complex Tachycardia in A Young High-Performance Athlete

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Abstract

A 21-year-old competitive cyclist presented to the emergency department complaining of palpitations. The electrocardiographic assessment showed two regular wide complex tachycardia with different morphologies. What would be the most likely mechanism of the arryhtmia.

Introduction

A 21-year-old competitive cyclist presented to the emergency department complaining of palpitations, chest pain, lightheadedness, and shortness of breath. He denied previous syncopal episodes or comorbidities. The family history was positive for premature coronary artery disease in his paternal grandfather; however, a history of sudden cardiac death (SCD) was not identified.

The electrocardiogram (ECG) on admission showed a wide complex tachycardia that is displayed in Figure 1A. He was electrically cardioverted to sinus rhythm, but soon thereafter went into a second tachycardia, shown in Figure 1B. A repeat cardioversion was performed, followed by the initiation of intravenous metoprolol and amiodarone. The patient was admitted for monitoring and cardiac workup. His ECG in sinus rhythm was unremarkable, with normal PR and QT intervals, and no evidence of Q waves, epsilon waves or Brugada pattern.

Based on the ECGs what is the most likely mechanism of the arrhythmia?

a) Bundle branch reentrant tachycardia
b) Idiopathic right ventricular outflow tract (RVOT) ventricular tachycardia (VT) with variable exit site
c) Left ventricular outflow tract (LVOT) and RVOT VT, respectively
d) Scar-related VT
e) Supraventricular tachycardia with aberrancy

Key Words

Wide complex tachycardia, electrocardiogram

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The correct answer is d: scar-related VT.

Figure 1A shows a regular, wide complex tachycardia (WCT) with left bundle branch block (LBBB) pattern, inferior QRS axis, negative lead I, and transition at V4, suggesting a VT originated in the anterior and septalaspect of the RVOT.Figure 1B shows a second VT, also with LBBB pattern and inferior axis, but with positive lead I and later transition (V5), suggesting a more posterior and lateral origin in the RVOT[1].

A transthoracic echocardiogram and a cardiac magnetic resonance imaging (MRI) revealed mild right ventricle (RV) dilatation and dysfunction, without areas of late gadolinium enhancement (LGE). The patient underwent an electrophysiology study under conscious sedation guided by electroanatomic mapping (Ensite Precision, Abbott, St Paul, MN). A voltage map of the RV showed endocardial voltage abnormalities in the perivalvular region and programmed stimulation under isoproterenol infusion easily and reproducibly induced VT (Figure 1A), which was hemodynamically tolerated. Mapping of VT1 showed earliest activation at the RVOT free wall, but the area of earliest activation was diffuse and pace map was poor. Ablation at this area resulted only in late VT termination with persistent inducibility. An epicardial origin was therefore suspected and percutaneous epicardial access was obtained. Detailed mapping in the epicardium revealed evidence of epicardial scar, with late and fractionated potentials at the basal anterior portion of the RV (Figures 2A and 2B). Both VT1 and VT2 were inducible and a full map of both arrhythmias was created. Activation and entrainment mapping were consistent with two reentrant circuits sharing a common isthmus at the basal RV while exhibiting more anterior and posterior exit sites, respectively (Figures 2C and 2D). Ablation of the isthmus site resulted in VT termination and none of the VTs were inducible at the end of the procedure. A diagnosis of arrhythmogenic right ventricular cardiomyopathy (ARVC)

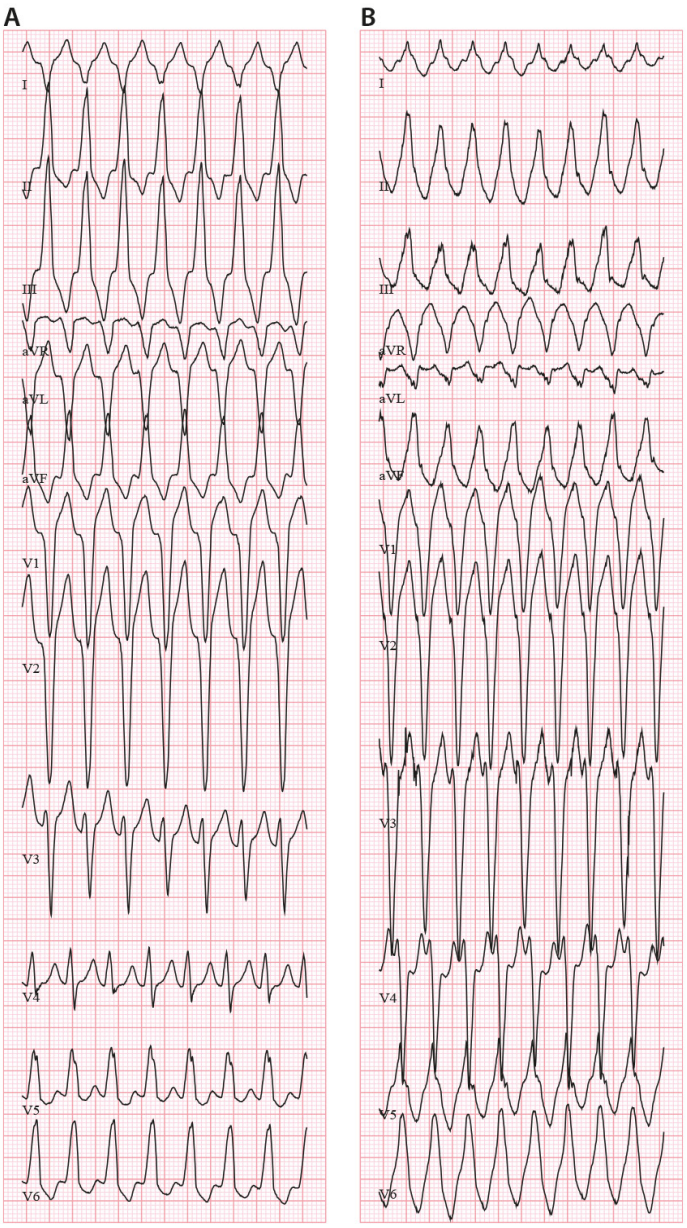

Figure 1: **12-lead electrocardiogram on admission.**

1A. VT with exit in the anteroseptal region of the RVOT, 1B. VT with exit in the posterolateral region of the RVOT.
RVOT: Right ventricular outflow tract, VT: Ventricular tachycardia

was made based on the clinical presentation and the finding of a pathogenic mutation in the plakophilin-2 gene (PKP2)[2]. The patient declined implantation of an ICD, but he has remained asymptomatic and arrhythmia-free after more than a year since ablation.

It is known that most RVOT VTs are idiopathic and carry a benign prognosis, but in a minority of cases, they can be the expression of an underlying cardiomyopathy. When multiple RV-origin VTs are present, ARVC should be strongly suspected, especially if some VTs have late precordial transition (V5 or later)[3]. Electroanatomic mapping has good sensitivity and specificity for the detection of abnormal substrate in ARVC and may identify areas of scar in patients with LGE-negative MRI. In this case, epicardial mapping was diagnostic for reentrant VT and supported the clinical suspicion of ARVC[2,3].

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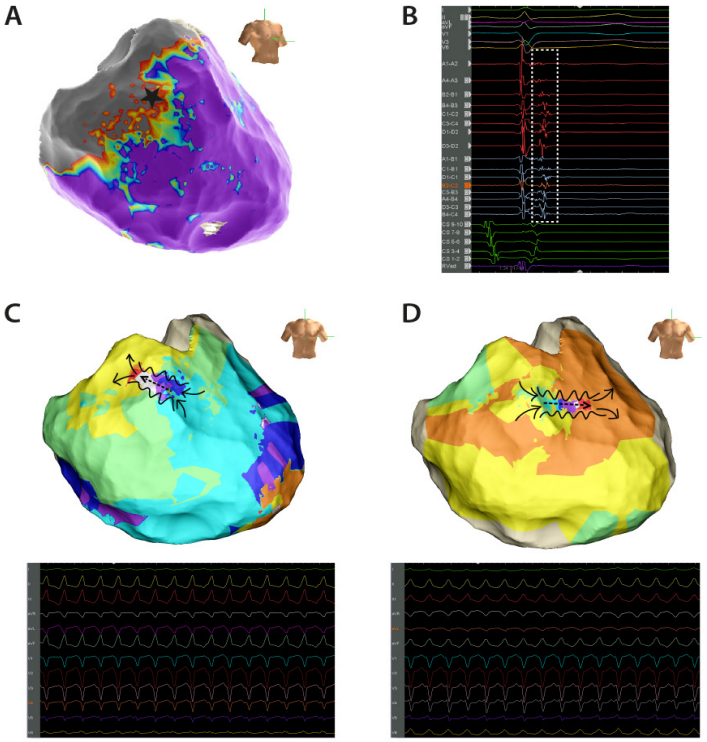

Figure 2: **Epicardial electroanatomic map**

2A.Epicardial voltage map showing voltage abnormalities at the base of the RV.
2B. Late potentials (dashed white rectangle) at the base of the RV (black star in figure 2A) during sinus rhythm as manifestation of abnormal substrate and activation delay.
2C. Activation map and 12-lead ECG of VT1, showing a reentrant circuit with central isthmus at the basal RV (central dashed arrow) and exit with toward the RVOT free wall.
2D. Activation map and 12-lead ECG of VT2, showing a reentrant circuit with a shared isthmus (central dashed arrow) with VT1, but a more anterior and septal exit.
ECG: Electrocardiogram, RAO: Right anterior oblique (RAO), VT: Ventricular tachycardia

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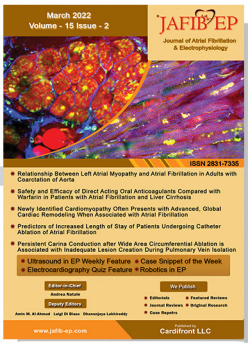

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Imaging in EP

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What is the finding on the intracardiac echo?*

Atrifact
Thrombus
Mitral Annal Calcification
Air
Mapping Catheter

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Overcoming Anatomic Barriers in the Right Ventricular Outflow Tract with 4D Intracardiac Echocardiography and Robotic Magnetic Navigation System

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Abstract

We report a 56 year old female with monomorphic PVCs of 23% burden and associated LV dysfunction (EF 40-45%). Cardiac MRI and FDG PET scan did not show evidence of inflammation or ischemia. In light of this clinical picture – EP study performed with activation mapping showed a technically challenging PVC localized to the RVOT with the earliest area of the activation seen in the free wall within a deep trabeculation. This case required 4D ICE guidance and precision technique with robotic magnetic navigation.

Case Synopsis

We report a 56 year old female with frequent monomorphic PVCs of outflow tract origin. PVC burden was 23% with associated LV dysfunction (EF 40-45%). Cardiac MRI with delayed hyper enhancement , T1/T2 weighted imaging along with cardiac FDG PET scan did not show evidence of prior injury, inflammation or ischemia. Patient had significant symptoms from palpitations and shortness of breath. In light of the clinical picture – patient was taken to the EP lab for possible mapping and ablation. RV activation map was done. The PVC localized to the RVOT freewall region. Robotic magnetic navigation (RMN) system (Stereotaxis) was used for mapping and ablation purposes. We also placed a 4D-ICE catheter (NuVision) into the RV and using the distal 360 degree distal tip dialing we were able to visualize the RVOT in greater anatomic detail. The earliest area of the activation localized to the free wall with a deep trabeculation that could only approached by looping the ablation catheter from the pulmonary valve. It was impossible to reach the deep crevice without the visual from the 4D ICE. We were able to reverse loop the RMT open irrigated catheter to get behind the trabeculation where the earliest signal was 30msec pre-QRS. Radiofrequency energy application at 40 watts for a total of 240 seconds completely eliminated the PVC. There was no further recurrence of PVC on Isoproterenol, calcium and phenylephrine.

Key Words

Atrial Fibrillation, Robotic Magnetic Navigation, PVC.

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Discussion

Often times the heavily trabeculated RVOT with deep pouches can create challenges in successfully delivering RF energy during ablation procedures. These structures are not well visualized with a regular 2D ICE even parked at the RVOT. The 360 degree wide scanning capability of the 4D ICE dramatically enhances the visualization of the RVOT anatomy. If delivering appropriate dose of RF in this region becomes difficult and what looks like an obvious site and difficulty eliminating the arrhythmias – mapping on the other side of the septum along with an attempt to visualize the RVOT better using 4D ICE may a reasonable option to consider. RMN provides greater stability and navigation capabilities in overcoming the anatomic barriers for successful ablation.

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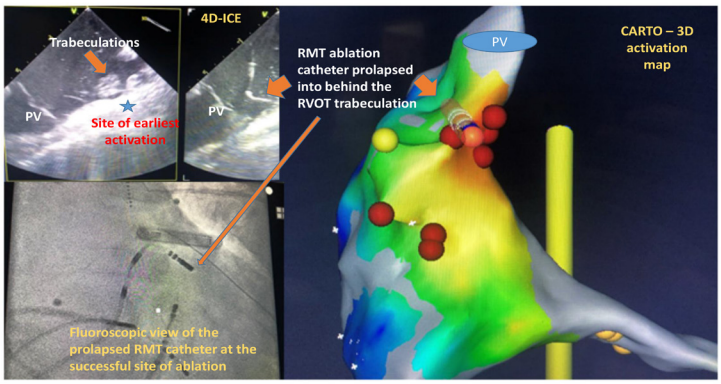

Figure 1: Top Left: 4-D intracardiac echocardiography (ICE) showing superior quality with mobile structures such as trabeculations (orange arrow), behind which lies the site of earliest activation (blue star) for this technically challenging right ventricular outflow tract (RVOT) originating PVC. Bottom Left: Fluoroscopy showing 4-D ICE guided looping of the robotic magnetic (RMN) catheter from the pulmonary valve to approach the activation site from behind the trabeculation and provide a more stable navigation. Right: Catheter tip seen in the CARTO Mapping system looping from the area of the pulmonary valve to achieve appropriate lesion sets.

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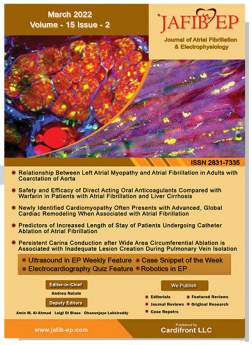

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When Robotics Makes the Difference: Robotic Magnetic Navigation Offers Advantages in Retrograde Approach During Catheter Ablation of Left-Sided Accessory Pathways

Krista Lesina[1]; Rita B Gagyi[1]; Tamas Szili-Torok[1]

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Abstract

A 57-year-old female with a history of palpitations, dizziness and documented supraventricular tachycardia on a 24-hour Holter recording was referred to electrophysiological study and catheter ablation (CA). Her ECG showed pre-excitation consistent with the presence of a left lateral accessory pathway. Although the first procedure was acutely successful, she developed recurring symptoms with recurrent delta wave on her ECG. CA was performed with transseptal approach and in three months follow-up period showed unsuccessful result. The redo catheter ablation was planned using retrograde mapping. Robotic magnetic navigation offers superior navigation capabilities, allowing to perform multiple curves which are impossible to perform with manually guided catheters.

Case Report

A 57-year-old female with a history of palpitations, dizziness and documented supraventricular tachycardia on a 24-hour Holter recording was referred for an electrophysiology study (EPS) and catheter ablation (CA). Her ECG showed pre-excitation consistentwith a left lateral accessory pathway. After EPS confirmed the presence of a left-sided pathway CA was undertaken utilizing a transseptal access. Although the first procedure was acutely successful, she developed recurring symptoms with recurrent delta wave on her ECG. The repeated CA was planned using retrograde mapping.

Discussion and conclusion

The main message of this case report is that the retrograde approach can be performed successfully using the robotic magnetic navigation (RMN) system (Niobe, Stereotaxis Inc., St. Louis, MO, USA).The RMN system offers several possible advantages including atraumatic catheter design and superior navigation capabilities with stable catheter positioning. When using the RMN, it is possible to gain access to difficult anatomy, and even a minor dislocation may bring the catheter into a close proximity to the conduction system or to another important cardiac structure[1]. The RMN catheter allows for reliable contact without increased risk of perforation and it maintains stable contact throughout the cardiac cycle even in the face of changes in cardiac rhythm[2]. Furthermore, it is possible to easily make several consecutive bends in different directions with the robotically guided catheter. Using the RMN system there is no need to develop specially curved catheters[3]. In this report as presented on the figure, using a transseptal approach due to the small size of the atrium, there was not enough space between the tip of the sheath and the target location. While using the retrograde approach, with multiple curves we gained enough space to get to the target location maintaining the catheter in a stable position. These curves are impossible to perform with manually guided catheters.

Key Words

Atrial Fibrillation, Robotic Magnetic Navigation, Ablation

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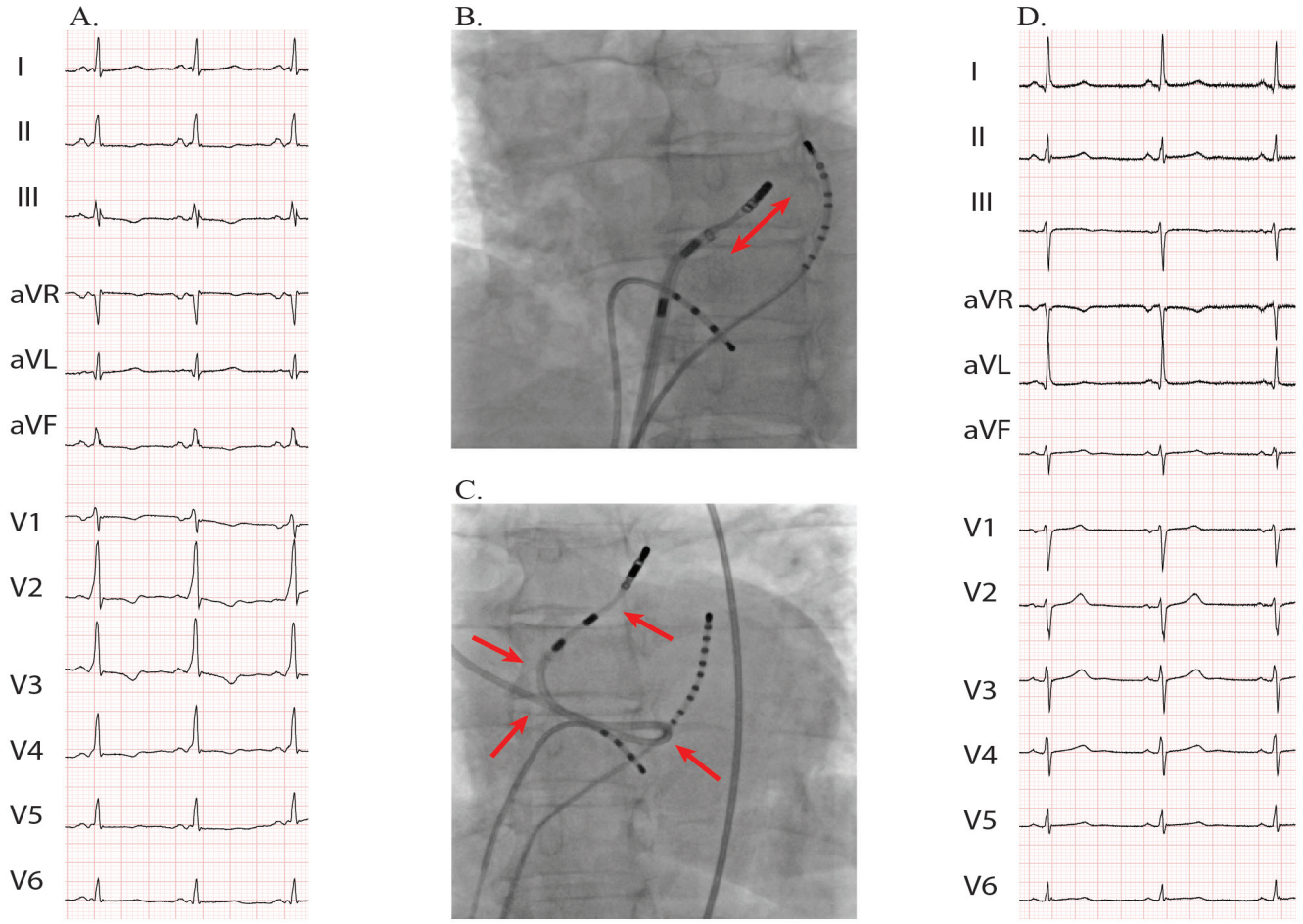

Figure 1:

A. The 12-lead electrocardiogram before the catheter ablation shows sinus rhythm (QRS 97 ms, PR interval 129 ms) and pre-excitation consistent with a left lateral accessory pathway.
B.Fluoroscopy image of the catheter position during the first CA procedure indicating a small left atrium with limited space between the ablation target and the tip of the Agilis steerable sheath. (red arrow, LAO view).
C.Redo catheter ablation with RMN Magnoflush catheter (Med Fact engineering GmbH, Lörrach, Germany)utilizing the retrograde approach. Taking advantage of the floppy and flexible catheter design four different-sized loops could be achieved resulting in a very stable position in a more antero-lateral and stable catheter than during the first procedure. Red arrows show the excessive curves on the magnetic catheter in a LAO view.
D.12-lead electrocardiogram after the catheter ablation shows sinus rhythm (QRS 90 ms, PR interval 135 ms) and normal atrioventricular conduction without pre-excitation.

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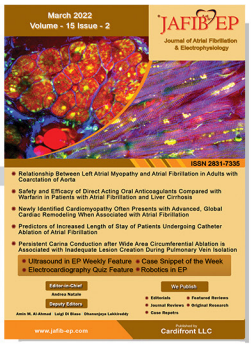

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Suboptimal Biventricular Pacing from Rate Dependent Left Ventricular Lead Proarrhythmia

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Abstract

A 74-year-old patient with permanent atrial fibrillation and symptomatic premature ventricular contractions was found to have a pro-arrhythmic left ventricularpacing at heart rates above 75 beats per minute in all left ventricularpacing vectors. He was successfully treated with AV node ablation and reprogramming of his cardiac resynchronization therapy device to a maximum heart rate of 70 bpm.

Introduction

Cardiac resynchronization therapy (CRT) via a pacing lead in a lateral coronary sinus branch has become an established therapy for patients with severe left ventricular (LV) dysfunction and wide QRS duration.[1] Ventricular arrhythmias in a CRT patient can be due pacing induced proarrhythmia;[2] hence, understanding the mechanism of the tachycardia and the its relationship to the location of the lead is important for appropriate management. We report a case that illustrates the challenge of recognizing proarrhythmic left ventricular pacing occurring at specific pacing rate range considered to be within the normal physiological range for an individual patient.

Case

A 74-year-old, morbidly obese male, with dilated cardiomyopathy and a CRT-D placed in 2016, was referred for suboptimal biventricular (BiV) pacing and persistent atrial fibrillation (AF) with fast ventricular rates. BiV pacing was noted to be <70% due to persistent AF with an uncontrolled intrinsic rhythm which was exceeding BiV pacing limits.

Electrocardiography revealed premature ventricular contractions (PVC's) and non-sustained ventricular tachycardia (NSVT) with a right bundle branch block (RBBB) morphology, inferior axis and late transition suggestive of basal to mid-lateral left ventricular origin (Figure 1). Current medication included chronic amiodarone therapy for suppression of PVCs and control of AF. Patient had worsening heart failure symptoms, including increasing fatigue, exercise intolerance, and dyspnea, both rest and exertional, categorizing him as New York Heart Association (NYHA) class IV stage D at the time of evaluation.

Baseline ECG revealed AF with BiV pacing, as well as a PVC with a RBBB morphology and inferior axis. QS in leads I and aVL suggested an epicardial origin.

On initial evaluation, pacing from the LV lead tip (LV 1-2)had a QRS morphology similar to his clinical PVC. He underwent AV node ablation initially and while being paced at VVI 40 bpm, PVCs and NSVT disappeared. LV or BIV pacing ≤75 bpm did not induce any clinical PVCs/NSVT, regardless of any vector in the quadripolar LV lead (Figure 2). However, when LV or BIV pacing rate was >75 bpm, PVCs returned, again regardless of which LV lead vector was used (Figure 3). This provided evidence of a LV lead straddling a border zone of an epicardial lateral wall scar, which exhibited pro-arrhythmia only at pacing rates >75 bpm. After successful AV node ablation, the lower pacing rate was programmed to 70 bpm without evidence of PVCs/NSVT.

He was cardioverted to sinus rhythm with maintenance amiodarone. At 6-month follow-up, patient remains in sinus with 95% BIV pacing and marked improvement in functional status (NYHA I).

Discussion

Despite the salutary effects of CRT, LV pacing induced ventricular arrhythmias have been reported [2-4]. A prior study showed that pacing in proximity to an epicardial scar (0.2 cm) significantly increased dispersion of repolarization in that region, and increased the propensity of unidirectional block, that may predispose to ventricular arrhythmias. [5] In our case, the unique finding was the association of PVC/NSVT

Key Words

Biventricular pacing, CRT programming, AV node ablation.

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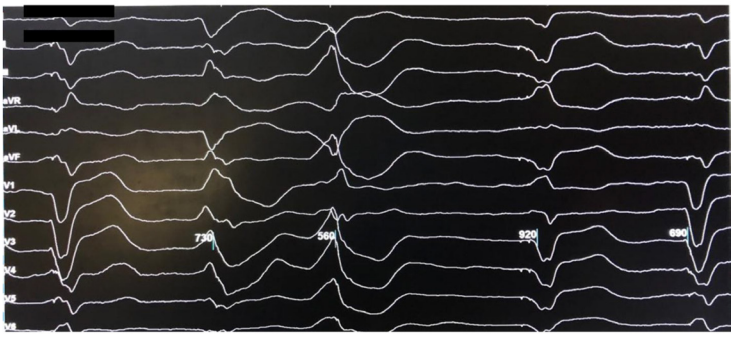

Figure 1: Baseline ECG showing atrial fibrillation with biventricular pacing, and fusion beats due to conducted atrial fibrillation, and 2 PVCs with a RBBB, inferior axis morphology with and QS complexes in lead 1 and AVL, suggestive of epicardial LV origin.

initiation with a pacing rate >75 bpm. Following AV node ablation, when pacing VVI 40 bpm, the arrhythmia completely disappeared and only reappeared with pacing at 80 bpm, suggesting that the alteration of activation and repolarization around dependent on pacing at a higher rate. Moreover, proarrhythmia was seen with pacing from all vectors of the quadripolar LV lead, suggesting that this lead likely straddled the border zone of a sizeable epicardial scar.

Conclusion

We describe a unique case of rate related LV lead pacing induced PVCs and NSVT contributing to suboptimal BiV pacing and worsening heart failure. The arrythmia was successfully treated with CRT reprogramming and AV node ablation.

Disclosures

Rakesh Gopinathannair: Consultant/Honoraria – Abbott Medical, American Heart Association, Biotronik, Boston Scientific, Zoll Medical

Dhanunjaya Lakkireddy: Consultant/Honoraria – Abiomed, Biosense Webster, Boston Scientific, Biotronik, Janssen, Abbott medical.

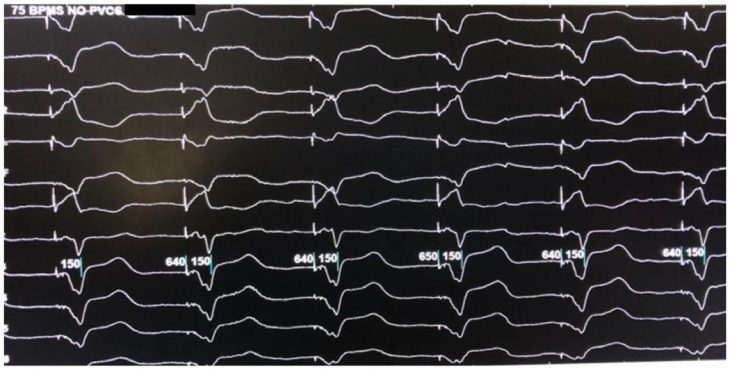

Figure 2: Following AV node ablation, biventricular pacing at 75 bpm did not induce any PVCs or non-sustained ventricular tachycardia.

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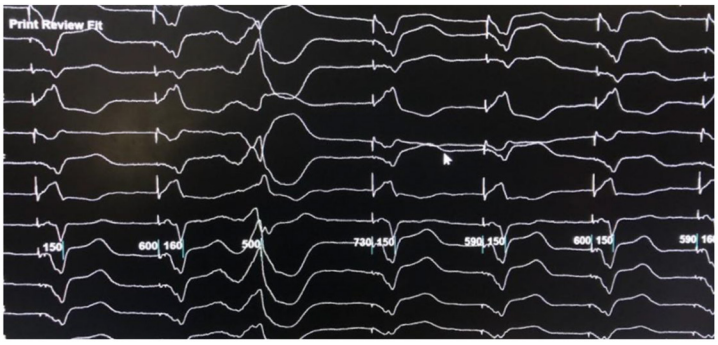

Figure 3: After AV node ablation, biventricular pacing at >75 bpm reproducibly induced PVCs from all electrodes of the quadripolar LV lead.

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Characterization and Management of Ventricular Arrhythmia in Myocarditis

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Abstract

Myocarditis is a complex inflammatory disease with both acute and chronic stages that have varying presentations of ventricular arrhythmias both upon presentation, as well as during the disease course. The continued expansion of knowledge regarding the arrhythmogenesis of myocarditis has allowed us to understand that ventricular arrhythmias can often occur in spite of resolution of myocardial inflammation, as well as be one of the most severe predictors of worse clinical outcomes.

Introduction/Epidemiology

Myocarditis refers to an inflammatory cardiac disorder secondary to various etiologies. Arrhythmic manifestations of myocarditis remain an evolving field, with continued understanding gaining traction regarding the arrhythmias seen not only during initial presentation, but during the entirety of active, prior, and remitting disease courses. The ongoing Covid-19 pandemic has led to an increased recognition of this clinical entity in routine practice. Arrhythmias in patients with myocarditis can manifest primarily or in combination with structural heart disease/LV dysfunction[1,2]. Noninfectious causes of myocarditis such as Giant Cell Myocarditis (GCM) and Cardiac Sarcoid (CS) also appear to have a higher predominance of arrhythmias[3]. Given that myocarditis itself is underdiagnosed and therefore underrepresented, the overall prevalence based on post-mortem assessment is highly variable and rages from 9%-44% [3]. Isolated pericardial involvement (i.e. pericarditis), or combined myocardial and pericardial inflammation (i.e. myopericarditis) have much lower rates or arrhythmic presentations, and if so, these tend to be more supraventricular in origin [3]. Bradyarrhythmias or any degrees of atrioventricular block tend to be rare, and if so, seem to have a higher predilection in GCM or CS. Ventricular Arrhythmia of wide spectrum, however are more commonly seen in viral or idiopathic myocarditis with up to 63% of patients with acute myocarditis presenting with premature ventricular contractions (PVC's), and 61% presenting with either ventricular tachycardia (VT) or non-sustained ventricular tachycardia (NSVT) [4]. Given that they arise from a multitude of pathophysiology not completely understood, their management continues to evolve[4]. In this review, we expand on our current understanding of management of ventricular arrhyhtmias in patients with myocarditis.

Key Words

Myocarditis, Ventricular tachycardia, Premature Ventricular Contractions

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Pathophysiology

Several mechanisms of inflammatory injury, dysfunction, and electrical instability have been proposed [3]. Each suspected pathophysiology can be further categorized based on their occurrence within the disease process during the 3 phases of myocarditis: 1.) viral replication (in infectious causes), 2.) direct myocardial inflammation and/or adaptive autoimmune response, and 3.) persisting, chronic inflammation leading to cardiomyopathy [2].

Etiologies of arrhythmia during the first phase of myocarditis include direct cytotoxic damage involving myocyte membrane breakdown with resultant electrical instability and microvascular injury resulting from endothelial dysfunction/tropism (Parvo B19, Covid) which often occur during viral replication and the initial stages of acute inflammation [2,3,5].

During the second phase involving direct damage from inflammation and/or autoimmune response, gap junction impairment and resultant ion channel disruption specifically by alteration of connexins in the myocardium have been seen in Coxsackievirus[2,3,5]. Additionally, further cellular metabolic disturbances such as calcium ion channelopathies occur[2,3,5]. Autoimmunity with antimyosin autoantibodies have also been detected, and have been associated with worsening LV systolic function in their presence [6]. In noninfectious etiologies, autoimmune deposition and changes (i.e. granulomas) can cause myocardial "mass

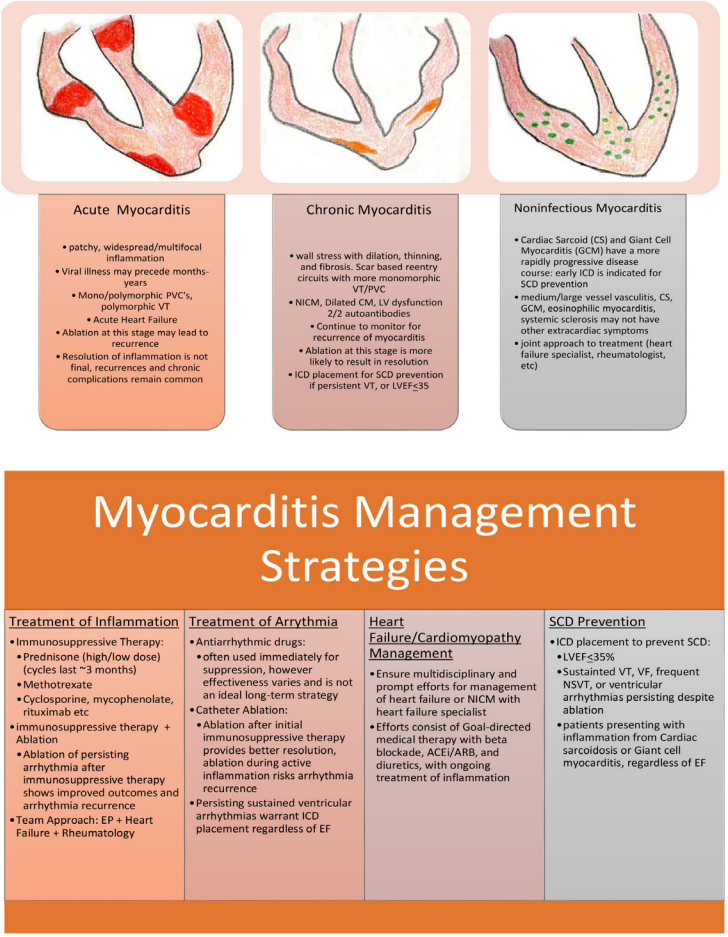

Figure 1: **Myocarditis Management Strategies.**

effect" and infiltration in addition to autoimmune cross-reactivity[3]. This phase can also exhibit more severe ischemia and vasculitis, leading to ischemic and inflammatory arrhythmia substrate [2,3].

In longer term, more chronic stages of inflammation, subsequent fibrosis, hypertrophy, and scar formation lead to resultant reentry circuits that have been implicated in both ventricular Arrhythmia, as well as increased risk of sudden cardiac death (SCD)[2,5].

Overall, the first 2 stage encompass the "hot" stage of myocarditis, or the stage consisting of either active or fulminant infection, with the 3rd stage of chronic inflammation being classified as the "cold" stage [4]. Both stages pose their own risks of ventricular arrhythmias, leading to long-term implications and therefore, long term monitoring and follow-up as well [4].

Diagnosis

Diagnosis of myocarditis itself is often done in the setting of high clinical suspicion for infectious/noninfectious causes, and more recently the understanding that an inciting infection may have occurred not only days to weeks but even months to years prior makes it difficult to often isolate a certain virus or pathogen[5,7]. Although conventionally the gold standard for diagnosis is endomyocardial biopsy, it is invasive, and often requires some guidance to ensure areas of inflammatory involvement are biopsied, and therefore if performed at all, it is usually done after imaging with newer but increasingly available modalities such as Cardiac MRI (CMRI) or 18 Fluorodeoxyglucose positron emission tomography–computed tomography (18FDG-PET)[8]. It is important to note that specific forms of myocarditis such as GCM, CS, or eosinophilic myocarditis require EMB for adequate diagnosis [8].CMRI gives a better ability to assess for prior or chronic inflammation, scar, and fibrosis, whereas FDG-PET provides the ability to assess for active/ongoing inflammation, and their utilization in conjunction can be synergistic due to this [9].

These imaging modalities have been more sensitive and specific to ensure adequate diagnosis of inflammation and can provide insight to areas of involvement if biopsy is pursued after imaging. Regarding diagnosis of Arrhythmia, baseline changes in ECG's are inconsistent and nonspecific, and Arrhythmia themselves are paroxysmal therefore continuous monitoring may be required to diagnose them, understand their characteristics, and assess their burden[3].

Ventricular Arrhythmia: Presentation and Clinical Implications

Ventricular Arrhythmia seen in patients with underlying myocardial inflammation often pose the highest predictor of morbidity/mortality, given that they encompass VT/VF, a significant cause of sudden cardiac death (SCD), as well as both NSVT and monomorphic/polymorphic PVC's, which are associated with increased cardiovascular mortality [4]. Furthermore, not only does the inflammation itself often lead to nonischemic cardiomyopathy (NICM) or dilated cardiomyopathy (DCM), but the Arrhythmia themselves can contribute to this either in the form of tachycardia induced cardiomyopathy (CM) or PVC induced CM [10].

Lakkireddy et al sought to evaluate patients in whom PVC's was the main presenting finding of underlying myocarditis in the MAVERIC registry, initially testing 107 patients with burdensome PVC's (>5000/24hr) and finding that 51% of these patients had underlying myocardial inflammation via 18FDG-PET imaging [7]. This is most notable for 3 main reasons: 1. even symptomatic and frequent PVC's are relatively common, and often either treated medically or with ablation without much workup to rule out myocardial inflammation, 2. Most patients did not have a correlating prior viral infection that could be linked to their myocarditis but rather a "silent" inciting event, and 3. There were almost no noticeably significant differences in patient characteristics between the patients with positive and negative PET findings [7].

Regarding the distribution of ventricular arrhythmias further, Peretto et al evaluated 185 patients with myocarditis, either active or prior and found an overall distribution of 32% sustained VT, 43% NSVT, and 100% PVC among their cohort [4]. Pavlicek et al evaluated a total cohort of 191 patients with either acute or chronic myocarditis or DCM secondary to myocarditis, and found that 50% of all ICD implantation was due to the presence of VT alone [11]. Persisting acute inflammation itself has a defining role in manifesting as ventricular arrhythmias as seen by the MAVERIC Registry, and this is compounded by Peretto et al when multivariate analysis showed acute myocarditis as the main predictor of VT recurrence. Interestingly, t resolution of myocardial inflammation does not equate to resolution of arrhythmogenesis, and continued fibrosis, remodeling, and scar formation can continue to

potentiate existing and new arrhythmogenesis [7,12]. Peretto et al further characterized the morphologies of various arrhythmias in acute and chronic myocarditis, finding that acute myocarditis more commonly manifested as irregular and polymorphic VT and PVC's, likely attributing to multiple areas of inflammation and electrical activity, whereas chronic/prior myocarditis was more likely to manifest as monomorphic VT/PVC's, likely a representation of more well defined scar formation with re-entry [4].

Casella et al further evaluated the association between scar formation and ventricular arrhythmogenesis in patients with prior myocarditis, given that similar scar formation is often seen in NICM of other etiologies, by initially using CMRI and electroanatomical 3D mapping [13]. 44% of a total 144 patients with prior myocarditis had evidence of scar, with 42% eventually undergoing catheter ablation (CA) [13]. Of the patients that underwent CA, 77% experienced ventricular Arrhythmia free survival, therefore potentiating underlying scar formation from previous myocardial inflammation as both a predictor as well as substrate for continued VT/VF as well as SCD [13].

Infectious Myocarditis: Acute or "Hot" Inflammation

Acute myocarditis itself is characterized by cytotoxic damage, channelopathies, and depending upon the time course autoimmune mediated damage as well [2,5]. This manifests as often patchy or widespread inflammation originating from multiple regions as the areas involved are ill-defined as opposed to chronic myocarditis which can have scar formation and clear borders with Arrhythmia originating from more specific locations; accordingly, polymorphic and irregular VT as well as polymorphic, burdensome PVC's are more common in this stage[4,7]. This stage itself often has a diagnostic delay as ischemic workup precedes myocarditis workup, and high clinical suspicion is required if ventricular arrhythmias or acute NICM and heart failure are the presenting manifestations. Prompt diagnosis and treatment is vital in this stage to prevent chronic, more insidious manifestations of myocarditis as detailed below [14]. It is important to note that while this stage of active inflammation may serve as the most arrhythmogenic, symptomatic stage, treatment or self-resolution of the myocardial inflammation itself does not necessarily associate with a decreased risk of SCD or persisting ventricular arrhythmias [3].

Infectious Myocarditis: Chronic/Prior or "Cold" Inflammation

Given the continued underdiagnosis of myocarditis, chronic effects including DCM, NICM, and persisting LV systolic dysfunction also continued to be underreported. Peretto et al have reported that nearly 2/3 of LV dysfunction from an unknown source can be attributed to underlying myocardial inflammation, and while they state myocarditis makes up 10% of all patients with DCM, Sagar et al have estimated this to be nearly 40% of all patients with DCM[3,5]. The true number is likely higher, however multiple factors are likely contributing to this. Inflammatory wall stress leading to dilation via thinning and expansion of the involved tissue, interspersed fibrosis, and hypertrophy of the uninvolved tissue in compensation occurs in a similar fashion to those seen in myocardial infarctions, and this may not always improve even after the initial inflammation resolves [10]. Furthermore, microvascular ischemia, vasculitis, and channelopathies leading to tachycardia induced CM can also contribute to continued or worsening CM and LV dysfunction [2]. As stated above, scar related ventricular arrhythmias also play a large role in persisting arrhythmogenesis in the late stage. Cross-reactivity and autoantibodies, which can play a role in both hot and cold stages of myocarditis can in fact play a role in both LV dysfunction and arrhythmogenesis if β-1 receptor cross-reactivity and autoantibodies are involved, as has been isolated in cases with enterovirus [15]. This leads to autonomic imbalance with propensity towards sympathetically driven tachyarrhythmias, PVC's and associated cardiomyopathies as well [15]. Finally, although not widely endemic, Chaga's disease has a particularly pathologic disease course with nearly 1/3 of all cases progressing to both DCM as well as ventricular arrhythmias [3].

Noninfectious Myocarditis

Noninfectious etiologies of myocarditis encompass many forms of autoimmune systemic diseases, as well as large and medium vessel vasculitis, with most common culprits being GCM, CS, eosinophilic myocarditis, systemic sclerosis, and spondyloarthropathies [3]. These diagnoses, while being often more uncommon in isolation compared to infectious causes, often require both imaging and biopsy for diagnosis, and should always involve a joint approach with a rheumatologist [14]. With cardiac sarcoidosis, only 55% of patients diagnosed have extracardiac manifestations, and therefore arrhythmic manifestations or infiltrative cardiomyopathy may be the sole presenting finding [14]. GCM is particularly uncommon, however given its tendency to afflict young individuals and its often-fatal progression, has important distinction, and must be diagnosed and treated promptly [14]. Both GCM and CS are indications for ICD placement even in patients with LVEF of >35% given their prognosis if left untreated [8,16].

Management

Initial management of myocarditis, regardless of type continues to remain supportive, with medical therapy for management of acute/chronic heart failure [3]. Despite the presence of multiple Arrhythmia, treatment with antiarrhythmic drugs is often trialed but with variable success, and norecommendations for specific drug therapy have been conventional[3]. Much of the long-term treatment strategy falls into 2 categories: 1. treatment of underlying inflammation and Arrhythmia, and 2. Prevention of SCD[3,8,16].

Immunosuppressive therapy

Despite their role in pericarditis, NSAID's and or Colchicine have no supported evidence or role in the treatment of myocarditis [16]. Immunosuppressive therapy has shown considerable promise for treatment of myocardial inflammation, with the MAVERIC Registry consisting of 83.6% of patients who were treated with immunosuppressive therapy or immunosuppressive therapy + catheter ablation, and this yielding a 67% optimal response to therapy [7]. Immunosuppressive therapy varies between prior trials with no definite treatment regimen at this time but can range from either high-dose prednisone (40mg daily) to low-dose prednisone (10mg daily) alone or in combination with low-dose methotrexate [7,8]. Treatment courses often run for 3 months before reevaluation is warranted. Careful pre-treatment workup should precede initiation of immunosuppressive therapy[7]. Treatment with immunosuppressive therapy often requires a multidisciplinary effort involving a rheumatologist (and/or Heart failure specialist, pharmacist, etc.) and other forms of immunosuppressive therapy such as Rituximab, mycophenolate, or treatment of underlying

autoimmune/vasculitis disorders also must be conducted with a multidisciplinary team as well [7].

Catheter Ablation

Patients with worsening arrhythmias and/or clinical deterioration are candidates for anti-arrhythmic drug therapy and catheter ablation (CA)[7]. Given the potential reentry circuits formed as well as scar formation associated with both acute and chronic myocarditis, this yields the substrate for persisting ventricular arrhythmias (both VT and PVC)'s and may require CA for absolute resolution [4,7]. Peretto et al have shown that CA during the acute stage of myocarditis may yield in VT recurrence, whereas CA during chronic/prior myocarditis yields more resolution, and should be preferred when possible [12].

Implantable cardiac defibrillator (ICD)

Among all patients with myocarditis, multiple studies have seen a range of 23.6-30% ICD placement either for persisting LV dysfunction or presence of VT [7,11]. Overall, persistent LV dysfunction with LVEF <35% similar to that seen in heart failure with reduced ejection fraction or ischemic heart disease continues to be an indication for ICD placement for SCD prevention, especially in the setting of treatment with either immunosuppressive therapy, Ablation, or both [16]. Specific parameters associated with worse outcomes also have indications for early ICD placement regardless of LVEF of VT, namely, presence of second degree atrioventricular block or higher, GCM, or CS [16]. Finally, much like in ischemic heart disease, presence of any degree of sustained VT/VF also remains an indication for ICD placement for SCD prevention [16]. Of note, participation in competitive sports should be halted until at least 3-6 months after myocardial inflammation is first diagnosed [3].

Conclusion

The characterization and management of ventricular arrhythmias in myocarditis is complex, and it involves a heightened clinical suspicion, the ability to understand both the short-term and long-term prognostication, and prompt treatment to ensure the best clinical outcomes.

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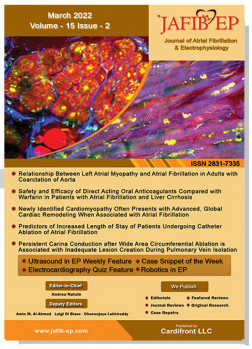

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Safety, Readmissions, and Cost-Effectiveness of Same-Day Discharge vs. Overnight Stay Following Ablation Therapy for Atrial Fibrillation

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Abstract

Atrial fibrillation is the most common cardiac arrhythmia, with therapeutic options including the use of cardiac ablation. Following ablation procedures, patients are traditionally recommended to be observed overnight for complications. Same-day discharge after ablation procedures may offer an alternative approach to postoperative care, shortening patient visits and reducing overall costs without negatively affecting patient outcomes. In the context of the COVID-19 pandemic, it may be increasingly useful to utilize same-day discharge, which canrelieve hospital resources and limit exposure. Our findings were organized into six narrative themes: (1) the perioperative and 30-day complication rates following SDD, (2) readmission rates after same-day discharge, (3) the implications of SDD on medical costs, (4) the effects of the COVID-19 pandemic on AF ablation and SDD, (5) the success of ablations after SDD, and (6) the characteristics, eligibility criteria, and implementation of SDD. In conclusion, the current literature indicates that same-day discharge is not associated with worsened clinical outcomes, including complication rates, readmissions, and procedure success. Consequently, same-day discharge presents an opportunity to minimize patient stays, reduce costs, and improve the recovery process.

Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia, being characterized by fast and irregular fibrillatory waves originating from the atrium [1]. Therapeutic options for managing atrial fibrillation include rate control strategies with AV nodal blocking agents, AV nodal ablation with pacemaker implantation, and rhythm control strategies with antiarrhythmics, electrical cardioversion, and atrial substrate ablation [2]. Either surgical or catheter-based approaches can be utilized [3]. Cardiac ablation is the most effective method for restoring sinus rhythm [4]. After ablation procedures, patients have traditionally been recommended to be observed via an overnight stay (ONS) in the hospital for complications [5]. Considering an overall perioperative complication rate of around 2.9% [6] and a 30-day hospital readmission rate of 10.9% [7], postoperative outcomes are of concern for ablation patients.

Key Words

Atrial Fibrillation; Ablation; Same-Day Discharge; Discharge

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Same-day discharge (SDD) after outpatient cardiac catheterization and electrophysiology procedures may offer an alternative approach to postoperative care, shortening patient visits and reducing overall costs. The same-day discharge protocol has been explored in other interventional cardiology and electrophysiology procedures, including percutaneous coronary intervention (PCI) and the implantation of cardiac implantable electronic devices (CIED) [8,9]. The current literature indicates that SDD in patients undergoing PCI or cardiac electronic device implantation does not compromise patient safety or outcomes.

To our knowledge, the earliest reported implementation of SDD in ablation procedures for atrial fibrillation was published in the literature by Marijon et al. in 2009 [10]. In recent years, and particularly during the coronavirus disease 19 (COVID-19) pandemic, there has been a growing body of literature studying SDD following ablation for atrial fibrillation. Same-day discharge is particularly well-suited for AF ablation due to the low likelihood for complications between 6 hours post-procedure and discharge the following day [11]. Most complications in ablation patients occur intraoperatively or within 6 hours post-operation, indicating that the implementation of SDD would not negatively impact patient care.

The current literature has indicated that SDD does not predispose worsened clinical outcomes, favoring its use over the conventional overnight observation. Our article intends to report a comprehensive review of the current literature regarding the safety, outcomes, and cost-effectiveness of SDD for patients undergoing catheter ablation for atrial fibrillation.

Narrative Themes:

We identified six narrative themes for discussion: (1) the perioperative and 30-day complication rates following SDD, (2) readmission rates after same-day discharge, (3) the implications of SDD on medical costs, (4) the effects of the COVID-19 pandemic on AF ablation and SDD, (5) the success of ablations after SDD, and (6) the characteristics, eligibility criteria, and implementation of SDD. Table 1 outlines characteristics of the primary studies evaluating SDD that were included in our review.

Perioperative and 30-Day Complication Rates Associated With Same-Day Discharge:

Same-day discharge following ablation procedures is only a viable option if it does not negatively affect patient safety. One metric for safety that several studies have utilized is the likelihood of perioperative complications.

An early study by Marijon et al. studied patients undergoing radiofrequency ablation, including a total of 1,342 patients in their sample [10]. Of the patients enrolled in the study, 94.6% (1,270 patients) were discharged on the same day of treatment, before being followed for one month. A total of 6 patients experienced significant puncture complications, 2 had symptomatic delayed pulmonary emboli, and 2 presented with new onset of poorly tolerated atrial flutter. None of the complications experienced were life-threatening, and no deaths occurred. Haegali et al. also investigated SDD after outpatient radiofrequency ablation in a cohort of 206 patients undergoing 230 procedures [12]. A total of 205 procedures allowed for SDD and major complications were only observed in seven patients (3%). The study found a small complication rate, supporting the use of SDD in patients. Though both studies suggested SDD is safe for patients, the lack of comparisons between SDD and traditional overnight stays limits their analyses.

Several studies have evaluated SDD in patients undergoing radiofrequency ablations. Recently, Ignacio et al. performed a longitudinal prospective study of patients receiving pulmonary vein ablation for persistent or paroxysmal AF [13]. Their study divided patients into both SDD (58 patients) and overnight stay (137 patients), with no differences in risk factors for complications. After the sixth hour, no complications were observed in patients of either group. Akula et al. also compared the complication rates of patients observed overnight (145 patients) and discharged via SDD (426 patients) [14]. They found a greater frequency of total complications in the group observed overnight (11.7% vs. 4.4%), with major complications being rare in both cohorts. These studies suggest that SDD does not increase the risks of complications following radiofrequency ablation.

A retrospective study by Kowalski et al. studied cryoballoon ablation patients, comparing a group of SDD patients with patients hospitalized overnight [15]. Their study reviewed 2374 patients (1119 SDD and 1180 overnight), finding no differences in total complications within 30 days. In both groups, hematoma was the most common complication. Opel et al. also investigated a cohort of cryoballoon patients at a local, non-cardiac hospital who had been treated using a high-throughput technique and discharged on the day of the procedure [16]. Their study included 276 patients matched 1:1 with patients treated with standard techniques at a regional cardiac center. The overall complication rate of

Table 1: Literature Search Results

Author & Year	Article Type	Description of Sample and Size
Marijon et al. (2009) [10]	Prospective, Multicenter Cohort Study	Patients undergoing radiofrequency catheter ablation procedures N = 1,342
Haegali et al. (2010) [12]	Prospective Cohort Study	Patients undergoing outpatient radiofrequency catheter ablation procedures for atrial fibrillation N = 206
Ignacio et al. (2018) [13]	Prospective Cohort Study	Consecutive patients undergoing pulmonary vein ablation for paroxysmal or persistent atrial fibrillation N = 195
Akula et al. (2020) [14]	Retrospective Chart Review	Consecutive patients treated with atrial fibrillation ablation from January 2005 to December 2015 N = 571
Kowalski et al. (2021) [15]	Retrospective Study	Patients undergoing cryoballoon ablations for AF N = 2,374
Opel et al. (2019) [16]	Prospective, Matched Cohort Study	Patients treated using a high-throughput atrial fibrillation ablation service N = 276 (Matched)
Deyell et al. (2020) [17]	Multicenter Cohort Study	All patients treated with AF ablation at two centers from the years 2010 to 2014 N = 3,054
Field et al. (2021) [18]	Retrospective Study	Patients undergoing AF ablation across the United States N = 6,247
Field et al. (2021) [19]	Retrospective Study	Patients undergoing AF ablation across the United States N = 6,600
Reddy et al. (2020) [20]	Retrospective, Single Center Study	Consecutive AF ablation patients from March 2017 to April 2018 N = 452
Bartoletti et al. (2019) [21]	Prospective Cohort Study	Patients discharged on the day of being treated with AF ablation from April 2014 to March 2017 N = 169
Creta et al. (2020) [22]	Retrospective Study	Consecutive patients undergoing AF ablation in a tertiary center and a district general hospital that received SDD N = 2,628
He et al. (2021) [23]	Retrospective, Multicenter Study	Consecutive patients undergoing radiofrequency or cryoballoon complex left-ablation procedures N = 967
Bailey et al. (2021)	Retrospective, Multicenter Study	Individuals undergoing outpatient PVI N = 13,567
Sahashi et al. (2021)	Retrospective Study	Patients undergoing AF ablation across the United States N = 1,751
Chu et. al (2021) [30]	Retrospective, Single Center Study	First case-of-the-day outpatient AF ablations N = 249
Rajendra et al. (2020) [35]	Cohort Study	Patients undergoing cardiac ablation for paroxysmal atrial fibrillation N = 44

the high-throughput ablations (5.4%) was comparable with those at the regional cardiac center (6.3%), reflecting a successful implementation of the SDD protocol.

Studies have also evaluated SDD in cohorts undergoing both radiofrequency and cryoballoon ablations. A multicenter cohort study performed by Deyell et al. included 3,054 patients, with 2,418 being discharged via SDD [17]. Complication rates within 30 days, excluding immediate procedural complications, were 0.37% for SDD and 0.36% for patients who stayed overnight. Similarly, a retrospective analysis by Field et al. found no differences in composite 30-day complication rates between SDD and ONS patients [18]. The study used the IBM MarketScan Commercial Claims and Encounters database and employed a 1:3 propensity score-matched analysis. A total of 1,610 SDD and 4,637 ONS patients were included. A second analysis by the same authors used the Optum SES Cliniformatics Extended Data Mart database to identify patients undergoing AF ablation [19]. Again, a 1:3 propensity score matching algorithm was used, finding no differences in 30-day complication rates between SDD and ONS groups.

A retrospective study conducted by Reddy et al. investigated a sample of 452 AF ablations, with 128 patients being discharged on the same day [20]. The likelihood of complications was not different between SDD and overnight stay patients, with an overall rate of 3.3%. Bartoletti et al. identified a total of 1,599 AF ablation cases, with 169 ultimately being discharged using SDD [21]. Patients were considered eligible for SDD if they underwent uncomplicated ablations on the morning lists using ultrasound-guided femoral access, had a reversal of intraprocedural heparin with protamine, and had uninterrupted warfarin or little interruption with novel oral anticoagulants. With 26 research cases excluded, 1 patient (0.7%) had transient right phrenic nerve palsy and 5 cases (3.5%) had minor problems which did not prevent the utilization of SDD. Three patients (2.1%) were rehospitalized, with one having pericarditic chest pain and two experiencing nausea/vomiting. In a retrospective study conducted by Creta et al., 727 subjects undergoing day-case ablations were identified from a total population of 2,628 patients [22]. The study's safety endpoint was determined to be any complication and/or presentation to the hospital, measured both within 48 hours and at 30 days post-operation. The study found a low overall perioperative complication rate, with 13 patients (1.8%) meeting the safety composite endpoint within 48 hours. Only 5 patients (0.7%) required hospitalization for at least 1 day.

A multi-center, retrospective study performed by He et al. evaluated SDD in patients undergoing complex, left atrial ablations [23]. They included a total of 967 patients undergoing both radiofrequency and cryoballoon ablations, with complications being low in both cohorts. Their study was the first to utilize SDD in complex ablation procedures and suggested that it may be viable in such cases.

The existing literature is robust, with all evaluated articles indicating that SDD does not lead to a greater risk of perioperative complications. Patients who were treated using SDD had low complication rates in all studies. When compared with the conventional overnight stay, SDD patients did not have greater complication rates, supporting the safety of utilizing the discharge pattern.

Readmission Rates and Same-Day Discharge:

With readmission rates being particularly of concern in AF patients undergoing ablation therapies, it is important to approach SDD with caution[24]. Common causes of readmission include postoperative recurrence of arrhythmia and heart failure (HF) [25].

The early study by Marijon et al. found a low overall readmission rate of 0.79% (95% confidence interval: 0.30 – 1.27); however, the lack of comparison with ONS limits their findings [10]. Several studies since then have compared the readmission rates of SDD patients with patients who were kept overnight in the hospital for traditional observation.

Deyell et al. found that hospital readmission rates at 30 days for SDD patients was 7.7%, while the rate for those who remained in the hospital overnight without complications was 10.2%, compared to 19.5% for those who remained in the hospital due to complications [17]. The study by Creta et al. found that out of the 2628 patients included in their sample, which included 727 SDD cases, only 3.7% of patients had complications and/or were admitted to the hospital [22]. They found that pericarditic chest pain and bleeding at the femoral access site were the most common reasons for readmission. In the study done by Bartoletti et al., hospital readmission was very low for SDD patients (2.1%), with chest pain and nausea being cited as common causes [21]. When comparing SDD patients to patients who stayed overnight, Ignacio et al. observed significantly more emergency department visits in the overnight hospitalization group (30.7%) than patients with SDD (15.5%) [13]. A study by Bailey et al. retrospectively evaluated 90-day all-cause readmissions and 90-day AF readmissions, finding no statistically significant differences between patients admitted overnight and those discharged on the day of the procedure [26].

A recent study by Sahashi et al. utilized the US Nationwide Readmission Database to compare 30-day,all-cause readmission rates in patients discharged using SDD and conventional overnight stay [27]. The study utilized a 1:3 propensity score-matched analysis, generating 1,751 pairs (440 in the SDD group and 1,311 in the ONS group). The readmission rate was not significantly higher in the SDD group than the ONS group (12.7% vs 9.7%; hazard ratio: 1.17; 95% CI: 0.76 – 1.81; P = 0.47).

In the study performed by He et al. investigating complex, left atrial ablation procedures, readmission rates were evaluated at four months post-operation [23]. They found 62 (6.4%) cases with readmission, with common reasons including hematomas and palpitation.

The existing literature indicates that SDD for AF ablation procedures does not increase hospital readmission rates. In the articles evaluated, SDD patients had low readmission rates, and evidence suggests that readmission rates may be lower for SDD cases when compared to overnight hospitalization cases. Readmission rates are not a barrier to the implementation of SDD, further supporting the utilization of the discharge pattern.

Cost-Effectiveness of Same-Day Discharge:

In recent years, alongside an aging population, atrial fibrillation has accounted for increased healthcare and economic burden [28]. High

readmission rates are directly associated with the costs of AF, with readmissions for primary diagnoses of AF being longer and more expensive than the index hospitalization [29]. Shortening the post-operative length of stay has the potential for reducing costs, as long as safety and readmission likelihood are not compromised.

A total of three hospitals participated in the multisite study performed by He et al. in the United Kingdom, which found that hospital costs for an overnight stay were£350 ($417.70) per night, resulting in total annual savings of £310,450 ($370,497.24) if SDD after AF ablation was performed [23]. Similarly, Creta et al. conducted a study in the UK evaluating cryoballoon ablations, concluding that SDD would result in the St. Bartholomew's Hospital saving an estimated £83,927 ($100,160.16) yearly [22]. Reddy et al. performed their study at Royal Papworth Hospital, finding that day-case procedures for AF would result in savings of £67,200 ($80,197.82) over a 13-month period [20].

Studies have also evaluated the cost-effectiveness of SDD in the United States. The study done by Kowalski et al. estimated that US hospitals can save between $45,825 and $83,313 annually if 50% of patients were discharged on the day of the procedure [15]. A study conducted by Chu et al. evaluated the barriers and cost-effectiveness of SDD, concluding that hospitals can save around $1.5 million yearly [30]. Their study retrospectively reviewed 249 first-case-of-the-day outpatient ablations to determine how many would have been eligible for SDD, finding that the discharge pattern could have been utilized in 157 patients (63%) without changes in management. If avoidable barriers were managed, a total of 200 patients (80%) would have been eligible for SDD. Barriers were defined as any incidences that prevented discharge by 8 p.m. and included logistical issues, prolonged recovery, and minor procedural complications. In all, the study attributed the yearly savings from using SDD to both reduced hospital operating expenses and increased revenue from chest pain management after procedures. In the study by Sahashi et al., healthcare costs were significantly higher in overnight stay patients than SDD patients ($30,749 ± 16,383 vs $25,237 ± 14,036; $P < 0.01$) [27].

Estimates regarding the savings in healthcare costs from SDD span a wide range. There remains limited data regarding cost-savings per patient, which would be a useful metric. Individual hospital systems may benefit differently from the use of SDD, but despite differences in magnitude, SDD is certain to make a substantial impact on reducing healthcare costs.

Success of Ablation Procedures Following Same-Day Discharge:

Several studies have evaluated the effectiveness of ablation procedures in patients undergoing SDD. Haegali et al. assessed patient outcomes at a timeline 6 months post-operation, finding that 86% of patients had a reduction in symptomatic AF incidences, with 68% noting a lack of symptoms [12]. In the study performed by Reddy et al., follow-up data indicated that the success rates of procedures were not different between SDD and overnight stay patients [20]. The acute procedural overall success rate in the cohort study by He et al. was 96% [23]. The study performed by Opel et al. found that, at 3 months, 91% of patients treated with high-throughput ablations and discharged on the day of treatment had restored sinus rhythm [16]. Comparatively, 80% of patients treated with standard regimens at the regional cardiac center restored sinus rhythm at the 3-month timeline. Both studies by Field et al. found no significant differences in composite AF recurrence rate at 1 year between SDD and ONS groups [18,19].

These studies indicate that SDD does not negatively affect outcomes of the procedure and that the likelihood of success is not affected by the choice of discharge pattern. Patients who are treated using an SDD pattern have high success rates that are not different from those who are hospitalized overnight.

Same-Day Discharge in the Setting of COVID-19:

The ongoing COVID-19 pandemic has presented significant challenges to the delivery of healthcare, including in cardiac electrophysiology. To limit exposure to the virus, guidance from professional societies recommended that electrophysiology programs prioritize urgent procedures [31], and a subsequent decrease in ablation procedures was noted [32]. Decreases in cases and greater availability of medical resources allowed for the greater utilization of elective procedures; however, recent upswings and the rise of new variants have made the future of the pandemic uncertain [33]. Notably, studies have identified increased morbidity and mortality associated with delays in cardiac care during the pandemic [34].

The severe shortage of hospital resources has increased the pressure for earlier discharge in most outpatient cardiology catheterization and electrophysiology procedures. Same-day discharge, as opposed to overnight monitoring, presents the ability to reduce exposure and preserve healthcare resources. As the pandemic continues, it may be increasingly beneficial to utilize the SDD protocol in eligible patients undergoing ablation procedures.

Characteristics, Eligibility Criteria, and Implementation of Same-Day Discharge:

Procedures performed using SDD may have different characteristics than those with traditional overnight stays. Studies have indicated that procedures performed using SDD are shorter and less likely to utilize general anesthesia [20,21]. These ablations may also be more likely to be redo procedures, and involve electrical cardioversion and linear lesions less often [21]. SDD procedures may be less complex than those with overnight stays involved.

Rajendra et al. discussed several eligibility criteria for patients undergoing SDD ablation [35]. The study implemented SDD in patients undergoing cardiac ablation for paroxysmal AF, including a total of 44 cases, of which 41 were discharged using SDD. The article suggested that patients who are discharged via this method should meet the following eligibility criteria prior to the procedure: 1) stable anticoagulation, 2) no history of pulmonary disease, 3) no systolic heart failure, 4) BMI < 35, 5) acceptable CHA_2DS_2-VASc stroke risk, 6) absence of bleeding history, and 7) no interventional procedure within 60 days of ablation. Their article also outlined postoperative discharge criteria for determining if SDD was appropriate, listing seven criteria: 1) no complications during the procedure, 2) confirmation from operator to proceed with SDD, 3) removal of purse-string suture, 4) stable hemodynamics, 5) ability to ambulate, 6) tolerates food/liquid, and 7) no postoperative groin or respiratory complications. The

implementation of these criteria ensures that safety and effectiveness was not compromised. Their study provides one example for a method of implementing SDD that can be used as a model by hospital systems, which will individually create similar guidelines.

Recent results from the AMBULATE trial by Natale et al. provide an instructive lesson in approaching SDD [36]. In their study, the authors evaluated the VASCADE MVP® Venous Vascular Closure System (Cardiva Medical), which is a closure device designed for electrophysiology procedures. Typically, hemostasis is achieved via manual compression of the femoral venous access sites; however, this technique requires patients to lay flat for several hours, is often uncomfortable, and demands greater postoperative resources. The study randomized VASCADE MVP® and manual compression 1:1, finding positive outcomes with the device, including early ambulation. The ability to ambulate patients earlier is associated with many favorable clinical and economic outcomes and can make it easier to implement a same-day discharge protocol.

A carefulapproach to utilizing SDD is necessary for optimal patient care, yet the evidence is strong regarding its benefits. Individual institutions may develop methodologies for determining eligibility for SDD, with the current literature providing examples to model from.

Conclusions

The existing research indicates that SDD is not associated with worsened patient outcomes, including complication and readmission rates. Procedure success also appears to be unaffected by same-day discharge. As a result, SDD presents an opportunity to minimize patient stays, reduce overall hospital costs, and improve the transition to recovery. The current body of literature supports the use of SDD in eligible patients, as it presents a safe and effective method of improving discharge patterns in ablation patients.

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Letter To Editor

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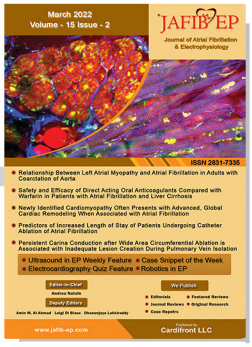

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Radiofrequency Catheter Ablation of Atrial Arrhythmias in Lung Transplant Recipients

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Condensed Abstract

Atrial arrhythmias (AA) are common post-lung transplant (LT). While the majority tend to be organized flutters, mechanistic data is lacking. We studied all LT recipients undergoing AA ablation at our institution over a 7-year period. We identified 20 ablations in 16 patients. The most common primary AA identified was macro-reentrant flutter originating at the pulmonary vein anastomosis sites. During follow-up, 9 patients experienced recurrence and 4 required repeat ablations. In univariable analysis, only left atrial enlargement was associated with repeat ablation. Our study demonstrates the safety and efficacy of AA ablation in a contemporary cohort of LT recipients.

Research Correspondence

Over 2,700 patients under wentlung transplantation (LT) in the United States in 2019[1]. Atrial arrhythmias (AA) affect up to 46% of LT patients in the early post-operative period and 14% long-term[2]. The occurrence of AAs has been associated with increased hospitalization, morbidity, and mortality[3]. The majority of AAs tend to be organized; however, mechanistic data from electrophysiology studies is lacking[3]. We investigated the clinical and procedural outcomes of radiofrequency catheter ablation of AAs after LT at our institution.

All LT recipients undergoing electrophysiology study from 2011-2018 were retrospectively reviewed. This study was approved by the institutional review board. Informed consent was obtained from all patients. A total of 20 radiofrequency atrial ablations were identified in 16 patients. Mean age was 55±13 years and 63% were male. The incidence of cardiovascular comorbidities was low (25% with hypertension, 31% with diabetes, and 25% with coronary artery disease). Four patients had a history of atrial fibrillation (AF) prior to transplant and 1had previously undergone pulmonary vein isolation. In regards to transplant history, 63% were bilateral LT and indications included interstitial lung disease (44%), chronic obstructive pulmonary disease(19%), and cystic fibrosis (19%). At time of first ablation, antiarrhythmic drugs and beta blockers were used in 44%and 75%, respectively. Immunosuppressive regimens consisted of tacrolimus in 87.5%, mycophenolic acid in 81%, and prednisone in 100%. Mean time from transplant to first ablation was 2.7±4 years. For the majority of patients, first onset of AA was >6 months prior to ablation.

Of the 20 ablations performed, the primary AA identified was macro-reentrant flutter in 15(75%), focal atrial tachycardia in 3(15%), and 1 patient each with AF and atrioventricular nodal reentrant tachycardia (Figure 1a). Mean tachycardia cycle length was 283.7±53.0ms. The most common ablation sites were pulmonary vein anastomosis (60%; Figure 1), mitral annulus (35%), and left atrial roof (30%). Notably, multiple AA types were observed in 9 procedures and 13 procedures involved >1 ablation site. All but one procedure resulted in immediate success (defined as no inducible atrial arrhythmias at the end of the procedure) and restoration of normal sinus rhythm. One complication occurred, which was a small pericardial effusion without evidence of tamponade. Over a mean follow up period of 4.1±2.9 years, 9 of 16 patients experienced recurrence of the same clinical AA and 4 required repeat ablations (Figure 21b); however, AAs were found to originate from different locations compared with the primary ablation procedure. Time from initial ablation to AA recurrence was 3.1±3.6 years. In univariable analysis, no medications or clinical, demographic, transplant or procedural characteristics were associated with AA recurrence; however, there was a significant association between left atrial enlargement and repeat ablation (p=0.03). Following AA ablation, anticoagulation was discontinued in 11 patients (8 permanently), all of whom had CHA_2DS_2-VASc score ≤2.

Our study demonstrates that in LT recipients undergoing AA ablation, the majority of AAs are macro-reentrant originating near the pulmonary vein anastomosis sites. Despite a high immediate success rate, AAs tend to recur, however, many patients remain free of recurrence

Key Words

Atrial Arrhythmias, Catheter Ablation, Lung Transplant

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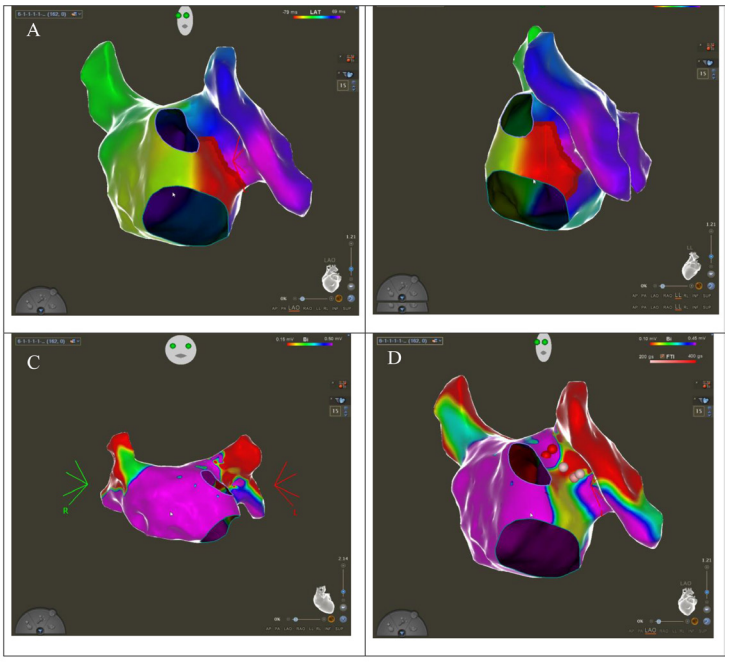

Figure 1: **Macro re-entrant atrial tachycardia originating from the left superior pulmonary vein anastomosis site on the left atrial ridge (CARTO3 mapping system). (A) Local activation time map in the LAO position; (B) Local activation time map in the left lateral position; (C) Voltage map in the AP position; (D) Ablation lesion set. AP, anteroposterior; LAO, left anterior oblique.**

for at least a few years. These findings support previous studies, implicating the donor pulmonary vein-left atrial anastomosis site as potentially creating a substrate for macro-reentrant tachyarrhythmias by generating lines of conduction block. This would also explain the low incidence of AF beyond the immediate post-operative period. However, left atrial enlargement, which is an established risk factor for AF ablation failure, was predictive of the need for repeat ablation in our study. The presence of structural heart disease increases the risk of having multiple arrhythmia circuits, which was likely the case in these patients as opposed to incomplete lines of conduction block, as block at the site of the primary ablation was confirmed during the repeat procedure in all cases. Further, AA ablation resulted in permanent discontinuation of anticoagulation in 50% of patients. Given the risk of bleeding associated with transbronchial biopsy is up to 53%, performing AA ablation and thus absolving the need for anticoagulation is an additional potential benefit of the procedure[4].

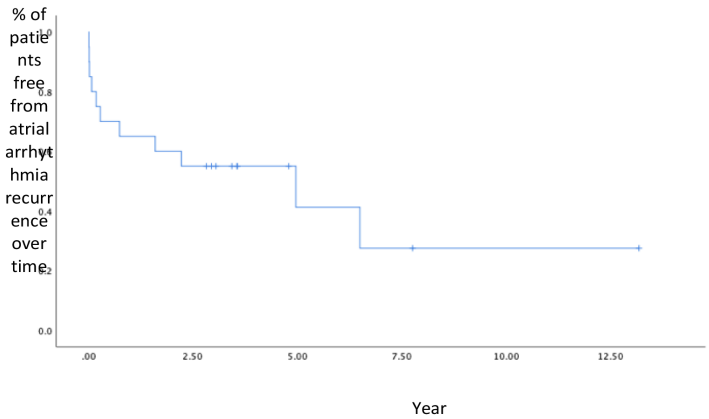

Figure 2: **Freedom from atrial arrhythmia recurrence following index radiofrequency ablation.**

Several limitations are worth noting. This study was single center, retrospective, and small. There was inherent selection bias regarding which patients were referred for ablation. Yet, this study adds to the existing literature in supporting the safety and efficacy of AA ablation in the LT population. Thus, in this contemporary cohort of LT recipients, AA ablation is not only feasible but often successful in providing relief from AA.

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