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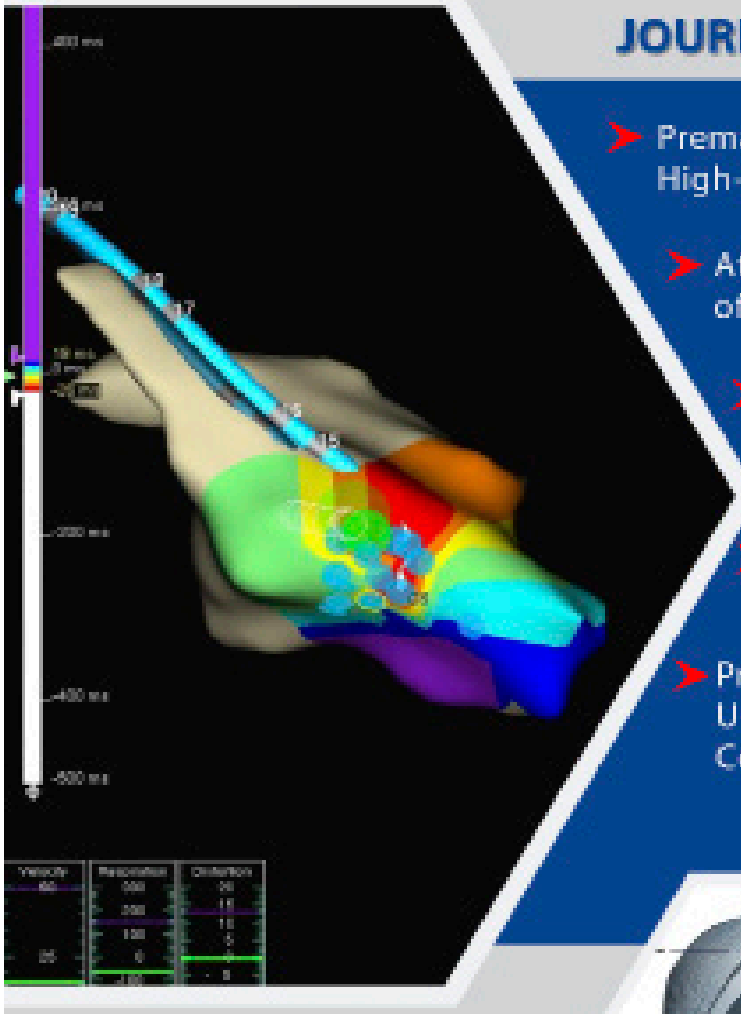

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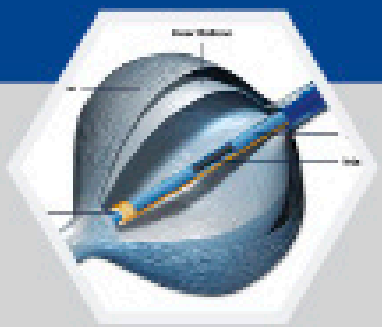

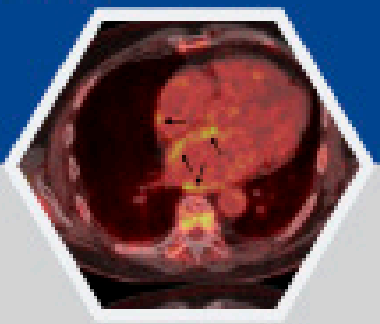

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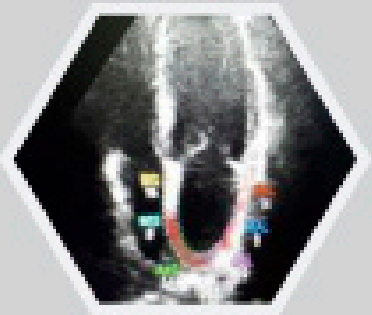

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Journal of Atrial Fibrillation (JAFIB)

Jun - July 2021

Issue 1

Volume 14

Dear Colleagues

Welcome to the October issue of JAFIB. There are many excellent manuscripts published in this issue of the journal covering a wider range of topics from epidemiology to basic sciences. Smartwatches are becoming increasingly prevalent for patient use in Atrial Fibrillation (AF) detection. The nuances involved in effective monitoring are discussed at greater length. Intravenous magnesium as a potential adjunct to AF therapy has been debated for many years. It is finally great to see some data on this subject. There have been several valuable demographic variables in predicting post operative AF, however in this issue we have a comprehensive assessment of echocardiographic predictors of the same. Ganglion plexi ablation has been around for severalyears now. A fresh look at the status of cardioneuro ablation will be an interesting one to read. Neurocardiogenic syncope is a common cardiac condition and diagnosis of which is limited by suboptimal tools. There is an interesting article that attempts to provide insights into why a head up tilt table test is still a good diagnostic tool in determining who needs permanent pacemaker. AF is increasingly prevalent, there is substantial data regarding the value of effective screening and early intervention. Effective community screening for AF has been outlined in one of the articles of the current issue.

The journal wants to congratulate the Heart Rhythm Society and the American College of Cardiology for their excellent work in fighting the most recent physician reimbursement cuts for ablation procedures, especially AF. It is most difficult to see such draconian cuts (over 35%) starting next year and their potential impact on physician practices especially when a global pandemic continues to rage through its variants. This issue brings to the forefront of discussion why physician involvement in societal activities and advocacy is important. If you have not already done so, please reach out to your congressman and also renew your support to HRS and ACC to help them continue to work on this issue.

A new editorial board and Editor in Chief are being finalized and you will hear from us soon.

Enjoy the fall and see you all soon.

Sincerely

Amin-Al-Ahmad

Amin-Al-Ahmad
MD, FACC, FHRS

Interim Editor-in-Chief
Journal of Atrial Fibrillation

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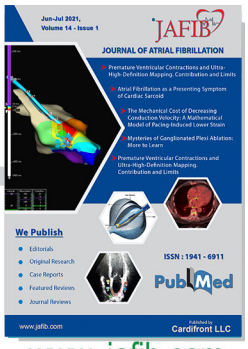

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Adjunctive Vein of Marshall Ethanol Infusion During Atrial Fibrillation Ablation: A Systematic Review and Meta-Analysis

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Abstract

Introduction: Catheter ablation (CA) for atrial fibrillation (AF) can be associated with limited efficacy. Due to its autonomic innervation, the vein of Marshall (VOM) is an attractive target during AF ablation. In this meta-analysis, we aimed to evaluate the efficacy and safety of adjunctive ethanol infusion of VOM (VOM-EI) in AF ablation.

Method: We performed a comprehensive literature search for studies that evaluated the efficacy and safety of VOM-EI in AF ablation compared to AF catheter ablation alone. The primary outcome of interest was late (≥3 months)AF or atrial tachycardia (AT) recurrence. The secondary outcomes included acute mitral isthmus bidirectional block (MIBB) and procedural complications (pericardial effusion, stroke, or atrio-esophageal fistula). Pooled relative risk (RR) and corresponding 95% confidence intervals (CIs) were calculated using the random-effects model.

Results: A total of four studies, including 804 AF patients (68.2% with persistent AF, the mean age of 63.5±9.9 years, 401 patients under went VOM-EI plus CA vs. 403 patients who had CA alone), were included in the final analysis. VOM-EI group was associated with a lower risk of late AF/AT recurrence (RR:0.63; 95% CI:0.46-0.87; P = 0.005), and increased probability to achieve acute MIBB(RR:1.39; 95% CI:1.08-1.79; P = 0.009) without an increase in procedural complications(RR:1.05; 95% CI:0.57-1.94; P = 0.87).

Conclusions: Our meta-analysis demonstrated that adjunctive VOM-EI strategy is more effective than conventional catheter ablation with similar safety profiles.

Introduction

Vein of Marshall (VOM) was first described by the British surgeon John Marshall in 1850 [1]. VOM represents the persistent left horn of the sinus venosus, and it drains the posterior wall of the left atrium into the coronary sinus[1,2]. It has unique electrophysiological properties as it is heavily supplied by both sympathetic and parasympathetic innervation. Thus, VOM can modulate the electrical potential of the atrial tissue and contribute to atrial fibrillation (AF)[1]. Furthermore, VOMis located within the mitral isthmus, which is commonly ablated to manage peri-mitral atrial flutter (PMF)[3].

Key Words

Ethanol infusion, Vein of Marshall, Ablation, Atrial fibrillation, Atrial tachycardia.

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In 1972, Benjamin Scherlag was the first to describe the arrhythmogenic role of VOM by induction of an ectopic atrial rhythm with stimulation of the left cardiac sympathetic nerve[4]. Since then, further studies have shown that the VOM is accountable for numerous atrial tachyarrhythmias in patients who underwent catheter ablation (CA) for AF[1,3,5].

Despite improved understanding of AF, the success rate for CA is still unsatisfactory, with only half of the patients attaining freedom from atrial tachyarrhythmias one year after the procedure[6]. Vein of Marshal ethanol infusion (VOM-EI) is a potential strategy to induce scar formation around the pulmonary vein (PV), thus facilitating its isolation [7]. In 2014, Yamashita et al. were the first to evaluate the use of adjunctive VOM-EI in AF-CA and found promising results [8]. Since then, additional studies have been performed to assess the outcomes of adjunctive VOM-EI in AF-CA [9-12]. However, the clinical use of VOM-EI in AF-CA remains controversial and has not been evaluated

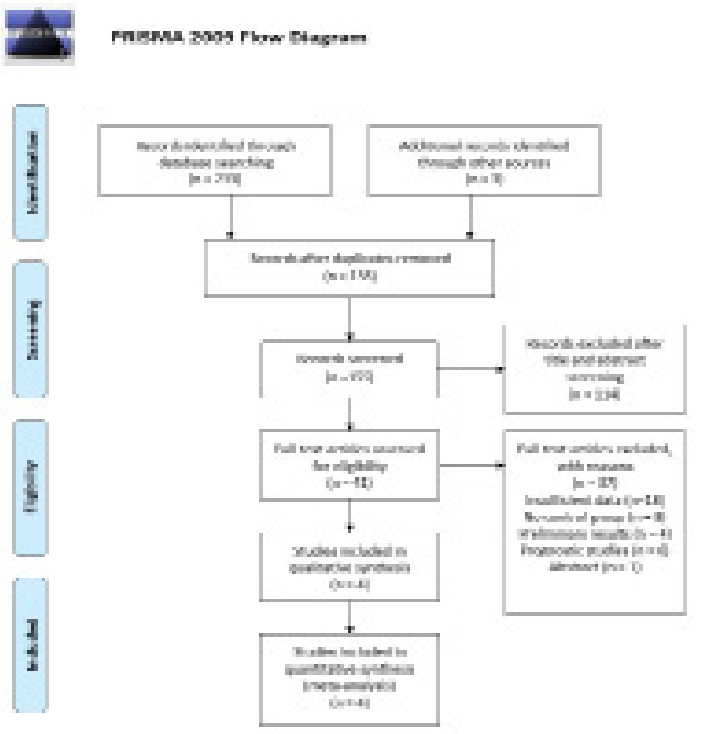

Figure 1: **PRISMA flow diagram for the selection of studies**

systematically. Therefore, we conducted this meta-analysis to evaluate all the available evidence to better assess the efficacy and safety of VOM-EI as an adjunct tool in AF ablation.

Methods

Data sources and search strategy

We performed a comprehensive search for published studies in PubMed/MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials from inception to January 22, 2021. We also performed a manual search for additional relevant studies using references of the included articles. The following search terms were used: ("Vein of Marshall" or "Ligament of Marshall"), ("Ethanol infusion" or "ablation"), and ("Atrial fibrillation" or "Atrial tachycardia"). The search was limited by the English language, but not to the study design, or country of origin. Online Supplementary Table 1 describes the full search term used in each database searched.

Study selection

We followed the preferred reporting items for systematic reviews and meta-analyses (PRISMA) and the meta-analysis of observational studies in epidemiology (MOOSE) guidelines to screen the studies[13,14]. We included full texts of randomized controlled trials, cohort studies, and case-control studies. We excluded abstracts, single-arm studies, animal studies, case reports, case series, reviews, editorials, and letters to editors. Two investigators (MM and AB) independently screened and selected the studies for the final review. Discrepancies were resolved by a third investigator (PC).

Data extraction

We extracted the following data from the final studies: the last name of the first author, publication year, study design, country of origin, follow-up duration, sample size, efficacy endpoints (including recurrence of AF or Atrial tachycardia [AT] and acute mitral isthmus bi-directional block [MIBB]) and safety endpoints (including peri-procedural complications such as pericardial effusion, atrio-esophageal fistula, stroke, cerebrovascular accident [CVA], and death). Finally, we extracted data for the number of patients who underwent VOM-EI + CA or CA alone, their age, and baseline comorbidities (including diabetes mellitus, hypertension, stroke, coronary artery disease [CAD], and heart failure) and pre-procedural characteristics (including left ventricular ejection fraction [LVEF], left atrial [LA] diameter, and CHA_2DS_2-VASc).

Outcomes

The primary outcome of our meta-analysis was AF or AT recurrence. Our secondary outcomes included acute mitral isthmus bidirectional block (MIBB) and peri-procedural complications (pericardial effusion, stroke, or atrio-esophageal fistula).

Statistical analysis

The meta-analysis was performed using the Review Manager 5.3 (Cochrane Collaboration, Copenhagen, The Nordic Cochrane Centre). The random-effects model was used to calculate the weighted pooled risk ratio (RR) and corresponding 95% confidence intervals (CI). We also performed a subgroup analysis for the late AF/AT recurrence and acute MIBB out comes based on the pathophysiology of the underlying atrial arrhythmia (de novo AF vs. post AF-AT (PMF)). A P-value <0.05 was considered statistically significant. Heterogeneity was assessed using the Higgins I^2 index, where I^2 values >50% implied

Table 1: **Characteristics of studies included in the meta-analysis**

Author, year	Study type	Country	AT subtype	Follow-up duration, months	VOM-EI + CA group, n	CA alone group, n	Efficacy endpoints	Safety endpoints
Liu, 2019	Observational study.	Taiwan	post AF-AT	12	32	64	Recurrence of AF or any atrial arrhythmia	Periprocedural complications
Nakashima, 2020	Observational study.	France	De novo AF	9.7±5.6	152	110	Acute MI block and MI reconnection	Periprocedural complications
Takigawa, 2020	Observational study.	France	post AF-AT	12	32	71	Bidirectional conduction block	Periprocedural complications
Valderrábano, 2020	RCT.	USA	De novo AF	12	185	158	Freedom from AF or atrial tachycardia	Acute procedural complications (Pericardial effusion, CVA and atrio-esophageal fistula) and total mortality

Abbreviations:AF: Atrial fibrillation, AT: Atrial tachyarrhythmia, CVA: Cerebrovascular accident, MI: Mitral isthmus, N: sample size, NR: not reported, PMF: peri-mitral flutter, RCT: randomized controlled trial.

Table 2: Baseline patients characteristics included in the meta-analysis

	Number of studies	All patients (n = 804), (% or mean ± SD)	VOM-EI + CA group(n = 401) (% or mean ± SD)	CAonly group (n = 403) (% or mean ± SD)	P value
Age (years)	4	63.5±9.9	64.5±9.8	62.6±9.9	<0.01
Male	4	78.5% (631/804)	76.3% (306/401)	80.6% (325/403)	0.14
Hypertension	3	65.1% (353/542)	73.1% (182/249)	58.4 (171/293)	<0.01
Diabetes mellitus	3	19.5% (106/542)	25.7% (64/249)	14.3% (42/293)	<0.01
CAD	3	24.9% (135/542)	26.9% (67/249)	23.2% (68/293)	0.32
Stroke	3	10% (54/542)	10% (25/249)	9.9% (29/293)	0.96
Heart failure	3	22.1% (120/542)	22.1% (55/249)	22.2% (65/293)	0.98
CHA_2DS_2□VASc	4	2.2±1.6	2.4±1.6	2.1±1.7	0.01
LVEF, %	4	55.3±9.3	55.3±10.2	55.4±8.4	0.88
LA diameter, mm	2	44.9±7.3	44.4±7.8	45.3±6.9	0.18
Pers/LSPers AF	3	68.2% (478/701)	71.2% (263/369)	64.7% (215/332)	0.07

Abbreviations: CAD: Coronary artery disease, LA: Left atrium,LVEF: Left ventricular ejection fraction, and Pers/LSPers AF: Persistent or long standing persistent atrial fibrillation.

the presence of substantial heterogeneity[15].

Quality assessment

We assessed the quality of the included studies using the Newcastle-Ottawa Scale for observational studies and the Revised Cochrane risk-of-bias tool for randomized trials (RoB 2) for RCTs[16,17]. Two authors (MM and OS) independently assessed each study for bias. Discrepancies were resolved by consensus. We did not evaluate for publication bias in our study because of the limited number of included studies[18].

Results

Study selection

A total of 236 studies were retrieved by our search strategy. Among these, 155 were eligible for the systematic review. Subsequently, based on the titles and abstracts, we excluded 151 studies that were not relevant, had insufficient data, were preliminary studies, single-arm studies, or being a prognostic study. Finally, four studies met our inclusion criteria and were included in the meta-analysis[9-12]. Figure 1 shows the PRISMA flow chart that illustrates how the final studies were selected.

Study characteristics

Table 1 shows the characteristics of the four studies that were included in our meta-analysis.The studies included a total of 804 atrial fibrillation patients, of whom 401 underwent VOM-EI plus CA, and 403 underwent CA only. The studies were published between 2019 and 2020. Based on the country of origin, two studies originated from France, one from Taiwan, and one from the USA. Based on study design, one study was a randomized controlled trial[12], and the rest were observational studies. All the included studieswere full-text publications. The mean age was 63.5±9.9 years, males represented 78.5% of total patients, and 68.2% of patients presented with persistent or long-standing persistent AF. Hypertension and Diabetes Mellitus were more prevalent in the VOM-EI+CA group. Furthermore, patients in the VOM-EI+CA group were older when compared to the patients in the CA-only group. These differences in the baseline characteristics lead to a higher CHA_2DS_2-VASc score in the VOM-EI+CA group when compared to the CA-only group. Both groups were similar regarding the rest of their baseline comorbidities. Table 2 summarizes the baseline comorbidities and pre-procedural characteristics, including LVEF, LA diameter, and CHA_2DS_2-VASc score.

Primary outcome

All the included studies reported the rate of late atrial arrhythmia recurrence (after three months of the index procedure) in the form of atrial fibrillation or atrial tachycardia. VOM-EI group was associated with a lower risk of late AF/AT recurrence (RR:0.63; 95% CI:0.46-0.87; P = 0.005). No significant heterogeneity was found in the measurement of AF/AT recurrence rate (I^2 = 49%, P = 0.12)(Figure 1A).

Secondary outcomes

The rate of MIBB attained was higher in the VOM-EI group compared to CA only group (RR:1.39; 95% CI:1.08-1.79; P = 0.009) (Figure 2B).The rate of periprocedural complications was not statistically differentbetween the two groups (RR:1.05; 95% CI:0.57-1.94; P = 0.87) (Figure 2C). Substantial heterogeneity was seen in the measurement of acute MIBB (I^2 = 87%, P<0.01). A sensitivity analysis was conducted by removing one study at a time to reduce heterogeneity and found no significant heterogeneity after removal of the Takigawa et al. study (I^2 = 0%, P heterogeneity = 0.73), with the results of the acute MIBB success rate continuing to be significantly different between the two groups (RR 1.51, 95% CI 1.36-1.69, P < 0.01) (Online Supplementary figure 1).No significant heterogeneity was found in the measurement of the risk of periprocedural complications (I^2 = 0%,

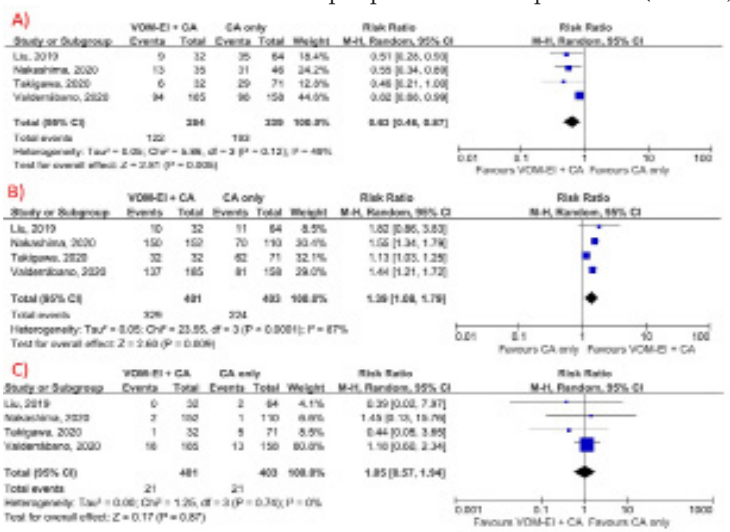

Figure 2: Forest plot showing the study outcomes (A) Late AF/AT recurrence, (B) Acute mitral isthmus bidirectional block, and (C) procedural complications. Results showed that VOM-EI group was associated with a lower risk of late AF/AT recurrence and increased probability to achieve acute MIBB with out an increase in procedural complications.Abbreviation

AF: Atrial fibrillation, AT: Atrial tachycardia, CA: catheter ablation, CI: confidence interval, VOM-EI: vein of Marshall ethanol infusion.

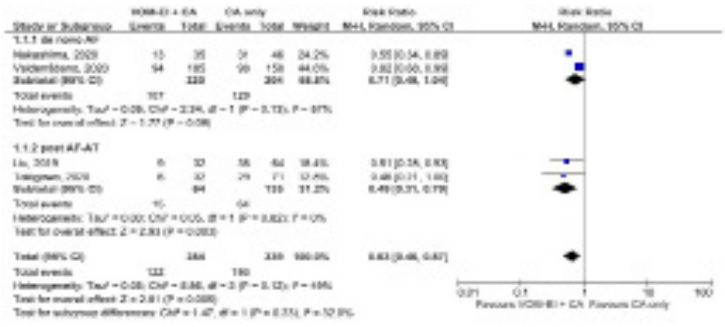

Figure 3: Forest plot showing subgroup analysis comparing VOM-EI + CA and CA only regarding late atrial arrhythmia recurrence rate based on the underlying pathophysiology of the atrial arrythmia. The two groups had similar rates regardless of whether the studies were conducted fora de novo AF or for a post AF-AT. Abbreviation

AF: Atrial fibrillation, AT: Atrial tachycardia, CA: catheter ablation, CI: confidence interval, VOM-EI: vein of Marshall ethanol infusion.

P = 0.88).

Subgroup analysis for late atrial arrhythmia recurrence

Figure 3 shows the forest plot that compares VOM-EI plus CA and CA only groups regarding late AF/AT recurrence based on the underlying pathophysiology of the atrial arrhythmia. The two groups had similar late AF/AT recurrence rates regardless of whether the studies were conducted fora de novo AF or for a post AF-AT (PMF) (test of subgroup difference: Chi^2: 1.47, df= 1, P-value (0.23), I^2: 32%) (Figure 3).

Subgroup analysis for late atrial arrhythmia recurrence

Figure 4 shows the forest plot that compares VOM-EI plus CA and CA only groups regarding the acute MIBB success rate based on the underlying pathophysiology of the atrial arrhythmia. The two groups had similar acute MIBB rates regardless of whether the studies were conducted for a de novo AF or for a post AF-AT (PMF)(test of subgroup difference: Chi^2: 0.07, df= 1, P-value (0.79), I^2: 0%)(Figure 4).

Quality assessment

We assessed the quality of the included studies by using the Newcastle-Ottawa Scale for cohort studies and the Revised Cochrane risk-of-bias tool for randomized controlled trials, as shown in Online Supplementary Tables 2 and 3. All studies scored low to moderate on the scales.

Discussion

This study was a systematic review and meta-analysis of published studies that investigated the efficacy and safety of the VOM-EI adjunctive strategy compared to conventional catheter ablation strategy in the management of AF. Our meta-analysis demonstrated that the VOM-EI adjunctive strategy significantly reduced the risk of AF/AT recurrence and increased therate of acute mitral isthmus bidirectional block achieved. Furthermore, there were no safety concerns regarding periprocedural complications.

AF continues to be the most common cardiac arrhythmia, with an estimated 12.1 million people are expected to have AF by 2030 in the United States [19]. AF is associated with increased all-cause mortality, with death often attributed to CAD or CVA[20].Treatment for AF aims to alleviate symptoms, reduce the risk of stroke, and prevent tachycardia-related cardiomyopathy[21]. The decision to pursue rhythm control depends on several factors, mainly to prevent the irreversible electrical and structural remolding in longstanding AF[21]. Several data reported comparable outcomes of either rate or rhythm control; however, in a secondary analysis of the AFFIRM trial of rhythm versus rate control in AF, rhythm control was associated with a statistically significant reduction in mortality (hazard ratio 0.53)[22]. Similar results were observed in the DIAMOND trial that compared Dofetilide to placebo in patients with reduced ejection fraction (RR 0.44) [23].

The recurrence rate of AF after CA varies significantly among different studies; early recurrences (within the first three months) occur in almost half of the patients after CA[24]. Late recurrence (after three months) was observed in more than 40% of patients as detected by continuous rhythm monitoring in the CIRCA-DOSE trial[6]. Thus, repeated procedures and the use of maintenance antiarrhythmic medications are usually necessary to achieve acceptable success rates[25]. The rate of repeated ablation procedures may reach up to 80%[26]. Despite added strategies beyond the isolation of PV, the success rate did not improve remarkably[27].

Given that VOM has dual sympathetic and parasympathetic innervation and its unique anatomical position by locating within the mitral isthmus, VOM is implicated in the generation and maintenance of AF [3,28]. Therefore, ablation of VOM can potentially eliminate its intrinsic arrhythmogenic properties by eliminating AF trigger in the mitral isthmus and the surrounding atrial tissue, and its PV connections[28].Valderrabano et al.[7] conducted an animal study showing that VOM-EI resulted in eliminating vagally-mediated decrease in the left atrial effective refractory periodby forming scar around the pulmonary veins. The use of VOM-EI in human was initially assessed by a small study on 14 patients; VOM-EI led to the formation of a low voltage area in the left atrium (LA) and isolation of the left inferior PV in 4 of 10 patients without acute complications [29]. Furthermore, a larger study on 61 patients demonstrated that VOM signals are consistently present in recurrent AF, and EI successfully eliminated PV reconnections with no reportable complications[30]. Kitamura

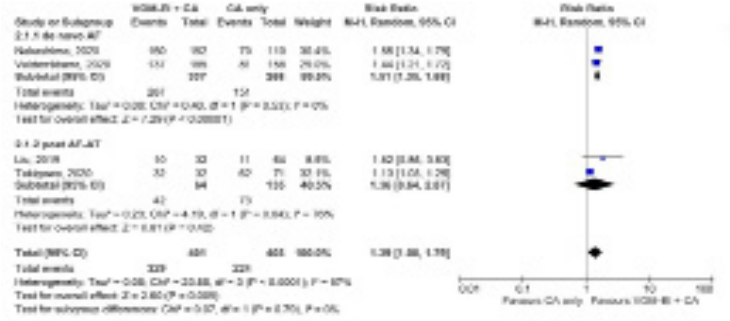

Figure 4: Forest plot showing subgroup analysis comparing VOM-EI + CA and CA only regarding acute mitral isthmus bidirectional block rate based on the underlying pathophysiology of the atrial arrythmia. The two groups had similarrates regardless of whether the studies were conducted fora de novo AF or for a post AF-AT. Abbreviation

AF: Atrial fibrillation, AT: Atrial tachycardia, CA: catheter ablation, CI: confidence interval, VOM-EI: vein of Marshall ethanol infusion.

et al.[31] showed that VOM was accessible in 92.5% of patients, and 56% of Marshall bundle-related atrial tachycardia (MB-AT) were terminated only by ethanol infusion without CA, and the low-voltage area was significantly larger after ethanol infusion (12.7 ± 8.3 versus 6.6 ± 5.3 cm2, p < 0.001).

Regarding the late AF/AT recurrence risk after ablation, our meta-analysis showed that VOM-EI adjunctive therapy was associated with a significantly lower risk of recurrence compared to the non-VOM-EI group; 57% of patients of the VOM-EI group attained late AF/AT freedom compared to 43% in the CA-only group (P-value = 0.005). Previous studies showed similar results to our meta-analysis [9,11].Liu et al. showed that VOM-EI was an independent predictor of freedom from AF recurrence[9]. In addition, Takigawa et al. showed that VOM-EI was significantly associated with less AT recurrence by multivariate analysis (hazard ratio = 0.35, P = 0.018) [11]. Previous studies have shown that CHA_2DS_2-VASc score was an independent predictor of AF recurrence after ablation[32]. In our study, despite having a higher CHA_2DS_2-VASc score, the VOM-EI group had a lower AF/AT recurrence when compared to the CA-only group. This further emphasizes the effectiveness of the adjunctive VOM-EI to the standard CA in patients with AF.

Our meta-analysis demonstrated a pooled success rate of acute bidirectional MIBB of 82% with the VOM-EI strategy, which is consistent with previous studies. Acute MIBB success achieved by CA in previous studies varied between 32%-92% based on various technical approaches[33]. Interestingly, adjunctive VOM-EI increased the success rate of acute MIBB up to 100%[34]. However, substantial heterogeneity was seen for acute MIBB in our study, which might be attributed to the limited number of studies. In addition, subgroup analysis showed that the heterogeneity was contributed more by Takigawa's study; this might be explained as that study was conducted amongst patients treated for post-AF demonstrated peri-mitral flutter rather than for AF demonstrated rhythm.

Concerning the safety of VOM-EI, our study showed that VOM-EI is a safe procedure with no significant periprocedural complications with a comparable incidence of adverse events between the two groups. Adverse events that may occur during VOM-EI include pericardial effusion (due to contrast leakage out of VOM), CVA, and atrio-esophageal fistula [9,12]. The most recent study by Valderrábano et al.[12] showed that adverse events were comparable between VOME-EI and non-VOM-EI groups.

Our study may represent heterogeneous populations of patients; Takigawa et al. enrolled patients with PMF, Nakashima et al. enrolled patients mostly with persistent AF (the number with peri-mitral flutter was not specified), and Valderrábano et al. enrolled persistent AF patients. However, we conducted subgroup analyses that showed no subgroup differences in the effectiveness of the adjunctive VOM-EI in terms of prevention of AF/AT recurrence or attaining acute MIBB whether the underlying arrhythmia was a de novo AF or a post-AF ablation demonstrated atrial tachycardia in the form of peri-mitral block.

There are certain limitations to our meta-analysis. First, the number of included studies was limited, with relatively small sample size; therefore, our outcomes should be interpreted with caution. Future RCTs are needed to validate our findings. However, a recently initiated MARS-AF trial evaluating the outcomes of adjunctive VOM-EI in the ablative therapy of patients with persistent AF is undergoing and expected to provide more evidence on the effectiveness of VOM-EI (NCT 01898221). Second, our study included only a single randomized controlled trial. Third, the included trials were of a single-blinded design. Therefore, investigator bias cannot be excluded. Additionally, we could not perform publication bias due to the small number of included studies.

However, there are several strengths to our meta-analysis. First, to our knowledge, this is the first meta-analysis to compare the clinical outcomes of adjunctive VOM-EI strategy with conventional CA strategy in terms of efficacy and safety. Second, we performed a subgroup analysis for the late atrial arrhythmia recurrence rate and acute MIBB success rate based on the pathophysiology of the underlying rhythm, adjunctive VOM-EI was effective for both de novo AF and post AF-AT (PMF). In addition, no heterogeneity was found in the measurement of our primary outcome (late AF/AT recurrence risk).

Conclusion

Our meta-analysis demonstrated that the VOM-EI adjunctive strategy reduced the risk of atrial arrhythmia recurrence and increased the success rate of acute mitral isthmus bidirectional block. In addition, the VOM-EI strategy had a similar safety profile compared to the conventional catheter ablation. However, furtherlong-term RCT with larger sample sizes are needed to testify the clinical application value of VOM-EI guided strategy in the ablative treatment of AF.

Click here for Supplemental Material

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Active Implantable cardioverter-defibrillators in Continuous-flow Left Ventricular Assist Device Recipients

Electrophysiology Collaborative Consortium for Metaanalysis – ELECTRAM Investigators

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Abstract

Introduction: Implantable cardioverter-defibrillator (ICD) in patients with heart failure with reduced ejection fraction reduces mortality secondary to malignant arrhythmias. Whether end-stage heart failure (HF) with continuous-flow left ventricular assist device (cf-LVAD) derive similar benefits remains controversial.

Methods: We performed a systematic literature review and meta-analysis of all published studies that examined the association between active ICDs and survival in advanced HF patients with cf LVAD. We searched PubMed, Medline, Embase, Ovid, and Cochrane for studies reporting the association between ICD and all-cause mortality in advanced HF patients with cfLVAD. Mantel-Haenszel risk ratio (RR) random-effects model was used to summarize data.

Results: Ten studies (9 retrospective and one prospective) with a total of 7,091 patients met inclusion criteria. There was no difference in all-cause mortality (RR 0.84, 95% CI 0.65–1.10, p=0.20, I^2=62.40%), likelihood of survival to transplant (RR 1.07, 95% CI 0.98–1.17, p= 0.13,I^2 =0%), RV failure (RR 0.74, 95% CI 0.44–1.25, p = 0.26,I^2=34%) between Active ICD and inactive/no ICD groups, respectively. Additionally, 27.5% received appropriate ICD shocks, while 9.5% received inappropriate ICD shocks. No significant difference was observed in terms of any complications between the two groups.

Conclusion: All-cause mortality, the likelihood of survival to transplant, and worsening RV failure were not significantly different between active ICD and inactive/no ICD in cf-LVAD recipients. A substantial number of patients received appropriate ICD shocks suggesting a high-arrhythmia burden. The risks and benefits of ICDs must be carefully considered in patients with cf-LVAD.

Key Words
Implantable Cardioverter-Defibrillator, Continuous-Flow LVAD, Mortality

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Introduction

Continuous flow left ventricular assist devices (cf-LVAD) are being increasingly utilized in patients with end-stage heart failure (on guideline-directed medical therapy) as a bridge to transplant or destination therapy, with improved overall survival[1,2]. Similarly, implantable cardioverter-defibrillator (ICD) is indicated in heart failure patients (New York Heart Association functional class I, II,

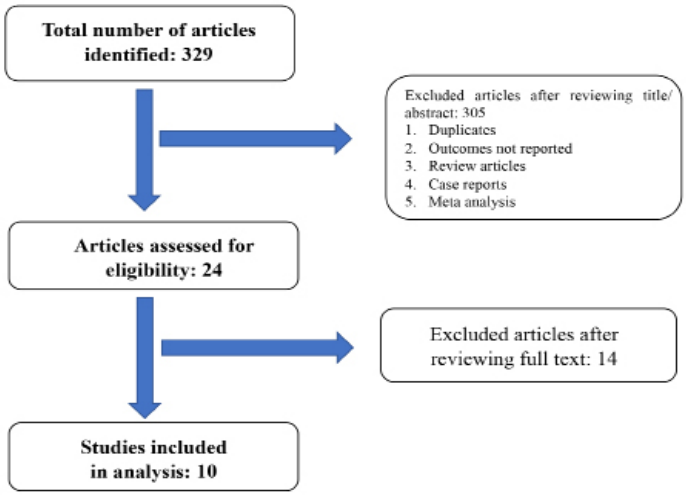


Figure 1: Flow Diagram illustrating systematic search of studies

III) for primary/secondary prevention of sudden cardiac death caused by ventricular arrhythmias.

Patients with cf-LVAD are at increased risk of ventricular arrhythmias either due to worsening underlying disease substrate, scarring around the inflow cannula, or arrhythmias resulting from suction events due to underfilling of the left ventricle[3,4]. However, it remains controversial if ICD offers any survival benefit in advanced heart failure patients with cf-LVAD. Patients with cf-LVAD have been able to tolerate prolonged periods of ventricular arrhythmias with minimal or no neurological sequelae, and are rarely associated with sudden cardiac death[5]. Based on the currently available literature, there are no strict guidelines on ICD utilization in advanced heart failure patients with cf-LVAD. Therefore, we performed a systematic review and meta-analysis of all the clinical studies examining the role of active ICD in end-stage heart failure patients with cf-LVAD.

Methods

Search strategy

The reporting of this systematic review and meta-analysis complies with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) guidelines(SupplementTable 1) [6].

The initial search strategy was developed by two authors (KS and RC). Systematic search, without language restriction, using PubMed, EMBASE, SCOPUS, Google Scholar, and Clinical Trials.gov from inception to November 10th, 2020, for studies comparing clinical outcomes between active ICD versus inactive ICD and/or no ICD in advanced heart failure patients with cf-LVAD was performed. We used the following keywords and medical subject heading: "continuous-flow left ventricular assist device,""implantable cardioverter-defibrillator," "end-stage heart failure."

Study Selection and data extraction

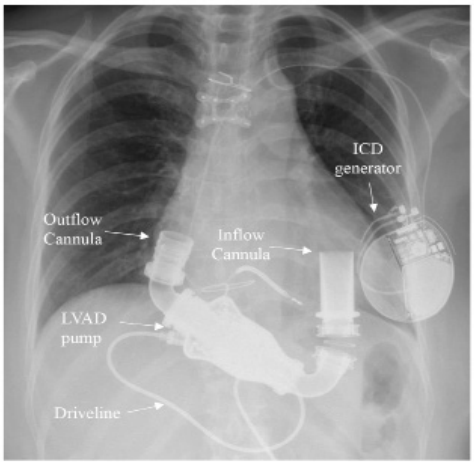
The eligibility criteria for our systematic review and meta-analysis included: (1) all studies reporting clinical outcomes comparing active ICD vs. inactive ICD/no ICD in end-stage heart failure patients with cf-LVAD and (2) studies that included human subjects aged ≥ 18 years. We included studies only published in the English language. Studies involving pulsatile flow LVAD (pf-LVAD), single-arm studies, case reports, editorial, or systematic reviews were excluded. Two investigators (KS and RC) independently performed the literature search and screened all titles and full-text versions of all relevant studies that met study inclusion criteria. The references of all identified articles were also reviewed for relevant studies meeting the eligibility criteria.

The data from included studies were extracted using a standardized protocol and a data extraction form. Any discrepancies between the two investigators were resolved with a consultation with the senior investigator (JG). Two independent reviewers (KS and RC) extracted the following data from the eligible studies: author name, study design, publication year, follow-up duration, number of patients, age, gender, body mass index, diabetes, smoking, etiology of cardiomyopathy, indications of cf-LVAD, medications, INTERMACS score. The Newcastle Ottawa Risk bias assessment tool was used to appraise the included studies' quality (Supplement Table 2).

Outcomes

Clinical outcomes

The primary outcome of our study was - (1) All-cause mortality. Secondary outcomes were the likelihood of survival to transplant, right ventricular (RV) failure, and ICD therapies (appropriate or inappropriate). Adverse events included were infectious complications (sepsis or bacteremia or driveline infections), LVAD related complications (pump thrombosis or driveline malfunction or



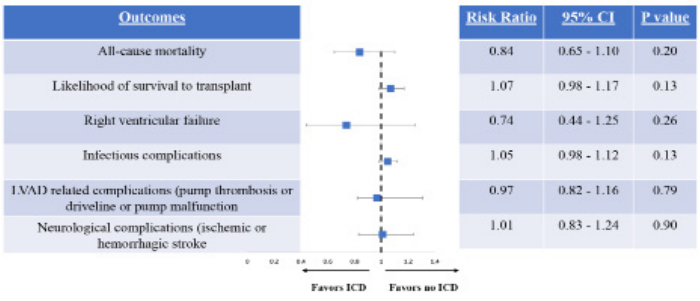


Figure 2: Active ICD versus inactive ICD/no ICD in end-stage heart failure patients with cf-LVAD

Table 1: Baseline characteristics of studies included in our meta-analysis

Study	Anderson et al	Enriquez et al	Garan et al	Lee et al	Clerkin et al. INTERMACS	Clerkin et al. UNOS	Kutyifa et al	Alvarez et al	Cikes et al	Simsek et al
Design	Retrospective	Retrospective	Prospective	Retrospective	Retrospective	Retrospective	Retrospective	Retrospective	Retrospective	Retrospective
Study period	2006-2008	2008-2012	2012	2004-2013	2006-2016	2004-2014	2008-2014	2004-2017	2006-2018	2010-2016
Sample size	ICD: 17 No ICD: 6	ICD: 62 No ICD: 36	ICD: 77 No ICD: 17	ICD: 63 No ICD: 31	ICD: 2209 No ICD: 2209	ICD: 506 No ICD: 506	ICD: 129 No ICD: 62 Of 62, 31 had ICD implanted after cf-LVAD	ICD: 387 No ICD: 99 Of 99, 52 had ICD after cf-LVAD	ICD: 240 No ICD: 208	ICD: 104 No ICD: 123
Follow up	ICD: 214 days No ICD: 52 days	253 ± 194 days	12.7 ± 12.3 months	364 ± 295 days	12.4 months (median)	ICD: 287.5 days (median) No ICD: 305Days (median)	2.1 ± 1 years	401 days (median)	1.1 years (median)	16.5 ± 11.8 months
Patient age mean ± SD (years)	-	ICD: 56.7 No ICD: 56.3	ICD: 63.1 No ICD: 58.1	ICD: 53.9 No ICD: 42.9	ICD: 59 No ICD: 59	ICD: 51 No ICD: 52	ICD: 57.4 No ICD: 54.9	ICD: 57 No ICD: 48.4	ICD: 54±12 No ICD: 50±14	ICD: 51.3 ± 12.2 No ICD: 49.3± 13.9
Bridge to transplant	19 total	ICD: 55 No ICD: 33	ICD: 37 No ICD: 9	ICD: 56 No ICD: 28	ICD: 512 No ICD: 512	ICD: 506 No ICD: 506	ICD: 98 No ICD: 23	ICD: 257 No ICD: 24	ICD: 168 No ICD: 137	ICD: 91 No ICD: 103
Device type	HeartMate II	HeartMate II	-	Ventrassist, Heartware	-	HeartMate II, Heartware	HeartMate II	-	HeartMate II HeartWare HVAD HeartMate3	Heartmate II, HeartMate III, HeartWare, HeartAssist5
Diabetes	-	-	-	ICD: 17.46% No ICD: 12.90 %	ICD: 4.5 % No ICD: 4.2%	ICD: 27.9% No ICD: 29.1%	ICD: 43% No ICD: 29%	ICD: 158 No ICD: 29	ICD: 22.1% No ICD: 17.8%	ICD: 26.9 % No ICD: 29.3 %
Body mass index	-	-	-	-	ICD: 27.7 No ICD: 27.8	ICD: 27.5 No ICD: 27.4	ICD: 29.8 No ICD: 29.9	ICD: 28.5 No ICD: 27.2	ICD: 26.2 ± 4.8 No ICD: 25.3 ± 4.4	-
INTERMACS profile ≤ 2	-	ICD: 45.2% No ICD: 66.7%	ICD: 67.5% No ICD: 88.2%	ICD: 73% No ICD: 74.19%	ICD: 59.7 % No ICD: 57.8%	-	ICD: 52.7% No ICD: 79%	ICD: 12.1% No ICD: 49.49%	ICD:31.6% No ICD: 56.7%	ICD: 27.9 % No ICD: 36.6 %
Ischemic cardiomyopathy	-	ICD: 30.7% No ICD: 58.3%	ICD: 50.6% No ICD: 58.8%	ICD: 31.74 % No ICD: 35.48%	ICD: 50.7% No ICD: 48.6 %	ICD: 42.5% No ICD: 42.1%	ICD: 47% No ICD: 74.19%	ICD: 39.8% No ICD: 48.48%	ICD: 42.5% No ICD: 50%	ICD: 46.2 % No ICD: 52.8 %
Medications	-	-				-		-		
Beta-blockers			ICD: 96.1% No ICD: 52.9%	ICD: 71.4% No ICD: 67.74%	ICD: 70.1% No ICD: 72.3%		ICD: 84% No ICD: 56.45 %		ICD: 78.3% No ICD: 43.5%	ICD: 73.1 % No ICD: 71.5 %
ACE Inhibitors /ARB			-	ICD: 65.07% No ICD: 67.74%	-		ICD: 30% No ICD: 22.58 %		ICD: 49.3% No ICD: 49.7% -	ICD: 31.7 % No ICD: 33.3 %
Antiarrhythmic medications			ICD: 37.7 % No ICD: 52.9 %	ICD: 41.26% No ICD: 38.70%	ICD: 40.4% No ICD: 41.4%		-			ICD: 25 % No ICD:12.2%

device malfunction), and neurological complications (hemorrhagic or ischemic).

Statistical Analysis

Mantel-Haenszel risk ratio (RR) random-effects model (DerSimonian and Laird method) was used to summarize data between the two groups[7]. For single arm proportion we used the Logit method to establish variance of raw proportions and then used random effects model (Der Simonian and Laird method) to combine the transformed proportions. The data of the pooled analysis was plotted on forest plots. Higgins I-squared (I^2) statistic was used to assess the test ofheterogeneity[8]. A value of I^2 of 0–25% represented insignificant heterogeneity, 26–50% represented low heterogeneity, 51–75% represented moderate heterogeneity, and more than 75% represented high heterogeneity. Publication bias was visually assessed using funnel plots and Egger's linear regression test of funnel plot asymmetry. A two-tailed $p < 0.05$ was considered statistically significant. Statistical analysis was performed using Comprehensive Meta-Analysis version 3.0 (Biostat Solutions, Inc. [BSSI], Frederick, Maryland).

Results

Search results

A total of 329 citations were identified (Figure 1) during the initial search. Three hundred five records were excluded. After a detailed evaluation of these studies,ten studies (9 retrospective and oneprospective) ultimately met the inclusion criteria (N=7,091

Table 2: Baseline characteristics of studies included in our meta-analysis evaluating ICD shocks (appropriate or inappropriate)

Study ID	Anderson et al	Lee et al	Enriquez et al	Kutyifa et al	Alvarez et al	Cikes et al	Oswald et al	Brenyo et al
Design	Retrospective	Retrospective	Retrospective	Retrospective	Retrospective	Retrospective	Prospective	Retrospective
Study period	2006-2008	2004-2013	2008-2012	2008-2014	2004-2017	2006-2018	2005-2008	2006-2010
Sample size	ICD: 17 No ICD: 6	ICD: 63 No ICD: 31	ICD: 62 No ICD: 36	ICD: 129 No ICD: 62 Of 62, 31 had ICD after cf-LVAD	ICD: 387 No ICD: 99 Of 99, 52 had ICD after cf-LVAD	ICD: 240 No ICD: 208	ICD only: 61	ICD only: 61
Follow up	ICD: 214 days No ICD: 52 days	364 ± 295 days	253 ± 194 days	2.1 ± 1 years	401 days (median)	1.1 years (median)	365 + 321 days.	622 days
Patient age mean ± SD (years)	-	ICD: 53.9 No ICD: 42.9	ICD: 56.7 No ICD: 56.3	ICD: 57.4 No ICD: 54.9	ICD: 57 No ICD: 48.4	ICD: 54±12 No ICD: 50±14	ICD only: 50+12	ICD only: 55.75
Bridge to transplant	19 total	ICD: 56 No ICD: 28	ICD: 55 No ICD: 33	ICD: 53 No ICD: 17	ICD: 226 No ICD: 55	ICD: 73% No ICD: 68.8%	-	ICD only: 72%
Device type	HeartMate II	Ventrassist, Heartware	HeartMate II	HeartMate II	-	HeartMate II HeartWare HVAD HeartMate 3	HeartMate II HeartWare	HeartMate II Jarvik
Diabetes	-	ICD: 17.46% No ICD: 12.90 %	-	**ICD: 43% No ICD: 29%**	ICD: 158 No ICD: 29	ICD: 22.1% No ICD: 17.8%	-	ICD only: 361%
Body mass index	-	-	-	ICD: 29.8 No ICD: 29.9	ICD: 28.5 No ICD: 27.2	ICD: 26.2 ± 4.8 No ICD: 25.3 ± 4.4	-	-
INTERMACS profile ≤ 2	-	ICD: 73% No ICD: 74.19%	ICD: 45.2% No ICD: 66.7%	ICD: 52.7% No ICD: 79%	ICD: 12.1% No ICD: 49.49%	ICD:31.6% No ICD: 56.7%	-	-
Ischemic cardiomyopathy	-	ICD: 31.74 % No ICD: 35.48%	ICD: 30.7% No ICD: 58.3%	ICD: 47% No ICD: 74.19%	ICD: 39.8% No ICD: 48.48%	ICD: 42.5% No ICD: 50%	ICD only: 49%	ICD only: 60.6%
Medications Beta-blockers		ICD: 71.4% No ICD: 67.74%	-	ICD: 84% No ICD: 56.45 %	-	ICD: 78.3% No ICD: 43.5%	**ICD only: 69%**	**ICD only: 90%**
ACE Inhibitors /ARB		ICD: 65.07% No ICD: 67.74%		ICD: 30% No ICD: 22.58 %		ICD: 49.3% No ICD: 49.7%	**ICD only: 67%**	**ICD only: 63.9%**
Antiarrhythmic medications		ICD: 41.26% No ICD: 38.70%		-		-	**ICD only: 71%**	**ICD only: 32.78%**

Table 3: Adverse events reported in studies included in our meta-analysis

	Garan et al		Enriquez et al		Lee et al		Clerkin et al. INTERMACS		Alvarez et al		Simsek et al		Cikes et al	
	ICD (72)	No ICD (22)	ICD (62)	No ICD (36)	ICD (64)	No ICD (36)	ICD (2209)	No ICD (2209)	ICD (439)	No ICD (47)	ICD (104)	No ICD (123)	ICD	No ICD
Infection	1	1	NR	NR	0	4	1046	992	110	9	5	11	risk ratio (separate events not reported)	
LVAD complications	NR	NR	43	25	NR	NR	487	497	23 Pump thrombosis: 20 Driveline malfunction: 2 Device malfunction: 1	0	2 Pump thrombosis: 2	8 Pump thrombosis: 8	NR	NR
Neurological complications	1	0	NR	NR	NR	NR	509	473	4	7	6	11	NR	NR

N.R = not reported, ICD = Implantable cardioverter defibrillator

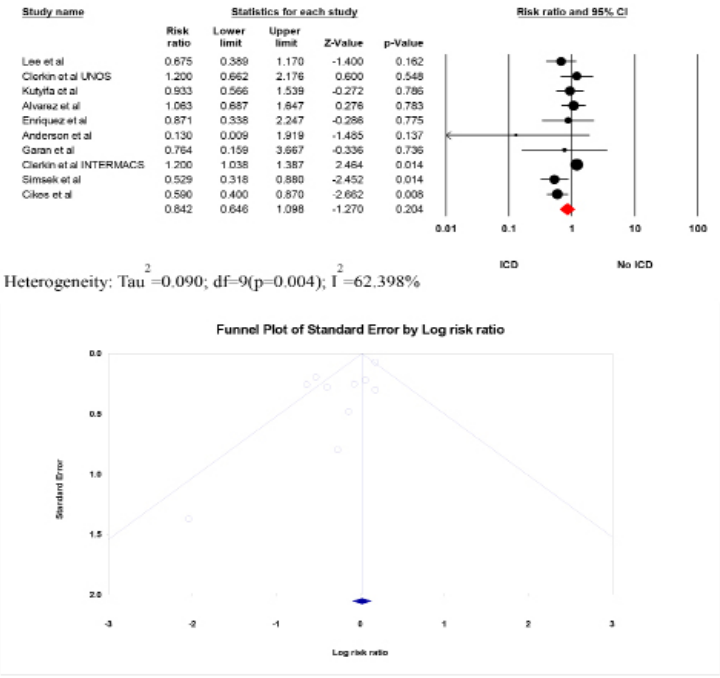


Figure 3: **All-cause mortality.The Forest plot shows the outcomes of the individual trials as well as the aggregate. Point estimates to the left favor active ICD. The funnel plot demonstrates publication bias**

patients)[9-18]. The follow-up duration for the studies ranged from 52 days to 3.1 years. Table 1 summarizes the study characteristics of the included trials.

Study characteristics

The study by Cantillon et al. evaluated outcomes of ICD in both pf-LVAD (n=354) and cf-LVAD patients; however, the baseline characteristics and outcomes of patients with cf-LVAD could not be delineated from those who underwent pf-LVAD. Hence, we excluded from our analysis [19]. In studies by Kutyfia et al., Alvarezet al., and Cikes et al., a total of 103 patients received ICD post-cf-LVAD implantation; and were therefore included in the ICD group[15-17]. In a study by Cikes et al.,[20] patients received ICD post-cf-LVAD, while 45 patients had their ICD deactivated or extracted post-cf-LVAD implantation, 34 of which underwent heart transplantation[17]. Studies by Clerkin et al. (INTERMACS and UNOS data) were propensity score-matched in order to ensure comparable groups (and similar baseline characteristics). This accounted for more than two-thirds (76.5%) of our study population (n=5,430)[13,14].

Overall, the patients' mean agewas 50.34 years in active ICD and 47.09 years in the inactive/no ICD group. Bridge to transplantation was the indication for LVAD placement in 3,174 patients (44.70%). Table 1 summarizes the study characteristics of the included trials.

Clinical Outcomes (Figure 2)

All-cause mortality

The data for all-cause mortality was available in all ten trials[9-18]. Active ICD was not associated with any difference in all-cause mortality as compared to Inactive/No ICD (RR 0.84, 95% 0.65-1.10, p = 0.20). Moderate heterogeneity was observed between trials (I^2 =62.40%). Publication bias was observed (Figure3).

Likelihood of SurvivaltoTransplant

The data for the likelihood of heart transplant was available in sixtrials[10-14,18]. No significant difference was observed between the two groups in the likelihood of survival to transplant (RR 1.07, 95% CI 0.98 – 1.17, p=0.13). No significant heterogeneity was observed between trials (I^2 =0%). No publication bias was observed (Figure4).

Right ventricular failure

The data for right ventricular (RV) failure was available in five trials[10-12,16,18]. No significant difference was observed in terms of RV failure between the two groups(RR 0.74, 95% CI 0.44 – 1.25, p=0.26). Mild heterogeneity was observed between trials (I^2 =34.44%). No publication bias was observed (Figure5).

ICD shocks

We conducted a separate literature search in PUBMED, MEDLINE, EMBASE, EBSCO, CINAHL, Web of Science, and Cochrane (March 10th, 2020) to identify eligible studies assessing ICD shocks (both appropriate and inappropriate) in end-stage heart failure patients with cf-LVAD. After a detailed evaluation of these studies, eightstudies (7 retrospective and oneprospective) clinical studies ultimately met the inclusion criteria (N=970 patients). Follow-up duration for the studies ranged from 52 days to 3 years. Table 2 summarizes the study characteristics of the included trials[9,10,12,15-17,20,21]. Studies by Oswald et al.[21] and Brenyo et al.[20] were only included to assess the incidence of ICD shocks (since both studies did not have any comparator arm).

The data for appropriate ICD shock was available in all eight trials

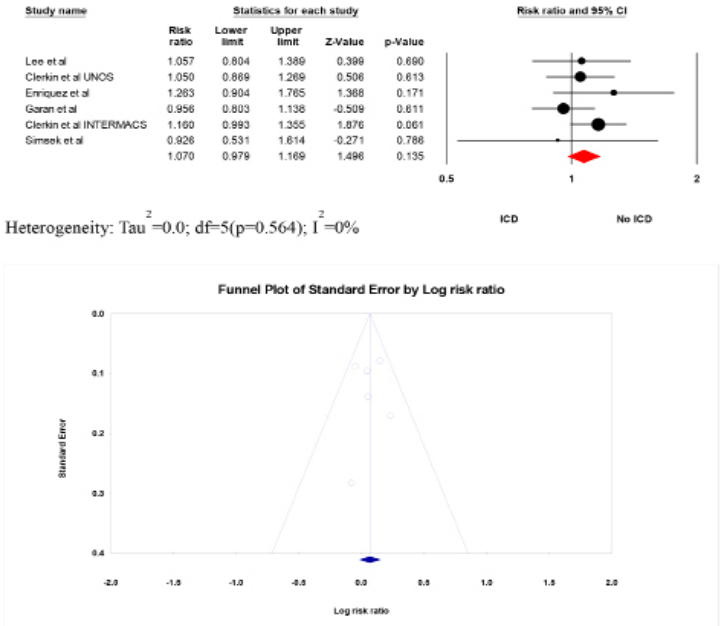


Figure 4: **Likelihood of Survival to Transplant.The Forest plot shows the outcomes of the individual trials as well as the aggregate. Point estimates to the left favor active ICD. The funnel plot demonstrates no publication bias**

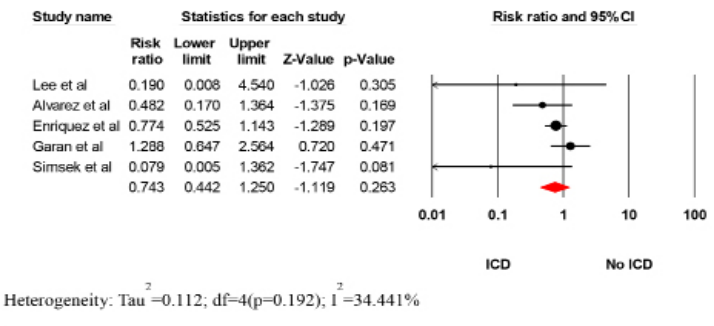


Figure 5: **Right ventricular failure. The Forest plot shows the outcomes of the individual trials as well as the aggregate. Point estimates to the left favor active ICD. The funnels plot demonstrates no publication bias**

[9,10,12,15-17,20,21]that included 970 patients, with an incidence of 27.5% (95% CI 0.22-0.33, I^2=61.36%) during the follow-up period (Figure6).

Inappropriate ICD shock was reported in sixtrials[9,10,12,16,20,21] that included 704 patients with an incidence rate of 9.5% (95% CI 0.05-0.18, I^2=81.69%) during the follow upperiod (Figure7).

Adverse events

The major adverse event rates were reported in six clinical trials (Table 3). There was no significant difference in terms of infectious complications (RR 1.05, 95% CI 0.98-1.12, p = 0.13, I^2=0%) (Figure 8)[11-13,16-18], LVAD related complication (19.72% vs 21.94%; RR 0.97, 95% CI 0.82-1.16, p=0.79, I^2=19.76%) (Figure 9)[10,13,16,18] and neurological complications (ischemic or hemorrhagic stroke) (19.68% vs 20.44%; RR 1.01, 95% CI 0.83-1.24, p=0.90, I^2=6.1%) (Figure 10)[11,13,16,18] between the two groups. The test of heterogeneity was not significant for either outcomes. No publication bias was observed.

Sensitivity analysis

A sensitivity analysis was performed to investigate the significant heterogeneity observed between the trials for all-cause mortality. Studies by Clerkin et al. (INTERMACS and UNOS data) [13,14] were propensity score-matched in order to ensure comparable groups (and similar baseline characteristics). This accounted for more than two-thirds (76.5%) of our study population (n=5,430), of which Clerkin eta l (INTERMACS) contributed 81.36% patients (n=4,418). While Clerkin et al. (UNOS) included all patients as bridge to transplant, only 23.17% of patients were as bridge to transplant in the Clerkinet al. (INTERMACS) trial. There was a significant reduction in all-cause mortality in cf-LVAD recipients with active ICD (RR 0.77, 95% CI 0.61-0.98, p = 0.03), with no significant heterogeneity (P forheterogeneity = 0.22, I^2 = 24.86%) after excluding Clerkin et al (INTERMACS) trial.

Finally, we performed a sensitivity analysis after excluding both Clerkin et al. trials (UNOS and INTERMACS). There remained a significant reduction in all-cause mortality in cf-LVAD with active ICD (RR 0.73, 95% CI 0.58 – 0.92, p = 0.01, I^2 = 15.12%, P for heterogeneity = 0.31).

Discussion

The main findings in this analysis are: (1) All-cause mortality and likelihood of survival to transplant did not differ between the Active ICD and Inactive/no ICD groups in end-stage heart failure patients with cf-LVAD; (2) the incidence rate of appropriate ICD shock was 27.5%, while inappropriate ICD shock was 9.5%; (3)no significant increase in the incidence of RV failure; and finally, there was no difference in the adverse events between the two groups. These findings have important clinical implications, and therefore, the risks and benefits of active ICD must be carefully considered (Figure 2).

This is the largest study assessing the role of active ICD in end-stage heart patients with cf-LVAD (either as destination therapy or bridge to transplant). Our findings strengthen the results of the previously reported trials and metanalyses, demonstrating no net clinical benefit of ICD in advanced heart failure patients with cf-LVAD[22,23]. Since then, new clinical trials and more contemporary data mandated an update to the prior meta-analyses. There are several potential explanations for the findings observed in our study. First, given the lack of randomized clinical trials (and exclusion of healthier patient population), no mortality benefit with ICD is a mere reflective of selection bias towards sicker patient population. Second, end-stage heart failure patients with

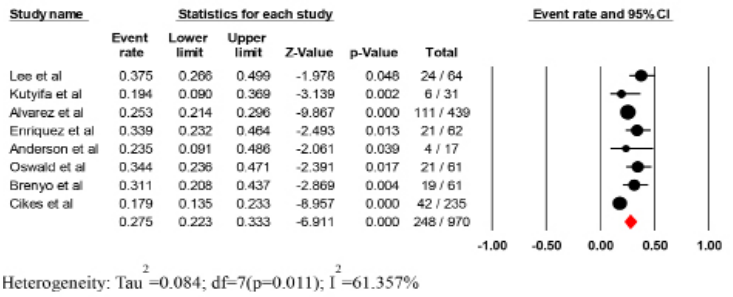


Figure 6: **Forest Plot of the Incidence of Appropriate ICD shock in patients with cf-LVAD**

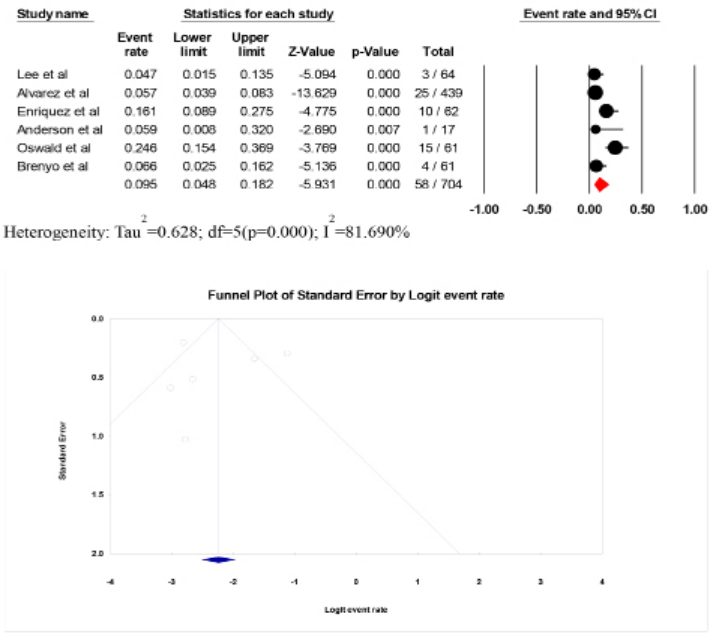


Figure 7: **Forest Plot of the Incidence of Inappropriate ICD shock in patients with cf-LVAD**

cf-LVAD are at increased risk of death from non-arrhythmic causes such as pump failure, infections, or device thrombosis, thus making it difficult to assess the net clinical benefit of ICD's. Third, patients with cf-LVAD may be less susceptible to unfavorable effects of ventricular arrhythmia (as noted in our study) [5,24]; consequently, are less likely to derive mortality benefit from ICD. Lastly, with improved cf-LVAD technology, patient management, and care transition teams, might have led to improved survival that counteracted the effect of ICD. This explains why there was no mortality benefit observed in our study in comparison to previously published meta-analysis assessing the role of ICD in advanced heart failure and pulsatile LVAD[22] (although results should be interpreted with caution given significant heterogeneity observed in our analysis).

The role of ICD in patients with cf-LVAD remains unclear, with no clear consensus from the American College of Cardiology/American Heart Association. The International Society of Heart and Lung Transplantation guidelines recommends the use of ICD [either reactivating previously implanted ICD (Class I, level of evidence A) or de novo implantation of ICD after cf-LVAD (Class IIa, level of evidence B)] [25]. This recommendation is solely based upon a single retrospective study in advanced heart failure patients with pulsatile LVAD[26]. Studies have shown pre-LVAD ventricular arrhythmia is a significant predictor of ventricular arrhythmias post-implant, with increased risk within the first 30 days following LVAD implant [27]. Mechanistically, pulsatile LVAD relies partially on intrinsic pump function, sustained and prolonged ventricular arrhythmias might, therefore, result in pump failure, hemodynamic decompensation, and unfavorable prognosis. On the contrary, cf-LVAD may permit preserved pump function and prevent hemodynamic decompensation during sustained ventricular arrhythmias. However, severe RV failure (due to unsupported RV) may result in adverse clinical outcomes (worst survival and increased heart failure hospitalizations) in 10-40% LVAD patients [28]. Therefore, termination of ventricular arrhythmias in cf-LVAD patients with unsupported RV might be a reasonable option. Besides, patients with cf-LVAD are also at increased risk of ventricular arrhythmias (from increased arrhythmogenic milieu from suction events) compared to pulsatile flow LVAD; therefore, having active ICD in situ seems logical. Furthermore, with a 27.5% incidence of appropriate ICD shocks (in contrast to 9.5% inappropriate ICD shocks), it appears more reasonable to activate ICD therapies following cf-LVAD implantation. Given increasing evidence of the decreased quality of life and increased mortality with ICD shocks, we, therefore, recommend delayed therapy approach (i.e., either prolonged detection time or higher rate cut-offs) in patients with cf-LVAD (Table 4 highlights proposed programming setting across different device vendors). We also recommend setting a lower VT monitor zone, and closer follow-up (either in electrophysiology clinic or remote monitoring) to look for arrhythmic burden.

In our study, no significant difference was observed in terms of infectious complications in cf-LVAD patients between the two groups. ICD related infections may disseminate locally (to cannula and pump) and systemically, requiring long-term suppressive antibiotics, and/or urgent heart transplant or LVAD exchange, which is associated with approximately 30% one-year mortality, and increased health care cost and burden. Despite no significant difference in the adverse effects between the two groups, it still remains unclear at this time if there is an added advantage of de novo implantation of ICD after cf-LVAD. However, it seems reasonable to pursue generator exchange in secondary prevention patients or those with any pacing indications (although our study was not designed to assess this outcome in particular).

Limitations

Our study has several important limitations. First patient selection bias due to the retrospective nature of the included studies could not be excluded. Second, the decision and timing for ICD implantation/ICD

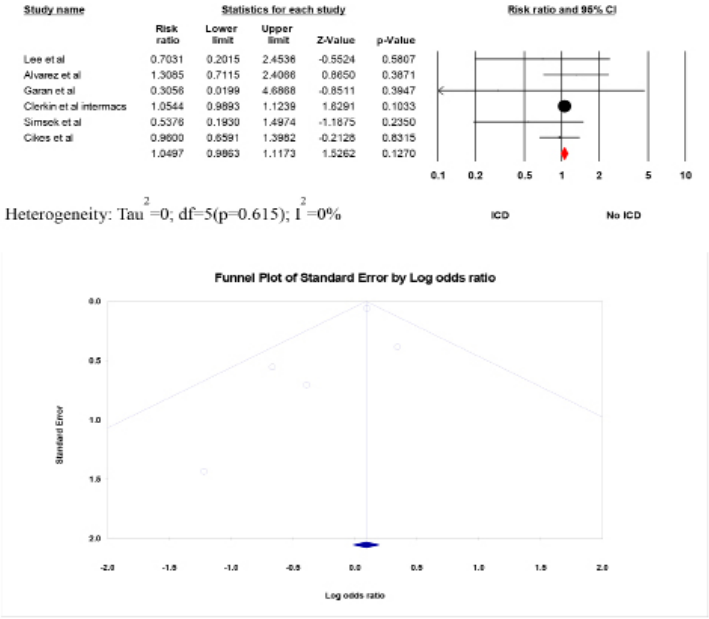


Figure 8: **Infectious complications (sepsis or bacteremia or driveline infection). The Forest plot shows the outcomes of the individual trials as well as the aggregate. Point estimates to the left favor active ICD. Funnels plot demonstrates no publication bias.**

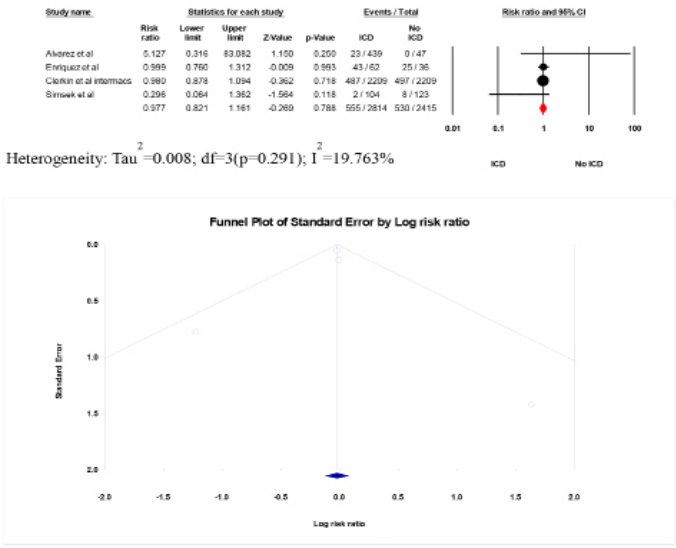


Figure 9: **LVAD related complications (pump thrombosis or driveline malfunction or device malfunction). The Forest plot shows the outcomes of the individual trials as well as the aggregate. Point estimates to the left favor active ICD. The funnel plot demonstrates no publication bias**

programming parameters in cf-LVAD patients were not well defined. Third, information on arrhythmia burden/morphology and its timing in relation to LVAD implantation were inaccessible. Forth patient-level data or right heart catheterization hemodynamics or arrhythmia details/ICD therapies stratified by LVAD typewere not available. Fifth, the etiology of death (cardiac, or non-cardiac) could not be ascertained in all trials. Our meta-analysis results wereprimarily driven by the two largest included studies (UNOS and INTERMACS), accounting together for more than two-thirdsof the total study population.

Conclusion

All-cause mortality, the likelihood of survival to transplant, and worsening RV failure were not significantly different between active ICD and inactive/no ICD in cf-LVAD recipients. However, there was an increased burden of ventricular arrhythmias in our pooled analysis, as evident by a 27.5% appropriate ICD shockrate, suggesting active ICD might bea practical decision in selected patients with cf-LVAD. Future research should be directed to study the safety and efficacy of active ICD's in end-stage heart failure patients with cLVAD in a dedicated randomized controlled study.

Table 4: **Proposedprogramming setting across different device vendors in patients with cf-LVAD and ICD**

	Biotronik	Boston Scientific	Medtronic	St. Jude Medical
VT detection	190 bpm 80 intervals to detect 20 intervals to redetect	190 bpm 60 seconds to detect	188 bpm 100 intervals to detect (33 seconds) 52 intervals to redetect	190 bpm 100 intervals to detect (33 seconds) 6 intervals to redetect
VF detection	250 bpm 30/40 intervals 12/16 intervals to redetect	≥250 bpm 15 seconds to detect	250 bpm 30/40 intervals 12/16 intervals to redetect 120/160 beats to detect (32.4 seconds) 30/40 beats to redetect	≥250 bpm 100 intervals to detect (25 seconds) 6 intervals to redetect

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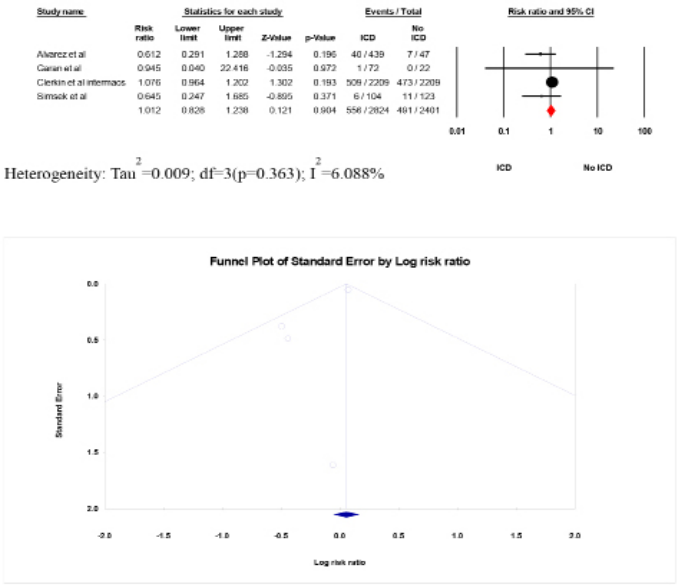

Figure 10: **Neurological complications (ischemic or hemorrhagic stroke). The Forest plot shows the outcomes of the individual trials as well as the aggregate. Point estimates to the left favor active ICD. The funnel plot demonstrates no publication bias**

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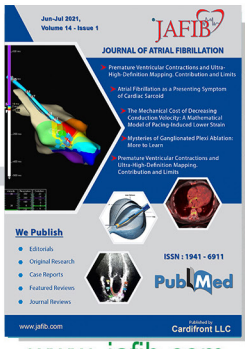

Elevated Left Atrial Volume Index Predicts Incident Atrial Fibrillation After Typical Right Atrial Flutter Ablation

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Abstract

Purpose: Incident atrial fibrillation (AF) is common after cavotricuspid isthmus (CTI) dependent atrial flutter (AFL) ablation. Risk factors for the development of AF post ablation are not well understood. The purpose of this study was to identify patients undergoing CTI ablation for AFL most likely to develop AF.

Methods: Retrospective chart review identified 114 consecutive patients without a history of AF or prior cardiac surgery who underwent typical CTI dependent AFL ablation between December 2013 to November 2018, who also had a complete preoperative transthoracic echocardiogram, and at least 1 year of follow-up at our medical center. We evaluated baseline characteristics, electrophysiology study (EPS) data and echocardiographic data for incidence of AF within 3 years.

Results: Incident AF was identified in 46 patients (40%) during 600 + 405 days follow-up. Left atrial volume index (LAVI) was significantly greater in patients who developed AF compared to those that did not (37 ± 12.2 ml/m² vs 30 ± 13.4ml/m², p=.004), with an area under the receiver operator characteristic curve based on the LAVI of 0.7 (p = 0.004). Kaplan-Meier estimated incidence of AF was significantly greater in patients with LAVI ≥ 30 ml/m² than LAVI < 30 ml/m² (66% vs 27%, p=0.004). Risk of incident AF in patients with LAVI > 40 mL/m² was similar to that of LAVI 30-40 ml/m² (67% vs 63%, respectively, p=0.97). In multivariable analysis LAVI remained the sole independent predictor of incidence AF after CTI AFL ablation.

Conclusion: LAVI ≥ 30 ml/m² is associated with significantly increased risk of incident AF following CTI ablation for typical AFL. HATCH <2 was notably not an independent predictor of AF after AFL ablation.

Introduction

Patients undergoing cavotricuspid isthmus (CTI) ablation of typical right atrial flutter (AFL) frequently develop new-onset atrial fibrillation (AF) within three years after ablation [1-3]. Previous studies investigating risk factors for incident AF after AFL ablation have not consistently identified LAVI as a predictor and have not commonly included detailed and complete echo cardiographic and electrophysiology study data[4-6]. Recently, the HATCH score, a risk score incorporating hypertension, age >75 years old, stroke/transient ischemic attack, chronic obstructive pulmonary disease, and heart failure, has been proposed as a predictor of AF after AFL ablation, [7-8] but its utility in clinical decision making remains unclear. Multiple randomized trials have demonstrated the benefit of prophylactic pulmonary vein isolation (PVI) for patients undergoing CTI dependent AFL ablation [9-13]. However, prophylactic PVI during AFL ablation is not widely performed, and not included in clinical guidelines [14]. Patients at greatest risk of developing incident AF after AFL ablation may derive the greatest benefit from either prophylactic PVI, or intensified monitoring to guide anticoagulation therapy [9-12]. We aimed to investigate risk factors, including detailed echocardiography data, and invasive electrophysiology study data, for development of incident AF followingAFL ablation.

Key Words

Atrial Fibrillation Flutter Cavotricuspid Isthmus Ablation Left Atrial Volume Index.

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Methods

Retrospective chart review identified 114 consecutive patients without a history of AF or prior cardiac surgery who underwent typical CTI dependent AFL ablation between December 2013 to November 2018, who also had a complete preoperative transthoracic echocardiogram,and at least 1 year of follow-up at our medical center. All available medical records, including baseline characteristics, medication history, ECG, echocardiogram, and electrophysiology study, were reviewed and analyzed by investigators. All available ECGs performed before ablation as well as outpatient telemetry monitoring

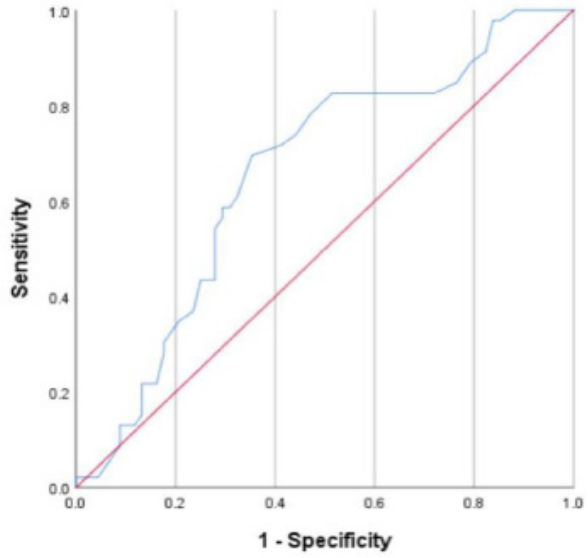

Figure 1: ROC curve for left atrial volume index as a predictor of AF after CTI dependent atrial flutter ablation

were reviewed. A total of 21 patients had outpatient telemetry evaluation which consisted of 12 patients with 24 hour monitors, 4 patients with 14 day monitors, 1 patient with a 30 day monitor, and 4 patients with an implanted monitor. The HATCH score was derived by calculation of appropriate variables [hypertension (HTN), Age >75, transient ischemic attack (TIA) /cerebrovascular accident (CVA), chronic obstructive pulmonary disease (COPD) ,congestive heart failure (CHF)] [7]. Valvular pathology was reported to be present if moderate or greater.

Data collection and analysis were performed according to protocols approved by the NYU Langone Health Institutional Review Board. Surface and intracardiac electrograms (EGMs) were digitally recorded and stored (EP Workmate, Abbott Medical, Inc.). All procedures were performed under conscious sedation after exclusion of left atrial thrombus by transesophageal echocardiography. A 7-French 20-pole catheter (Daig DuoDeca 2-10-2, Abbott Medical, Inc.) was used with the distal poles placed within the coronary sinus and the proximal electrodes located along the tricuspid annulus in the lateral and inferior right atrium. The diagnosis of CTI dependent AFL was confirmed by entrainment or activation mapping at the discretion of the primary operator. Arrhythmia induction by burst pacing was performed in patients presenting in sinus rhythm. 32 patients were found to have atrial tachycardia as their presenting rhythm. Attempted induction of AF was not routinely performed. The primary goal of the procedure was to create a line of bidirectional conduction block in the CTI. Bidirectional block was confirmed by differential pacing with electrodes immediately adjacent to the ablation lesion set. Ablation was performed in each group with a radiofrequency ablation catheter with non-fluoroscopic 3-dimensional mapping (Carto 3, Biosense-Webster, Inc., and NavX, Abbott Medical, Inc.).

Patients were followed for up to 3 years after the date of their procedure. Patient follow-up was censored for the purposes of survival analyses at time of last follow up if less than 3 years after their first procedure. Patients received routine outpatient follow-up at 1 month post-ablation and subsequently at the discretion of their referring cardiologist. Oral anticoagulation was continued for at least 1 month during which a 2 week ambulatory arrhythmia monitor was recommended. The primary outcome was survival free of incident atrial fibrillation after CTI dependent AFL ablation. Diagnosis of AF was defined by the presence of AF >30s duration on ambulatory arrhythmia monitoror implanted device, or on 12 lead ECG.

Categorical data were analyzed across the 2 groups with the chi squared test and were reported as frequencies and percentages. Continuous data were analyzed using the Mann-Whitney U test and were reported as mean + standard deviation. Univariate analyses were performed to evaluate for independent predictors of AF after typical CTI AFL ablation. Univariate and multivariable analyses using the Cox proportional hazard model were performed to evaluate the relationship between LAVI and incidence of AF, and multivariable analysis was adjusted for differences in significant baseline characteristics. A p value criteria of < 0.1 was used to determine which covariates could be included in the multivariable analysis. A receiver operating characteristic (ROC) curve was constructed to test the ability of LAVI to predict new-onset AF and identify an optimal cutoff value. Kaplan-Meier analysis was performed with a log-rank test to determine how LAVI related to the cumulative risk of incident AF. A two-sided P value<0.05 was considered statistically significant. SPSS Statistics

Table 1: Baseline Demographic Data.

Baseline Characteristics	All patients (N= 114)	AF on follow up (N= 46)	No AF on follow up (N= 68)	p value
BSA	2.07 + 0.2	2.1 + 0.3	2.1 + 0.2	0.9
BMI	29.9 + 8.0	30 + 8.9	29 + 7.5	0.7
Age (yrs)	67.5 + 10.5	68.9 + 11.8	66.5 + 9.5	0.1
Male Gender (%)	103 (90%)	42(91%)	61(90%)	1.0
DM (%)	21 (18.4%)	7(15%)	14(21%)	0.6
HTN (%)	68 (59.6%)	28(61%)	40 (59%)	0.9
CAD (%)	23 (20.1%)	13(28%)	10(15%)	0.1
CVA/TIA (%)	9(7.9%)	3(7%)	6(9%)	0.7
CHF (%)	10 (8.8%)	6(13%)	4(6%)	0.2
OSA (%)	21 (18.4%)	10 (22%)	11 (16%)	0.5
COPD (%)	18 (15.8%)	7 (15%)	11 (16%)	1.0
NYHA Class (%)				0.3
I	31 (27%)	12 (26%)	19 (28%)	
II	30 (26%)	12 (26%)	18 (26%)	
III	7 (6%)	5 (11%)	2 (3%)	
CHADS-VASc ≥ 2 (%)	71 (62.3%)	28 (61%)	43(63%)	1.00
HATCH Score	1.3 + 1.2	1.4 + 1.2	1.2 + 1.2	0.3
HATCH Score>=2 (%)	42 (36.8%)	22 (48%)	20(30%)	0.05
Days in Atrial Flutter (days)	88.1 + 186	113.3 + 255	70.6 + 116	0.9
Medications				
Beta Blockers (%)	59 (51.8 %)	29 (63%)	30 (44%)	0.06
CCB (%)	29 (25.4%)	10 (22%)	19 (28%)	0.5
ACEI/ARB/ARNI (%)	37 (32.5%)	13 (28%)	24(35%)	0.5
Anticoagulation (%)	72 (63.2%)	27 (59%)	45 (66%)	0.4

ACE/ARB/ARNI= angiotensin converting enzyme inhibitor/angiotensin receptor blocker/angiotensin receptor-neprilysin inhibitor; BMI=body mass index; BSA=body surface area; CAD=coronary artery disease; CCB=calcium channel blocker; CHF=congestive heart failure; COPD=chronic obstructive pulmonary disease; CVA/TIA=cerebrovascular accident/transient ischemic event; DM=diabetes mellitus; HTN=hypertension; NYHA=New York Heart Association; OSA=obstructive sleep apnea.

Table 2: Baseline Transthoracic Echocardiography Data

Echocardiographic Data	All patients (N= 114)	AF on follow up (N= 46)	No AF on follow up (N= 68)	p value
LV EF (%)	56.7 + 14.0	55.7 + 15.4	57.4 + 13.1	0.99
TTE LA diameter (cm)	4.2 + 0.7	4.4 + 0.6	4.1 + 0.8	0.06
TTE LA Volume Index (cm/m^2)	32.8 + 13.2	36.8 + 12.2	30.2 + 13.4	0.004
LVEDD (cm)	4.6 + 0.9	4.8 + 1.1	4.5 + 0.7	0.07
IV Septum (cm)	1.2 + 0.2	1.2 + 0.2	1.1 + 0.2	0.6
Inf-Lateral Wall (cm)	1.2 + 0.5	1.2 + 0.7	1.1 + 0.2	0.4
Aortic root (cm)	3.4 + 0.4	3.5 + 0.3	3.3 + 0.4	0.09
RAP>5 (mm Hg)	30 (26.3%)	14 (36.8%)	16(29.1%)	0.7
PASP (mmHg)	30.1 + 9.1	32.2 + 10	29 + 7.9	0.1
Aortic regurgitation moderate or severe (%)	6 (5.2%)	3 (7%)	3 (4%)	0.7
Aortic stenosis moderate or severe (%)	3 (2.6%)	0	3 (4.4%)	0.3
Tricuspid regurgitation moderate or severe (%)	10 (8.8%)	7 (15%)	3 (4%)	0.09
Mitral regurgitation moderate or severe (%)	6 (5.2%)	3 (7%)	3 (4)	0.7
Mitral stenosis (%)	0	0	0	N/A

EF= ejection fraction; IV=interventricular; LA=left atrium; LVEDD=left ventricular end diastolic diameter; PASP= pulmonary artery systolic pressure; RAP=right atrial pressure; TTE=transthoracic echo

software 25.0 (IBM, Armonk, NY) was used for data analysis.

Results

Of 114 patients study patients, 46 patients (40%) were found to develop incident AF during the follow-up period. Of the 32 patients who presented with atrial tachycardia during EPS,all of which were confirmed to be CTI dependent flutter, 12 patients developed AF at follow-up, with an incidence of 37.5%. Of the remaining 82 patients, 34 developed AF, with an incidence of 41%. Baseline characteristics, including age, BMI, and HATCH score were similar amongst patients who developed AF and those that did not develop AF (Table There was a non-significant trend towards increased incidence of AF in patients with HATCH score ≥ 2 (48% vs 30%, respectively, p= 0.05). There was no significant difference in left ventricular dimension, left ventricular function, or frequency of significant valvular disease between study groups (Table 2). There was a trend towards increased left atrial diameter in patients that developed incident AF (4.4±0.6 vs 4.1±0.8, p=0.06), while LAVI was significantly greater in patients with incident AF when compared to those that did not (37±12 cm/m^2 vs. 30 ±13cm/m^2, p= 0.004). CTI block was achieved in all patients. There were no significant differences in electrophysiology study data between those that developed AF and those that did not (Table 3).

Study patients were followed for 600 + 405 days after AFL ablation. Intra-procedure cardioversion of atrial fibrillation was required in a total of 5 patients and this did not significantly differ between patients that developed AF and those that did not (9% vs 2%, respectively, p-0.09). There were no post-procedural complications, which included development of hematoma, arteriovenous fistula/pseudoaneurysm, stroke, transient ischemic attack, or cardiac tamponade. One patient developed recurrent CTI dependent atrial flutter at 3 years follow-up.

Routine post AFL ablation ambulatory arrhythmia monitoring was completed in 48 patients (42%). Frequency of routine monitoring did not significantly differ between groups that developed AF and those that did not (39% vs. 44%, respectively, p= 0.7). Symptom driven ambulatory arrhythmia monitoring was performed in 17 patients (15%), and was performed with similar frequency in patients that developed AF and those that did not (19% vs. 12%, respectively, p= 0.3).Cardiac implantable electronic devices(implantable loop recorder, permanent pacemaker, or implantable cardioverter defibrillator) providing longitudinal arrhythmia monitoring were present in 16 patients (14%), and was present in similar frequency in patients that developed AF and those that did not(15% vs. 13%, respectively, p= 0.8).

Figure 1 shows the receiver operator curve (ROC) curve for predicting AF after AFL ablation based on LAVI.The area under the curve for LAVI as a predictor of AF was 0.7.A cutoff point of LAVI ≥ 30 ml/m^2 derived from ROC curve analysis yielded a sensitivity 71%, specificity 60% for the ability to predict incident AF post-ablation. Univariate analyses identified LAVI >30 and HATCH >2 as statistically significant predictors of incidence of AF after CTI AFL ablation. (Table 4), Multivariable analysis including LAVI ≥ 30 ml/m^2 and HATCH ≥ 2 as predictors of AF showed that LAVI ≥ 30 ml/m^2 remained the only significant predictor of incidence of AF after CTI AFL ablation (adjusted HR=2.25 [1.14-4.45]. HATCH >2 was notably not an independent predictor of AF after AFL ablation after multivariable analysis. Patients were further stratified according to LAVI < 30 ml/m^2 vs. LAVI ≥ 30 ml/m^2 and clinical and echocardiographic data were reported for each group (Table 5-6). Figure 2 demonstrates the Kaplan-Meier estimates of AF-free survivalstratified by LAVI ≥ 30 ml/m^2, which shows that at a follow up of 3 years, the incidence of AF after CTI AFL ablation is significantly greater in those with LAVI >30 ml/m^2 than those with LAVI <30 ml/m^2 (66% vs. 27%, p=0.004). A sensitivity analysis of Kaplan-Meier estimates of long term incidence of AF comparing patients with severely increased LAVI ≥ 40 ml/m2 to those with LAVI 30-40 ml/m^2 demonstrated no significant difference (67% vs 63%, p= 0.97).

Discussion

Prior studies investigating risk factors for the development of AF after atrial flutter ablation have yielded inconsistent results, [1-2, 4-6,15-16] and effective risk stratification for development of AF after AFL

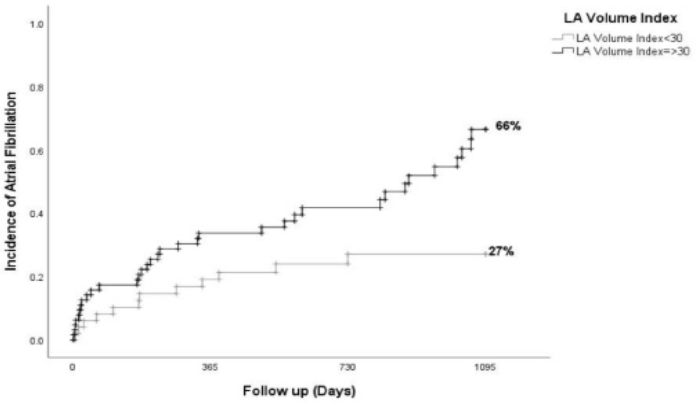

Figure 2: Kaplan-Meier estimates of long-term incidence of AF after cavotricuspid isthmus dependent typical atrial flutter ablation

Table 3: Procedural Data

Procedural Data	All patients (N= 114)	AF on follow up (N= 46)	No AF on follow up (N= 68)	p value
Atrial flutter cycle length (ms)	263 + 120	276 + 172	254 + 64	0.9
RF time (min)	17.0 + 9.4	17.1 + 11.6	16.7 + 7.0	0.9
Trans-Isthmus Conduction Time (ms)	158 + 58	161 + 59	156 + 58	0.9
AV node wenckebach (ms)	441 + 127	428 + 132	451 + 123	0.1
Atrial effective refractory period (ms)	278 + 99	296 + 126	258 + 60	0.9
AV nodal effective refractory period (ms)	367 + 138	339 + 84	386 + 165	0.5
Fluoroscopy time (min)	14.4 + 11.9	15.1 + 15.8	14 + 8.6	0.5
Fluoroscopy dose (mGy)	302 + 325	274 + 387	321 + 278	0.1
Procedural duration (min)	80 + 50	83 + 71	78 + 32	0.9

AV=atrioventricular; CTI=cavotricuspid isthmus; RF=radiofrequency

ablation remains an important, unmet clinical need. Our primary findings are as follows:1) An overall incidence of AF after CTI AFL ablation of 40% in 114 consecutive patientsat 3 years follow-up with routine clinical care 2) LAVI was the only independent predictor of AF after CTI AFL ablation and 3) LAVI >30 ml/m^2 identified patients significantly more likely to develop AF with a hazard ratio of 2.25, with similar risk of incident AF observed with LAVI 30-40 ml/m^2 compared to LAVI ≥ 40 ml/m^2.

While incidence of AF after typical AFL ablation in patients with no known history of AF at 3 years follow-up has been reported to be up to 82%,[5] the 40% incidence observed in the present analysis is consistent with that of several prior studiesin which incidence of AF after typical AFL ablation was observed to be 25-50% at 3 years follow-up [1,6]. Routine, ambulatory arrhythmia monitoring was performed in ~40% of analyzed patients, and monitoring intensity was similar between patients who developed AF and those who did not develop AF.

Chen et al. investigated predictors of incident AF, including HATCH score, in 216 patients after CTI AFL ablation and found that patients with a HATCH score ≥ 2, and those with increased LA diameter were significantly more likely to develop incident AF [7].The area under the receiver operator curve for HATCH score as a predictor of incident AF after AFL ablation was 0.7. The authors postulated that the HATCH score likely represented those patients with enlarged and remodeled left atriums; however, LAVI was not evaluated in that study [7].The significance of the HATCH score was subsequently investigated by Garcia-Seara et al. in 408 patients who underwent typical AFL ablation andit was found that neither a HATCH >2, nor a HATCH > 3 were significant predictors of incidence of AF after typical AFL ablation [8]. They did find LA diameter to be significantly associated with incidence of AF, with degree of enlargement correlating with risk of incident AF; however, LAVI was not investigated in this study either. Neither HATCH score, nor any other clinical or electrophysiologic parameterhave been established as reliable predictors of AF after AFL ablation. Our data are largely consistent with these prior studies suggesting modest utility of HATCH score and LA diameter as predictors of incident AF after typical AFL ablation.

Studies investigating incidence of AF after AFL ablation have not consistently included LAVI as a variable of interest. Limitations of LA size assessment by LA diameter are well recognized [17]. Left atrial volume index is calculated via the biplane disk summation technique, which incorporates fewer geometric assumptions than the area-length methods and thus is perceived to be more accurate. Body surface area is also known to largely impact left atrial size; therefore indexing the calculated left atrial volume to body surface area also allows for more accurate interpretation of left atrial volume measurement. In the only prior study that we are aware of that assessed LAVI as a predictor of AF after typical AFL ablation, Lee et al. found a LAVI of 42.6 ml/m^2 to be predictive of AF after AFL ablation with a 69% sensitivity and 69.8% specificity [16]. TheLAVI cutoff proposed by Lee, et al. is considerably greater than our proposed cutoff of 30ml/m^2, and may have been related to greater prevalence of structural heart disease and other comorbiditiesin their study. Sensitivity analysis in our cohort comparing incidence of AF after CTI AFL ablation in patients with LAVI 30-40 ml/m^2 to that of patients with LAVI >40 ml/m^2 showed a similarly elevated risk of incident AF in both groups. Discordance of prognostic significance between LA diameter and LA volume for development of AF was previously shown by Abecasis, et al. in patients who have undergone PVI and CTI ablation for drug resistant AF [18]. In this study, LA volume derived from CT scan was a significant predictor of arrhythmia recurrence; however, echocardiographic parameters including LA diameter did not have significant predictive value [18]. LAVI determined by echocardiography was recently found to be significantly associated with incidence of cardioembolic stroke and incident AFin patients with prior cryptogenic stroke [19].This study result supports the importance of utilizing LAVI in identifying patients at high risk for developing AF post AFL ablation. Typical AFL is strongly associated with coexistent AF, and identification of coexistent AF has significant clinical implications including consideration of anticoagulation.The consistency of association between elevated LAVI and incident AF across study cohorts and disease states provides greater credibility for the potential utility of LAVI for risk-stratification.

Three randomized clinical trials have evaluated prophylactic PVI in patients with typical AFL and no prior history of AF, each of which hasyielded results favoring combined PVI and CTI AFL ablation [4-6].These studies of relatively unselected patients undergoing typical AFL ablation found that CTI plus prophylactic PVI ablation resulted inabsolute risk reductions for incident AF of 10-28% compared to CTI ablation alone [10].The benefit of prophylactic PVI would be expected to be greatest in patients at greatest risk for development of AF.The established benefit of prophylactic PVI may be substantially greater than previously demonstrated in patients with LAVI of>30 ml/m^2, particularly with use of improved ablation techniques for PVI [20].

Table 4: Association between left atrial volume index and incidence of atrial fibrillation after CTI dependent atrial flutter ablation

	Unadjusted Analysis			Adjusted Analysis		
Variables	HR	95% CI	p-value	HR	95% CI	p-value
LAVI >30	2.54	1.31-4.90	0.006	2.25	1.14-4.45	0.02
HATCH >2	1.91	1.07-3.42	0.03	1.54	0.85-2.82	0.16

LAVI= Left atrial volume index; HR=Hazard ratio; CI= Confidence interval

Table 5: Baseline Demographics data stratified by left atrial volume index

Baseline Characteristics	LAVI>30 (N=64)	LAVI <30 (N= 50)	p value
BSA	2.0 + 0.3	2.1 + 0.2	0.1
BMI	30.3 + 9.4	29.2 + 5.3	0.6
Age (yrs)	69 + 10	65 + 11.4	0.06
Male Gender (%)	56 (88%)	47 (94%)	0.3
DM (%)	13 (20.3%)	8 (16%)	0.6
HTN (%)	43(67.2%)	25 (50%)	0.08
CAD (%)	13 (20.3%)	10 (20%)	1.0
CVA/TIA (%)	7 (10.9%)	2 (4%)	0.3
CHF (%)	8 (12.5%)	2 (4%)	0.2
OSA (%)	14 (21.9%)	7 (14%)	0.4
COPD (%)	12 (18.8%)	6 (12%)	0.4
NYHA Class (%)			0.4
I	14 (21.9%)	17 (34%)	
II	14 (21.9%)	16 (32%)	
III	5 (7.8%)	2 (4%)	
CHADS VASc ≥ 2 (%)	27 (58.7%)	44 (80%)	0.015
HATCH Score	1.5 + 1.3	1.1 + 1.2	0.003
HATCH Score >2 (%)	31 (48.4%)	11 (22%)	0.006
Days in Atrial Flutter before index procedure (days)	84 + 207	89 + 139	0.7
Beta Blockers (%)	36 (56.3%)	23 (46%)	0.3
CCB (%)	14 (21.9%)	15 (30%)	0.4
ACEI/ARB/ARNI (%)	21 (32.8%)	16 (32%)	1.0
Anticoagulation (%)	43 (67.2%)	29(58%)	0.3

ACE/ARB/ARNI= angiotensin converting enzyme inhibitor/angiotensin receptor blocker/angiotensin receptor-neprilysin inhibitor; BMI=body mass index; BSA=body surface area; CAD=coronary artery disease; CCB=calcium channel blocker; CHF=congestive heart failure; COPD=chronic obstructive pulmonary disease; CVA/TIA=cerebrovascular accident/transient ischemic event; DM=diabetes mellitus; HTN=hypertension; NYHA=New York Heart Association; OSA=obstructive sleep apnea

There were several limitations to this study. Although patients' medical records including all available ECG documentation were carefully reviewed to exclude the presence of AF before ablation, minimally symptomatic AF may have been present and undiagnosed. Similarly, the frequency of post-ablation AF may be underestimated due to the absence of longitudinal arrhythmia monitoring in all patients. LAVI was also collected directly from echo reports instead of re-calculated, thus the possibility of echocardiographer variability in measuring LAVI is present. Furthermore, the lack of consistent long term ambulatory monitoring post ablation limits this study as well. Additionally, this was a predominantly male patient population, and therefore, these results cannot be generalized to females. Finally, there are limitationsto this study that are inherent to its retrospective nature.

Table 6: Echocardiographic data stratified by left atrial volume index

Echocardiographic Data	LAVI >30 (N=64)	LAVI <30 (N= 50)	p value
LV EF (%)	53.1 + 16	59.7 + 7.3	0.3
TTE LA diameter (cm)	4.5 + 0.6	3.8 + 0.7	<0.001
LVEDD (cm)	4.7 + 1.0	4.5 + 0.7	0.1
IV Septum (cm)	1.2 + 0.3	1.1 + 0.2	0.05
Inf-Lateral Wall (cm)	1.2 + 0.6	1.1 + 0.2	0.2
Ao root (cm)	3.4 + 0.4	3.4 + 0.3	1.0
RAP>5 (mm Hg)	19 (30%)	11 (22%)	0.5
PASP (mmHg)	31.2 + 10	30 + 7.3	0.5
Aortic regurgitation moderate or severe (%)	4 (6.3%)	2 (4%)	0.7
Aortic stenosis moderate or severe (%)	1 (1.6%)	2 (4%)	0.6
Tricuspid regurgitation moderate or severe (%)	10 (15.6%)	0	0.002
Mitral regurgitation moderate or severe (%)	6 (9.4%)	0	0.03

EF= ejection fraction; IV=interventricular; LA=left atrium; LVEDD=left ventricular end diastolic diameter; PASP= pulmonary artery systolic pressure; RAP=right atrial pressure; TTE=transthoracic echo

LAVI ≥ 30 mL/m^2 may provide a simple, intuitive, and clinical meaningful risk stratification for development of AF after CTI AFL ablation. The utility of elevated LAVI in patients undergoing typical AFL ablation to identify patients most likely to benefit from prophylactic PVI ormore intensive monitoring prior to discontinuation of anticoagulation requires further evaluation.

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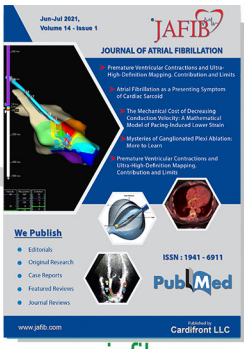

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Outcomes Of Manifest Right Free Wall Accessory Pathway Ablation: Data From A Single Center

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Abstract

Background: Radio frequency ablation (RFA)is an important treatment option for patients with atrial fibrillation (AF). During RFA, a significant amount of energy is delivered into the left atrium (LA), resulting in considerable LA-injury. The impact of this damage on mechanical and endocrine LA-function, however, is often disregarded. We therefore aimed to evaluate the endocrine- and mechanical function of the heart 4-months after RFA of AF.

Methods: In total, 189 patients eligible for RFA of AF were studied. The levels of the N-terminal pro-B-natriuretic peptide (NT-proBNP) and the mid-regional fragment of the N-terminal pro-atrial natriuretic peptide (MR-proANP) were measured. The maximum LAvolume (LAVmax), the LAejection fraction (LAEF) and the LA peak longitudinal strain (PALS), were measured using transthoracic echocardiography. The measurements were performed before and 4-months after the intervention.

Results:87 patients had a recurrence during a mean follow-up of 143±36 days. NT-proBNP and MR-proANP decreased significantly at follow-up. This reduction was greater in patients who did not suffer any recurrence after RFA.

The LAVmax decreased significantly, where as the PALS only improved in patients who did not suffer from any recurrence. On the other hand, LAEF did not change significantly after RFA of AF.

Conclusions: Despite extensive ablation during RFA of AF, the endocrine function of the heart improved 4-months after the index procedure. Patients with no arrhythmia recurrence showed a more pronounced improvement in their endocrinal function. Mechanically, the LAV max was reduced, and the LA strain improved significantly.

Introduction

Catheter ablation of accessory pathways (AP) has proven to be a safe and effective first-line therapy for treatment of Wolff-Parkinson-White (WPW) Syndrome. Ablation success is, however, influenced by AP location. Right free wall (RFW) AP have higher rates of procedural failure and recurrence than their left-sided counterparts [1]. Early ablation outcomes reported significantly greater radiofrequency (RF) applications, procedure durations, and fluoroscopy times with lower rates of success (75%to 85%) and higher rates of recurrence (14% to 35%) for RFW AP ablation[2-4]. Poor catheter stability and tissue contact at the tricuspid annulus (TA) are responsible for these suboptimal outcomes [5,6]. Ablation via the superior approach (right internal jugular vein) [7,8], incorporation of advanced diagnostic catheters [4,9,10], availability of electroanatomic mapping systems [11-13], and use of intra-cardiac echocardiography (ICE) guidance [14,15] may improve the outcomes. In this manuscript, we present our center's experience with RFW AP ablation.

Key Words

Accessory Pathways, Right free wall pathways, Cryoablation, Radiofrequency ablation, Wolf Parkinson White.

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Methods

A retrospective chart review of all patients undergoing electrophysiological study (EPS) and ablation of manifest RFW AP at our institution between January 2008 and September 2018 was completed. Baseline demographics of all identified patients including age, gender, body mass index, comorbidities, medications, ejection fraction, and results of prior EPS were noted. Baseline electrocardiograms (ECG) were reviewed in addition to AP characteristics including pathway location, "malignant" vs. "non-malignant" properties, and effective refractory period (ERP). A malignant AP was defined as a:

a. Pathway with an ERP< 250 ms or
b. The presence of preexcited atrial fibrillation (AF) with an R-R interval < 250 ms or

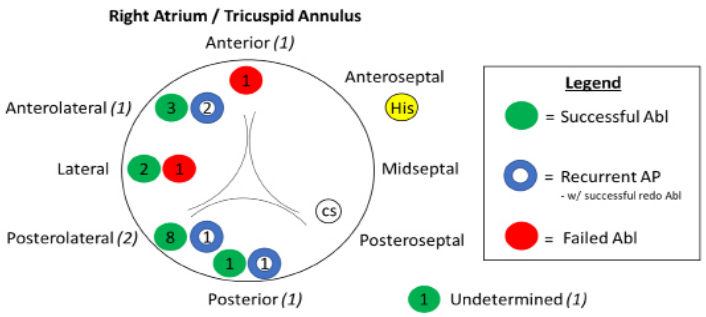

Figure 1: **Right Free Wall Accessory Pathway Location and Ablation Outcomes in 21 Patients Undergoing Index Ablation at Our Institution.**

Pathway Location (#) indicates number of patients with this type of pathway who had previously undergone EPS +/- ablation attempt at an outside institution. [Figure Adapted from Jan et al. BMC Cardiovascular Disorders (2020) 20:210]

c. The occurrence of unexplained syncope in patients with RFW AP.

Detailed analysis of catheter ablation techniques including access approach, procedure and fluoroscopy duration, mapping system and steerable sheath use, and ablation catheter type and energy were also recorded. Procedural success, recurrence, and complications were main outcomes of interest. Acute procedural success was defined as complete elimination of anterograde and retrograde conduction along the AP. The Emory University institutional review board (IRB) approved the study protocol.

RFW APEPS Protocol

Our EPS is typically a 3-catheter study utilizing: (1) high right atrial, (2) his bundle, and (3) right ventricular diagnostic catheters proceeding via right femoral venous access. A multi-electrode steerable catheter (Livewire™ St Jude Medical, Minneapolis, U.S.A) is at times used in lieu of the diagnostic right atrial catheter. Isoproterenol is used as needed to assess AP ERP and supraventricular tachycardia induction. Fluoroscopy and 3D mapping are used in all cases: NAVIX/ESI (St Jude Medical, Minnesota) was used in 24 procedures while CARTO (Biosense Webster, Irvine California) was used in the one remaining. Ablation catheter choice is subject to user preference and in most cases involved the combination of an 8 mm tip large curve non-irrigated RF ablation catheter (Blazer™ Boston Scientific, Marlborough, Massachusetts) through a steerable sheath (Agilis™ Abbott, Chicago, Illinois). However, a variety of alternative ablation catheters with and without a steerable sheath were also utilized including 4 mm tip non-irrigated RF ablation catheters (Blazer™ Boston Scientific, Marlborough, Massachusetts or Carto®Navistar®Biosense Webster, Irvine, California), 3.5 tip irrigated RF ablation catheters (Carto®ThermoCool®SFBiosenseWebster, Irvine, California or FlexAbility™ Abbot, Chicago, Illinois), and 8 mm tip cryoablation catheter (FREEZOR MAX™, Medtronic, Fridley, Minnesota).

Indications for RFW AP Ablation

Wolff-Parkinson-White (WPW) syndrome is defined as WPW ECG pattern and (1) the presence of palpitation, (2) documented spontaneous SVT, or (3) inducible SVT during EPS. During EPS, a RFW AP ablation attempt was performed (1) if the AP ERP was ≤ 250 ms, (2) if a SVT was inducible, or (3) if pre-excited atrial fibrillation with a short RR interval ≤ 250 ms was documented. In this study, each patient met at least one of these criteria and was therefore targeted for catheter ablation. Our ablation strategy relied first on localization of the earliest local ventricular signal along the tricuspid annulus during atrial pacing aiming to have maximal preexcitation. Also mapping during ventricular pacing or ORT was performed to localize earliest retrograde conduction in cases where mapping during maximal preexcitation proved challenging.

RF therapy was typically applied for 60 seconds at the effective site with additional lesions to follow unless no effect on AP conduction was observed after an initial 7-10 seconds. A power of 80 Watts was applied with an 8 mm tip large curve ablation catheter while a 35 to 40 Watts was used with an irrigated catheter. Cryo lesions were delivered at the effective site for 240 seconds with one additional lesion to follow unless no effect on AP conduction was observed within 30 seconds of lesion initiation.

Figure 1: **Patient Demographics**

Patient Characteristics	Right Free Wall n = 21
Age [avg, years]	39.3 +/- 13.7 [19 - 65]
Body Mass Index (kg/m^2)	30.6 +/- 7.0 [21 - 44]
Sex [% male]	6 / 21 (28.6%)
Medical Conditions (n, %)	
- Palpitations	20 (95.2%)
- (Pre)syncope	13 (61.9%)
- Hyperlipidemia	8 (38.1%)
- Hypertension	7 (33.3%)
- Diabetes	4 (19.0%)
- CAD	3 (14.3%)
- OSA	3 (14.3%)
- Asthma	1 (4.8%)
Medicines (n, %)	
- Beta Blocker	11 (52.4%)
- None	9 (42.9%)
- Class IC AAD	2 (9.5%)
- CCB	0
- Class III AAD	0
LVEF (%)	56 +/- 8 [40 - 73]
Prior RF/Cryo Ablation	6 / 21 (28.6%)

Abbreviations: avg = average, CAD = coronary artery disease, OSA = obstructive sleep apnea, AAD = antiarrhythmic drug, LVEF = Left Ventricular Ejection Fraction, RF = Radiofrequency.

Figure 2: Electrophysiologic Study and Associated Ablation Techniques and Outcomes

Procedural Analysis		Right Free Wall [n = 21]
EP Studies		N = 25
Ablations		N = 25
Acute Success Rate (%)		19/21 (90.5%)
Recurrence Rate (%)		4/19 (21.1%)
Total Success Rate, including redo ablation *Pathways Ablated / Pathway Patients (%)*		19/21 (90.5%)
Ablation Techniques & Outcomes *# Abl Success / # Abl Attempts (% Success)*	8 mm tip non-irrigated RF *w/ Steerable Sheath*	17/17 (100%) *13 (100%)*
	4 mm tip non-irrigated RF *w/ Steerable Sheath*	2/2 (100%) *1 (100%)*
	8 mm tip non-irrigated RF + 8 mm tip cryoablation *w/ Steerable Sheath*	1/2 (50%) *1 (0%)*
	4 mm tip non-irrigated RF + 8 mm tip non-irrigated RF	1/1 (100%)
	8 mm tip cryoablation	1/1(100%)
	4 mm tip non-irrigated RF + 3.5 mm tip irrigated RF *w/ Steerable Sheath*	1/1 (100%) *1 (100%)*
	4 mm tip non-irrigated RF + 8 mm tip non-irrigated RF + 4 mm tip irrigated RF *w/ Steerable Sheath*	0/1 (0%) *1 (0%)*
Failed Procedures *AP Loc: Ablation Technique, Reason*		- A: 4 NI + 8 NI + 4 IR RF + SS; Temp - L: 8 NI RF + 8 Cryo + SS; Temp
Recurrences *AP Loc: Initial Abl, Recur Time, Repeat Abl*		- P: 8 NI RF + SS, 1 d, s/p 8 NI RF + SS - PL: 8 NI RF, 2 mo, s/p 8 NI RF + SS - AL: 8 NI RF, 3 mo, s/p 4 NI RF + SS - AL: 8 NI RF + SS, 4 mo, s/p Cryo

Abbreviations: Abl = Ablation, AP = Accessory Pathway, Loc = Location, RF = Radiofrequency, A = Anterior, L = Lateral, P = Posterior, PL = Posterolateral, AL = Anterolateral, and SS = Steerable Sheath.

Statistical Analysis

Continuous data are expressed as the mean +/- standard deviation. Acute success rate refers to the ability to successfully ablate a patient's RFW AP during the index procedure whereas total success rate accounts for all ablation procedure attempts for a given patient. The relation between patient/ablation characteristics and recurrence/failure was evaluated by using an unpaired Student t-test. All analyses were performed using IBM SPSS ver. 26 (2019; IBM SPSS Statistics for Macintosh, Version 26.0. Armonk, NY: IBM Corp).

Results

Demographic Data

Twenty-one patients underwent an EPS and ablationfor symptomatic WPW syndrome patients with a RFW AP location. The mean age of patients was 39.3 +/- 13.7 (19 - 65) years with over two-thirds female and 7 with hypertension, 3 with coronary artery disease, and 3 with obstructive sleep apnea (Table 1).

Nearly all patients presented with palpitations (95.2%) and almost two-thirds had experienced syncope (Table 1).The most common medical therapy prescribed prior to ablation was beta blockade with 11 patients on various agents, 1 using flecainide in combination with beta blockers, while 1 other patient was prescribed flecainide monotherapy. Nine patients were not on any medical therapy prior to ablation.Six patients (28.6%) had priorablations before establishing with our center, one of whom had undergone 4 prior EP procedures.

Right Free Wall Accessory Pathway Characteristics

APs were localized fluoroscopically and with the aid of 3D mapping software and categorized in reference to their position about the TA: anterior (1), anterolateral (7), lateral (3), posterolateral (10), and posterior (3) with one undocumented site (Figure 1).Five patients (23.8%)had malignant APs based on unexplained syncopal events (2),evidence of pre-excited atrial fibrillation with an R-R interval < 250 msec and or an AP ERP < 250 ms(1).The average AP Effective Refractory Period was 303 +/- 56 (210 – 440)msec.

Ablation Techniques and Outcomes

Ablation was acutely successful in 19/21 (90.5%) patients. Two patients had unsuccessful attempts at ablation during the index procedure, in both cases due to poor catheter stability and inadequate tissue contact. In one case, the AP was located in an anterior location and in the other was in the lateral RFW. (Figure1).Pathway conduction recurred in 4 out of 19 acutely successful cases (21.0%). All 4 patients underwent successful repeat attempt at ablation, resulting in a total of 25 EPS/ablation procedures in 21 patients. Procedures on average lasted 2:10 +/- 0:45 hours with 21.6 +/- 16 minutes of fluoroscopy time for 18 +/- 13 ablation lesions over a range of power 78.5 +/- 14 (50 to 100) watts. A variety of catheters were used, sometimes separately within the same procedure, to facilitate ablation success with all procedures proceeding via right femoral venous access.An 8 mm tip non-irrigated RF ablation catheter alone was used in 17 (68%) procedures and combined with a steerable sheath in 13 of those. A 4 mm tip non-irrigated RF ablation catheter alone was used in 2 (8%)

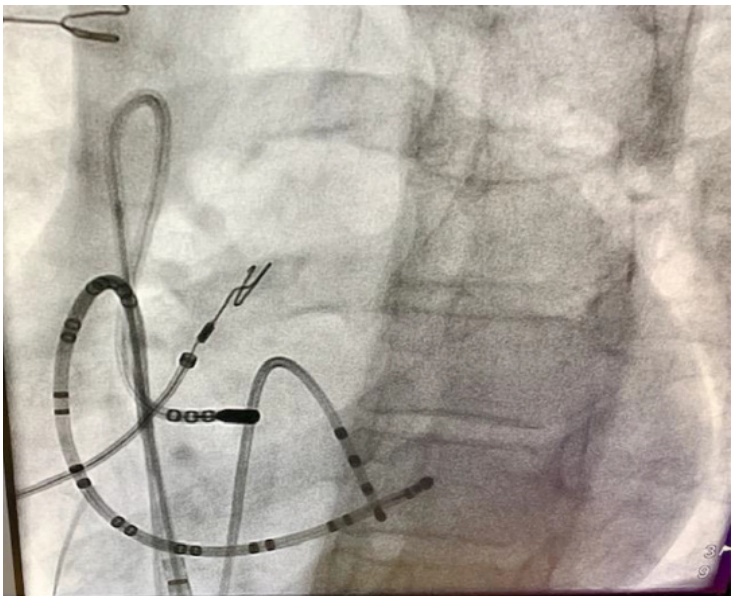

Figure 2: Catheter looped in the SVC down to the anterior tricuspid annulus to target a right free wall AP.

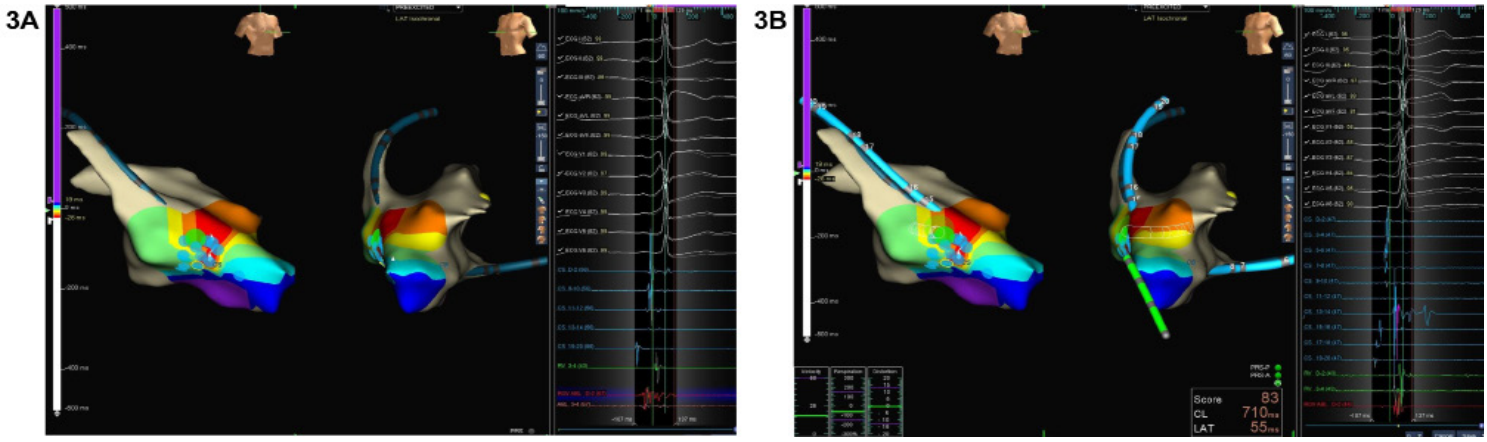

Figure 3: **3D mapping with ESI showing a lateral RFW AP with electrograms at the site of successful ablation (3A). Note disappearance of preexcitation after ablation (3B)**

procedures and combined with a steerable sheath in only one of those. An 8 mm cryoablation catheter alone was used in a single procedure (4%). The remaining 5 procedures utilized severalof the above catheters in isolation (Table2). Three of those remaining procedures included use of a steerable sheath for a total of 17 (68%) procedures utilizing this technology. Two complications were observed: 1 pericardial effusion in a patient who underwent epicardial mapping and ablation of RFW and a posteroseptal (PS) AP as well as 1 access site hematoma.

Out comes of Patients with Prior Ablation Attempts

Sixpatients (28.6%) had previously undergone at least one EPS +/- ablation at outside institutions of variable RFW AP locations before establishing at our center. Four of these patients with 2 posterolateral, 1 anterolateral, and 1 undocumented RFW AP location underwent successful repeat ablation of at our site using an 8 mm tip non-irrigated RF ablation catheter with or without a steerable sheath. None have had signs of recurrence at follow-up. One of these six had already undergone 4 EPS with ablations at prior institutions and upon repeat attempt at our site was found to have both a posterior RFW AP and a PS AP necessitating extensive epicardial mapping before successful ablation of both sites. This posterior RFW AP then recurred a single day after the procedure, but was successfully ablated again with the same combination of an 8 mm tip non-irrigated RF catheter and steerable sheath the following month.

The final of these six patients had undergone an EPS as a child and on reattempt at our institution was found to have a non-malignant, anterior RFW AP. Attempt at ablation during this procedure failed to eliminate the AP despite use of both small (4 mm) and large (8mm) tip non-irrigated catheters followed by 3.5 mm irrigated tip catheter with a steerable sheath.

Outcomes of Patients with No Prior Ablation Attempts

Among the 15 patients without prior EPS/ablation attempts, three patients had recurrence of their RFW AP and one patient had a failed ablation.

The three patients with a recurrent path way underwent successful repeat RFW AP ablation at [2, 4], and 11 months post-prior ablation. For a recurrent posterolateral RFW AP, an8 mm tip non-irrigated RF catheter was used but this time combined with a steerable sheath. For two recurrent anterolateral RFW APs, one repeat ablation utilized an 8 mm tip cryoablation catheter while the other combined a 4 mm tip non-irrigated RF catheter with a steerable sheath.The failed ablation occurred in a patient with a lateral RFW AP despite attempts with both an 8 mm tip non-irrigated RF catheter and an 8 mm tip cryoablation catheter combined with a steerable sheath.

Comparing patients and AP ablation characteristics between recurrent/failed and successful RFW AP did not reveal any univariate predictors of AP recurrence or ablation failure. All patient and procedural characteristics were found to be similar (Table 3). The median follow-up of these patients after index ablation at our center was 658 (IQR 127-1307) days with a range of 22 – 2828 days.

Discussion

This is a single center study with a 21 patients undergoing 25 ablations for RFW AP. Almost 30% had failed an ablation in a different center indicating that these ablations are typically challenging procedures. The outcomes of these ablations in a contemporary setting demonstrate some improvements over historical reports (91% vs. 75-85%). Recurrence rates however remain concerning (20%) comparable to previously reported recurrence rates (14%-35%). Ablation of APs on the tricuspid annulus is fraught with challenges of catheter stability and poor tissue contact. The use of steerable sheath is helpful in achieving stability[10]. In this study ≈ 70% of procedures involved the use of a steerable sheath. The use ofcryo catheter has the ability to adhere to the targeted ablation site and may overcome contact and stability problems encountered at the tricuspid annulus[16]. If the AP conduction is eliminated within 30 seconds, cryo application is typically continued for 240 seconds. In our practice, the use of cryo is often considered after failure of a large tip RF catheter. Its use as a first line ablation tool is uncommon mainly because of the higher recurrence rate with cryo therapy as compared to RF[16]. While the use of a superior approach (i.e. Right IJ) has been described to increase catheter stability and ablation success[8], we have not adopted this approach in our practice. Forming a Loop with the catheter from a starting position in the RA/SVC junction and maneuvering the catheter to the tricuspid annulus (Figure 2) may accomplish similar stability to a superior approach. We have

Figure 3: **Comparing Patient and Pathway Characteristics from those with recurrent or failed ablations to those with successful ablations at our institution**

Patient/Pathway Characteristics	Recurrent/Fail (n = 6)	Successful (n = 15)	P-Value
Age	39 +/- 10.8	39 +/- 14.7	0.98
Male (#, %)	4 (66.7%)	4 (26.7%)	0.13
BMI	30.5 +/ 4.4	30.6 +/- 7.4	0.95
Prior EPS +/- Abl (#, %)	2 (33.3%)	4 (26.7%)	0.79
AP Location (#, %)			0.62
Anterior	1 (16.7%)	0	
Anterolateral	2 (33.3%)	3 (20.0%)	
Lateral	1 (16.7%)	2 (13.3%)	
Posterolateral	1 (16.7%)	8 (53.3%)	
Posterior	1 (16.7%)	1 (6.7%)	
Undetermined	0	1 (6.7%)	
AP ERP (ms)	340 +/- 60	291 +/- 47	0.27
Procedure Duration (hr:min)	2:47 +/- 0:35	2:03 +/- 0:45	0.14
Fluoroscopy Duration (min)	46 +/ 19	15 +/- 6	0.06
Ablation Lesions (#)	42 +/- 22	14 +/- 10	0.11
Ablation Power (watts)	84 +/- 12	76 +/- 14	0.37
Ablation Duration (min)	15.6 +/- 7.3	18.5 +/- 17.4	0.7
Energy Used (#, %)			0.45
Non-irrigated RF	6 (100%)	15 (100%)	
Irrigated RF	1 (16.7%)	1 (6.7%)	
Cryo	1 (16.7%)	1 (6.7%)	
Steerable Sheath Used (#, %)	5 (83.3%)	9 (60.0%)	0.29

Statistics reported as average +/- standard deviation or occurrence (%) unless otherwise specified. Abbreviations: AP ERP = Accessory Pathway Effective Refractory Period, RF = radiofrequency.

utilized this technique when the typical femoral approach has failed (Figure 2). In our experience this approach works best with anterior RFWAP (AP located at 11 and 12 o'clock along the tricuspid annulus). The high recurrence rate seen in this study and in prior similar studies is probably related to the poor tissue contact and catheter stability, which result in reversible tissue damage. Another explanation for the higher failure rate of RFW AP ablation is the presence of multiple atrial insertions. Li et.al. reported on the presence of multiple atrial insertion sites in 10 patients with RFW AP. Ablation was successful only after targeting all atrial insertion sites[17].

Several factors could explain the improved outcomes in this study compared to older published reports. The use of steerable sheath, large tip ablation catheters or irrigated catheters could help achieve more stability and a more effective temperature delivery. The availability of cryocatheter also provide another mean for success when traditional RF ablation fails. The use of intracardiac echocardiography could help overcome some anatomical barriers for success. The use of 3D mapping is paramount in localizing the area of interest especially in this setting where catheter stability is suboptimal.

Contact force catheter is a technology that could improve the outcomes of RFW AP ablation; an ablation that is fraught with challenges related to poor tissue contact and catheter stability.

Study Limitations

This is a single center study with a relatively small number of patients. Contact force catheter was not used routinely nor, were some advanced mapping techniques such as "open window" mapping. Nevertheless, ablation of RFW APis relatively uncommon in adult patients and this study reports on contemporary ablation outcomes in patients with RFW AP.

Conclusion

Ablation of RFW AP in a contemporary setting is associated with good success rate but high recurrence rates. Future technologies and procedural technique should focus on means to increase catheter stability and effective temperature delivery.

Conflict of Interest

Mikhael El-Chami is a consultant for Medtronic, Boston Scientific and Biotronik.

All other authors have no conflict of interest to report. The IRB approval number and date are iIRB00111508 and May 7th, 2019.

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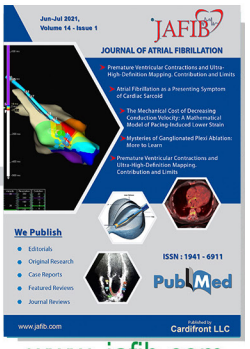

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Premature Ventricular Contractions and Ultra-High-Definition Mapping. Contribution and Limits

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Abstract

Background: The utility of ultra-high definition mapping (UHDM) for ablation of premature ventricular contractions (PVC) remains undetermined. The aim of this study was to investigate UHDM for PVC ablation, and additionally to compare to conventional technique.

Methods: Twenty patients investigated using UHDM were prospectively included and analyzed. Electrophysiological caracteristics and results were compared to 40 patients ablated using fluoroscopy only.

Results: 2541±2033 EGMs and 331±240 PVC beats were recorded for each patient. Surfaces of isochronal activations were 2.3±1.7 and 6.9±6.1 cm2 (first 10 and 20 ms). Local scar was present in 40% and local block in 65%. Areas of pace-mapping > 95, 90 and 85% concordance were 1.5±3.4, 2.1±3.9 and 3.3±5 cm2. Mean distance between the ablation site and the site of best pace-mapping or of earliest activation was 8±8 mm and 5±7 mm. Pre-potential was noted in 17% vs 26% controls (ns). QS pattern was present in 83% vs 83% controls (ns), and earliest activation was - 31±50 vs - 25±14 ms in controls (ns). Procedure (100±36 vs 190±51 min, p< 0.0001) and fluoroscopy duration (15±9 vs 24±9 min, p=0.005) were shorter in controls. Acute success was achieved in 65% patients with UHDM and in 72% controls (p=ns) with lower residual PVC burden in the control group. Over a follow-up of 19±12 months, long-term success was similar between groups (65 vs 68%).

Conclusion: UHDM may reveal poorly recognized activation features and PVC mechanism. In this series, conventional mapping was quicker and did clinically as well as UHDM.

Introduction

Percutaneous catheter ablation has become a therapeutic of choice for patients with premature ventricular contractions (PVC), because of a safe and efficient procedure with good long-term results [1] and because of increasing evidence for the potential deleterious effects of frequent PVCs. Current guidelines favor ablation over antiarrythmic drug therapy for PVC in many situations [2], probably leading to an even more relevant increase in the number of procedures in the future.

The best mapping and ablation technique for PVC remains undetermined. Conventional techniques associate pace-mapping and/or activation mapping based on fluoroscopy only, currently reaching satisfying although imperfect acute and long-term success rates [2-4]. 3D mapping techniques are now largely utilized for many if not most ablation of atrial or ventricular tachyarrhythmias, reducing radiation exposure and allowing more precise mapping, but their true interest for other substrates remains debated. 3D mapping has been occasionally [5-7] or more largely [8-12] used for PVC ablation, but it remains unclear what is the real interest regarding mechanisms and precision in anatomical location of the PVC foci, and which are the benefits in comparison to conventional technique [11].

Ultra-high definition mapping using the Rhythmia ™ system seems to more precisely highlight complex mechanisms [13,14]. This system could be useful for achieving a high level of precision for PVC ablation, while speeding and refining the acquisition process because of the high number of collected EGMs while automatically rejecting interfering nonclinical PVCs. However, it has been rarely reported for PVC ablation so far, with a few case reports [5-7] and descriptive short series [15,16].

The aim of this study was to prospectively investigate the additional capacities of ultra-high definition mapping (UHDM) for PVCs using the Rhythmia ™ system and additionally to compare the characteristics

Key Words

Ablation ; Fluoroscopy ; Mapping ; Premature Ventricular Contraction

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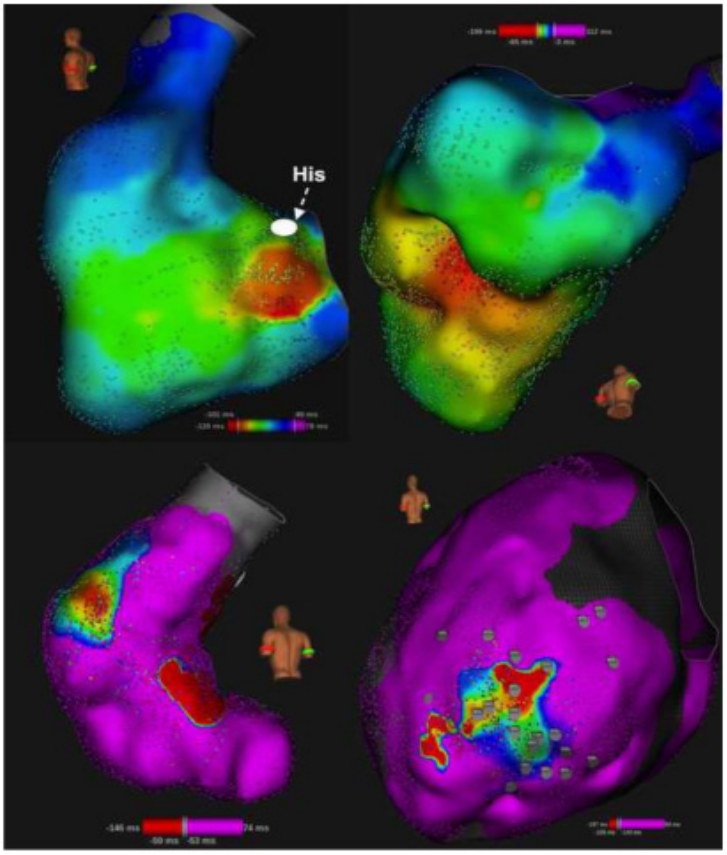

Figure 1: Four exemples of ultra-high definition mapping of various PVCs. Upper left: para-hisian PVC. Upper right: papillary muscle PVC. Lower left: RVOT PVC with dual breakthrough (arisng in fact form the right aortic cusp). Lower right: post-myocardial infarction PVC (grey tags = sites of pace-mapping with % of correlation compared to the QRS template of the PVC as calulated by the Boston Scientific LabSystem™ PRO recording system).

and efficacy of PVC ablation using UHDM compared to conventional technique.

Methods

Twenty consecutive patients referred for ablation of PVCs using the Rhythmia system ™ at our center were prospectively included.

1. Activation mapping :

Activation mapping was performed with the Rhythmia ™ system (Boston Scientific, Inc, Cambridge, MA) in each patient. Briefly, PVC were mapped using the Orion ™ multipolar basket-like catheter (64 electrodes of 0.4 mm2 surface and 2.5 mm interelectrode spacing) with the following operator-defined beat acceptance criteria : respiration gating, stable catheter location, tracking quality and QRS morphology analysis as compared to the template of a reference PVC. Maximal distance of electrodes to anatomical shell was 3 mm. Bipolar electrograms were filtered at 30 and 300 Hz and unipolar electrograms at 1 and 300 Hz, without a notch filter. Local activation time was automatically set to the timing of maximal amplitude of events on bipolar recording.

UHDM was especially performed in the area of earliest activation. Surfaces of isochronal activations –i.e. areas activated over a given range of time – were calculated using system proprietary calipers and serve as a harbinger for local depolarisation velocity. Presence of local block –i.e. some curvature or delay in some direction of the propagating activation wavefront coming from the focal area of origin- was noted.

Presence of a pre-potential (isolated presystolic potential in front of the QRS complexe) was also noted. At the site of interest, precession of the earliest activity on bipolar recordings compared to the QRS onset was measured, as well as the presence of QS pattern on uniporal recordings. Presence of local scar – i.e. < 0.2 mV in bipolar voltage map - [17] before ablation at the area of interest was noted.

The Lumipoint ™ algorithm and especially the « skyline » graph was aslo tested. In addition to usual voltage and activation time annotation, each electrogram was processed to detect all activity even if mutiple during the same cycle, reflecting the presence of deflections for each time point [18]. The "Skyline" graph reflects the surface area associated with active electrograms at each time as a fraction of the total surface area of the map and may therefore be indicative for specific PVC related activation characteristics.

2. Pace-mapping :

Pace-mapping was performed in each patient in the area of interest using the Orion ™ catheter (using the dipoles in closest contact to the endocardial surface) or the ablation catheter, with 10 V output and 1 msec duration. For each site of pace-mapping, the % of correlation compared to the QRS template of the PVC was calulated by the Boston Scientific LabSystem™ PRO recording system [19]. For patients with a sufficiant number of good pacing sites, areas of sites with pace-mapping > 95, 90 and 85% concordance were calculated using the system calipers.

Finally, the distances between the successful ablation site and the sites of best pace-mapping and of earliest activation were measured on the maps.

In a second part of the study, fourty age and gender-matched consecutive unselected patients undergoing conventional fluoroscopic-guided ablation without 3D mapping system during the same period and by the same operators were retrospectively collected and serve as the control group. Ablation was performed in these patients under fluoroscopy only and according to standard techniques, mainly based on activation mapping (earliest activation in bipolar recordings compared to the QRS and QS pattern in unipolar recordings) and limited pace-mapping (analysis based on visual inspection and simply quantified as the proportion of ECG leads where the paced QRS were

Table 1: Clinical characteristics of the population

	Ultra-high density mapping n=20	Conventional mapping n=40	p value
Male gender	13 (65%)	21 (52%)	ns
Age (years)	53±21	60±13	ns
Structral cardiomyopathy	8 (40%)	12 (30%)	ns
PVC induced CM	7 (35%)	16 (40%)	ns
LVEF (%)	46±15	46±15	ns
Anti-arrhythmic drugs or beta-blocker	16 (80%)	32 (80%)	ns
Redo procedure	6 (30%)	2 (5%)	0.007
PVC number/24 hours	12944±9714	18889±12554	ns

Table 2: Location of PVC in each group

	Ultra High density mapping n=20	Conventional mapping n=40	p value
Right/left/PVC ablated from both ventricles	5/14/1	12/22/6	ns
RVOT	5 (25%)	15 (37%)	ns
LVOT/aortic cusp/LV summit/CS/MA cont	8 (40%)	19 (47%)	ns
Papillary muscle	4 (20%)	1 (2.5%)	0.02
Multiple locations	0 (0%)	7 (17%)	0.04

RVOT: right ventricular outflow tract, LVOT: left ventricular outflow tract, LV: left ventricle

visually similar in shape and morphology to the reference PVC, with attemps to achieve matching between paced QRS complex and PVC in ≥11/12 ECG leads) [11, 20, 21]. Mapping in this group was performed using the ablation catheter only.

Ablation was performed with 4 mm tip irrigated catheters (Thermocool Biosense™ or Mifi OI Boston ™) and 30 to 50 W power in both groups, without contact force assessment. Acute success was defined by the complete elimination of PVC at the end of the procedure, with and without isoproterenol infusion. Twenty-four hours ambulatory recording was performed in each patient during the following days and again at least once during the follow-up. Long-term ablation success was defined by a 80% decrease in PVC burden [4, 22] on latest ambulatory recording. Signed informed consent was obtained from each patient. The study was approved by national ethical comity n° RCB 2017-A005777-46 on the 28/04/2017.

Statistics

Continuous variables are reported as mean±SD and compared with unpaired t-test. Categorical variables were compared using Fischer's exact test. Analysis and calculations were performed using StatView ™ program (Abacus Concepts, Inc. Berkeley, CA 1992-1996, version 5.0). A p value < 0.05 was considered statistically significant for each analysis.

Results

Twenty patients were included in the UHDM group and forty in the control group. Clinical characteristics are shown in table I.

Except for more redo procedures in the first group, there was no other difference between patients with UHDM and controls. Underlying structural heart disease associated ischemic cardiomyopathy (n=4), valvular (n=6), congenital (n=2) or dilated cardiomyopathy (n=8) (ns between groups). Fifteen (75%) and 7 (35%) patients from the UHDM group were on beta-blockers or class I or III anti-arrhythmic drugs versus 25 (62%) and 12 (30%) in the control group respectively (p=ns). PVC origin was depicted in table II.

There was no significant différences in PVC origin between groups, except for a higher prevalence of papillary muscle sites in the UHDM group, while more multiple locations were present in the conventional group.

Patients with UHDM:

A mean of 2541±2033 EGMs and 331±240 PVC beats were recorded for each procedure, with a mean duration of mapping of 42±17 minutes.

Surfaces of isochronal activations were 2.3±1.7 cm2 for isochronal 10 ms and 6.9±6.1 cm2 for isochronal 20 ms. Local scar was present in 8 cases (40%) and more frequently in case of cardiomyopathy (p=0.01) but not related to redo cases. Presence of local block or curvature of the wavefront was noted in 11 of the 17 cases (65%) where PVCs were present during mapping, without correlation with local scars or existing cardiomyopathy. Mean number of pace-mapping sites for each patient was 10±5. Best concordance was 89±11%. Areas of pace-mapping > 95, 90 and 85% concordance were 1.5±3.4, 2.1±3.9 and 3.3±5 cm2 respectively.

Mean distance between the final ablation site and the site of best pace-mapping and the site of earliest activation was 8±8 mm and 5±7 mm respectively. The "Skyline" graph, even if interesting, was deceptive due to the lack of available quantitative measurements/datas and this hindered to objectively investigate this algorithm.

Examples of PVC mapped using UHDM are seen in fig 1.

Control group : pace-mapping achieved similar QRS morphology compared to the PVC in a mean of 11.2±1.4 out of 12 ECG leads.

Comparisons with the control group: More patients in the UHDM group displayed bi/trigeminy patterns of PVCs during the procedure (nine in each group, p=0.07). Presence of a pre-potential was noted in 3 of 18 patients (17%) with UHDM and in 8 of 36 controls (25%) (ns). At the site of interest, QS pattern on unipolar recordings was noted in 15/18 (83%) UHDM patients versus 29/35 (83%) controls (ns), and precession of the earliest activity on bipolar recordings compared to the QRS onset was - 31±50 ms and - 25±14 ms in controls (ns).

Number of RF application was 9±5 vs 6±5 for conventional ablation (p=0.08). PVC morphology changed during RF ablation in 7 patients (35%) with UHDM and in four controls (10%) (p=0.02), leading to new targeting and new lesions. Procedure duration was significantly shorter in conventional procedures (107±43 vs 190±51 minutes, p<0.0001), as was fluoroscopy duration (16±11 vs 24±9 minutes, p=0.008).

Acute success was achieved in 13 patients with UHDM (65%) compared to 29 controls (72%) (p=ns), with significant reduction in PVC number on post-ablation ambulatory recording in the whole population (from 15523±11499 to 2791±5603, p<0.0001). PVC number decreased more in the conventional group (12249±92529 PVC less vs 6154±11857, p=0.05) with lower residual PVC burden (4622±8316 vs 1852±3266 in controls, p=0.07) with borderline differences.

No anti-arrhythmic drug was prescribed in 28 patients (47%), while 23 patients were discharged or later treated with beta-blockers and 9 were prescribed class I or class III drugs (ns between groups). Three patients were lost to follow-up. Over a mean follow-up of 19±12 months (ns between groups), long-term success was achieved in

38/57 patients (67%), without difference between groups (65 vs 68%). There was no difference in long-term success when redo procedures or patients with papillary muscle PVCs were excluded.

Discussion

We analyzed in this study the characteristics of PVC ablation using UHDM and further compared with conventional fluoroscopic techniques in another group of patients. Beside obtaining interesting datas on UHDM for PVC, we found that procedures performed using UHDM were longer and led to longer fluoroscopy duration, but did not translate in higher acute or long term success, despite achieving refined location of the focus and obtaining interesting findings.

The best mapping and ablation technique for PVC remains undetermined. Satisfying although imperfect acute and long-term success rates are currently achieved using conventional techniques based on fluoroscopy and combining pace-mapping and/or activation mapping [2-4]. The advent of 3D mapping techniques dramatically changed the paradigm of catheter ablation, so that most atrial or ventricular tachyarrhythmias are currently managed using 3D electroanatomic systems, reducing radiation exposure and allowing more precise mapping. However their true interest and cost-effectiveness for other substrates remains to be proved. 3D mapping has been casually [5-7] or more widely [8-12] used for ablation of PVC, but additional benefits in comparison to conventional technique remain unclear, for example regarding efficacy, mechanisms and precision in anatomical location of the PVC foci. Conventional fluroscopy-based ablation of VT and PVC from the right ventricular outflow tract (RVOT) had been shown to be comparable to first generation-3D mapping systems in terms of acute results, with or without shorter fluroscopy/procedure duration [11, 23], but multipolar catheters were not used at that time. To date, no study has compared UHDM to fluorscopic techniques for PVC ablation, and no data on the PVC characteristics using UHDM is available.

UHDM using the Rhythmia ™ system found a 86% acute and long-term success rate in a short series of 7 cases, emphasizing the automatic ECG template matching algorithm used as a beat selection criteria in this system [15]. Safety and full acute efficiency was recently reported in a series of 17 cases with significant long-term PVC burden reduction [16].

UHDM using the Rhythmia ™ system in our series revealed still unexplored features of myocardial activation during PVCs and of pace-mapping.

1. Local scar was present in 40% of cases, more frequently - but not only - in presence of structural heart disease, together with some local block or curvature of the wavefront in 65%, without correlation with local scars or presence of cardiomyopathy. This may imply some local conduction disturbance and/or fibrosis, even in apparent healthy hearts, and that PVCs may be caused by local reentry in some cases, although local activation during the preceding sinus beat was not studied. Additionally, PVC may arise remote from scar areas in patients with cardiomyopathy.

2. Analysis of isochronal activations shows that a mean of 2.3 cm2 of endocardial surface is activated during the first 10 ms and 6.9 cm2 during the first 20 ms. This means that averaged velocity of activation is around 0.85 m/sec at the breakthrough of activation, then decreases to 0.65 m/sec, possibly due to less recruitment of Purkinje cells or more fibrosis as the activation spreads or because of more tightly coupled cardiomyocytes at the focus location.

3. Areas of good pace-mapping ranged from 1.5 to 3.3 cm2, which were of the same order to the area of 10 ms earliest activation. However, best pace-mapping sites and earliest activation sites located relatively remote to the final ablation site, with a mean distance of 8 mm and 5 mm respectively. This may signify that these refined and detailed patterns using UHDM are in fact not really relevant for locating the effective focus site. When compared to conventional mapping, neither the presence of pre-potential (present in only a minority), nor local precession on bipolar activation or QS pattern in unipolar recordings (present in a majority) benefited from UHDM. This implies that conventional mapping alone is sufficiant to provide these informations.

Beside giving some additional information about the focus location regarding anatomical structures and mechanisms, 3D systems are expected to decrease radiation exposure, although this was not the case in our series. Reasons for this are the more direct targetting of the culprit focus without building unnecessary complete map of the whole ventricle with its associated additional duration and fluoroscopic exposure, even if minimized due to the use of electroanatomical system. Unavoidable shifts and mistrust in the reliability of anatomical reconstruction and catheter location implies also relevant additional durations of fluoroscopy to correct maps and check true catheter location in our experience, while simple fluoroscopic navigation does not suffer from these drawbacks. Moreover, recent progress in fluoroscopic equipments are currently leading to very low irradiation dosings, sometimes close to the level of radiations met in leisure activities (unpublished data). Finally, changes of PVC morphology during ablation was more frequent using UHDM, possibly because of incomplete initial ablations changing the PVC exit, needing new targeting and new lesions and thus increasing the duration of the procedure and fluoroscopy. This was also reflected by the larger number of RF application needed in UHDM patients.

Acute and long-term success were similar using conventional or UHDM techniques in this series, recognizing that the UHDM group included more redo procedures and more papillary muscle, which may have selected more challenging cases, but less multiple foci and more bigeminy/trigeminy which may render procedures more easy. Even if these differences may favor one technique or another, they probably do not have true relevance in interpretating the results. Moreover, there was no difference in acute and long-term success when patients with papillary muscle PVCs or redo procedures were excluded. Thus, PVC ablation may not beneficiate from UHDM techniques in trained hands, because achieving higher anatomical precision in activation or pace-mapping does not translate into a better result, or because of the lack of true enhanced precision provided by 3D systems.

No such comparison seemed to have been performed using UHDM before. There is probably no reason to achieve more reliable activation mapping using UHDM. In fact unipolar QS patterns or earliest bipolar activation did not differ compared to fluoroscopic mapping in our study. Visual analysis of EGMs are probably at least

as good as automated annotations by the 3D system, because some early activations are difficult to correctly annotate, while being highly suggestive at visual inspection, and because detection of QS pattern in unipolar recordings cannot be currently automatized.

Studies investigating automated versus visual analysis of pace-mapping are scarce : using a software available within the Boston Scientific EP system (LabSystem™ PRO) there was a significant correlation between automated template-matching and visually judged pace-map scores [24]. However, the template matching score reached a larger area under the ROC curve than the pace-map score for successful ablation sites, meaning that automated template matching was a better discriminator than the visual judgment by experienced electro-physiologists [24].

Automated template matching of the Rhythmia™ system has been demonstrated in-vivo to have high specificity and sensitivity, with a pace-mapping spatial resolution of 2 mm [25]. The automated pace mapping system software (PaSo ™ module, CARTO XP v9, Biosense/Webster) allows direct comparisons between paced ECGs and the PVC [12,26]. Impressive results have been described using PaSo ™ module and contact force catheter in a retrospective study [12], which are not consistant with results from most other groups. Interestingly, local precocity of the signal during PVC was not correlated to pace-mapping in this study, and additional RF were needed in surrounding areas in patients with ineffective RF applications based on the PaSo ™ module [12]. Pace-mapping alone using the PaSo ™ module was associated to a more usual 76% long-term success in another study [9].

Other template-matching techniques has been proposed such as manual scoring (similar R/S ratio and fine notching in each lead, maximal 24 points) [27] or using diverse sophisticated mathematical calculations by custom written softwares [21, 28] such as correlation coefficient (from - 1 for completely opposite waveform to + 1 for identical waveforms) and mean absolute deviation (from 0% for two identical waveforms to 100% for completely different waveforms, tending to be more sensitive to differences in waveform amplitude) [28] or others [28,29].

Using these techniques in patients with PVC from RVOT, pace maps with good correlation coefficient were confined to an area of 1.8 cm2 while the area of the first 10-ms isochrone measured 1.2 cm2, and pace-mapping was unreliable in identifying the site of origin in a fifth of patients [21]. However to the best of our knowledge, no comparison with visual analysis using simple scoring on the 12 ECG leads has been made.

In conclusion, conventional mapping techniques do as well as UHDM for PVC ablation, probably needing more experience than physicians dependent on 3D mapping, while achieving comparable acute and long-term success. UHDM however may reveal still unrecognized activation features and PVC mechanism the conventional techniques cannot do, whose clinical interest could only be demonstrated by additional works.

Limitations

Intra-cardiac echocardiography was not used in this study. Although potentially useful, especially for PVC from the papillary muscles, it requires additional costs and learning curve and is not widely utilized in France to date.

Non invasive ECG imaging (30) was not used here. Even if potentially interesting in planing ablation procedure and technique, it remains to be proved that this technique achieves better results compared to UHDM or conventional mapping for PVC ablation.

Although we tested the Lumipoint ™ algorithm, the lack of available quantitative data avoided any objective investigation. Additional improvements of the algorithms are needed before exploring its capacities in PVC mapping.

Finally, unexplained catheter displacements using 3D system have recently been demonsrated for PVC mapping and considered as an issue [31]. This is said to be possible using the Rythmia ™ system also [31] and may explain some discrepancies between catheter locations between sinus beats and PVC. This does not happen of course with conventional mapping.

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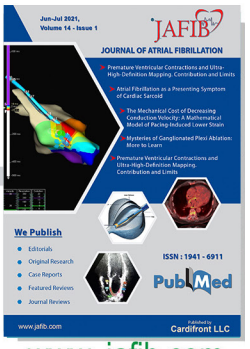

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Procedural Safety and Efficacy for Pulmonary Vein Isolation with the Novel Polarx™ Cryoablation System: A Propensity Score Matched Comparison with the Arctic Front™ Cryoballoon in the Setting of Paroxysmal Atrial Fibrillation

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Abstract

Background. The novel Polarx™ cryoablation system is currently being studied for atrial fibrillation (AF) ablation. To the best of our knowledge, no study comparing the novel cryoablation system with the standard Arctic Front™ cryoballoon is available in today's literature. This study aims to compare Polarx™ and Arctic Front™ cryoballoon in terms of safety and efficacy.

Methods. From a total cohort of 202 patients who underwent pulmonary vein (PV) isolation for paroxysmal AF through cryoablation, a population of 30 patients who used Polarx™ were compared with 30 propensity-score matched patients who used Arctic Front™.

Results. Pulmonary vein occlusion and electrical isolation were achieved in all (100%) veins with a mean number of 1.09 ± 0.3 occlusion per vein using Polarx™ and 1.19 ± 0.5 occlusion per vein using Arctic Front™ (p = 0.6). Shorter procedure and fluoroscopy time were observed with Polarx™ group (60.5 ± 14.23 vs 73.43 ± 13.26 mins, p = 0.001; 12.83 ± 6.03 vs 17.23 ± 7.17 mins, p = 0.01, respectively). Lower cumulative freeze duration per vein was also observed with Polarx™ (203.38 ± 72.03 vs 224.9 ± 79.35 mins, p = 0.02). There was no significant difference in isolation time between the two groups (34.47 ± 21.23 vs 34.18 ± 26.79 secs, p = 0.9).

Conclusion. The novel Polarx™ cryoablation system showed similar efficacy in vein occlusion and isolation and safety profile when compared to Arctic Front™ cryoablation system. Procedure time, fluoroscopy time, and cumulative freeze duration were significantly lower with Polarx™ cryoablation system.

Introduction

The pulmonary veins (PV) play a key role in the pathogenesis of atrial fibrillation (AF) and their isolation is associated with freedom from AF [1]. PV isolation using catheter ablation is achieved through different sources (laser, radiofrequency, cryoenergy) and is being increasingly performed worldwide. Cryoablation has high efficacy in isolating PVs, low rate of complications, more reproducible and less operator dependent outcomes, and is proven superior to antiarrhythmic drugs (AADs) in preventing AF recurrence [2-4], making it standard of care for numerous institutions for AF management. Over the years, Arctic Front™cryoballoon(Medtronic, USA) has been paving the way for the science of AF cryoablation [5-9]. The Polarx™ cryoablation system (Boston Scientific, USA) has been very recently released on the market, with modifications designed to potentially improve workflow for PV isolation. The present study aimed to compare the safety and efficacy of the new Polarx™ cryoablation system with the standard Arctic Front™ cryoablation system.

Key Words

Atrial fibrillation; Cryoballoon; Arctic Front; Polarx.

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Aim of the study

The aim of the study was to compare the new Polarx™ cryoablation system with the standard Arctic Front™ cryoballoon in terms of safety and efficacy during PV isolation for AF.

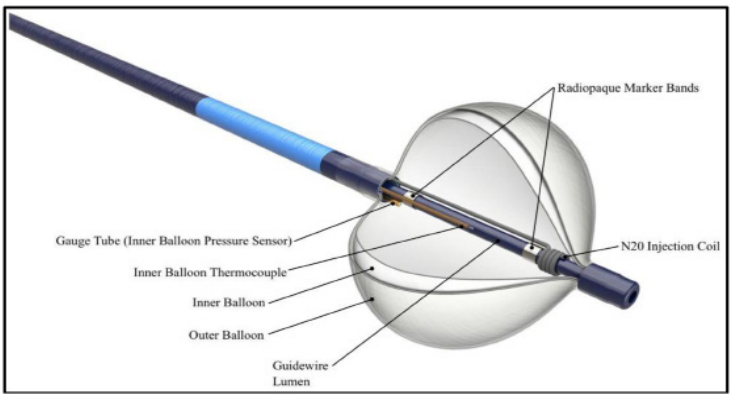

Figure 1: Cross section of the novel POLARx™ cryoballoon catheter, showing integral parts of the balloon catheter. Image courtesy of Boston Scientific.

Methods

Study Population. All patients who underwent PV isolation for paroxysmal AF using Polarx™ cryoablation system and Arctic Front™ cryoablation system from March 2 to October 16, 2020 were included in this study. The study was retrospective in nature and approved by the local ethics committee of our institution. All patients underwent cryoablation procedure with standard protocol in our institution.

Preprocedural management. All patients provided written informed consent to the ablation. A transthoracic echocardiogram (TTE) was performed one week prior to ablation for assessment of structural heart disease. To exclude the presence of thrombi, transesophageal echocardiography (TEE) was performed on the day of the procedure. All patients underwent pre-procedural cardiac computed tomography (CT) scan to assess left atrium (LA) and PV anatomy. The LA anteroposterior diameter was assessed by TTE on parasternal long-axis M mode and indexed to body surface area. Antiarrhythmic drugs (AAD) were discontinued at least 3 days before the scheduled ablation.

Polarx™ cryoablation system. The novel cryoablation system is composed of a Polarx™ cryoballoon (Boston Scientific, USA) that is maneuvered in the left atrium through a steerable sheath (PolarSheath™, Boston Scientific, USA). Aninner-lumen mapping catheter (ILMC) (PolarMap™, Boston Scientific, USA) is placed inside the cryoballoon inner lumen and positioned in the ostium of each PV. The system is connected to a console (SmartFreeze™, Boston Scientific, USA) which controls, monitors, and records the different phases of cryoablation (inflation, freezing, deflation). For this study, we used the short-tip Polarx™ cryoballoon catheter. See Figure 1 for Polarx™ cryoablation system.

Arctic Front™ cryoablation system. The standard cryoablation system is composed of the Arctic Front Advance Pro™ cryoballoon catheter (Medtronic, USA) that is maneuvered in the left atrium through a steerable sheath (FlexCath Advance™, Medtronic, USA). AnILMC (Achieve™mapping catheter, Medtronic, USA) is placed inside the cryoballoon inner lumen and positioned in the ostium of each PV. The system is connected to a console (CryoConsole™, Medtronic, USA) which controls, monitors, and records the different phases of cryoablation. See Table 1 for description and difference between the 2 cryoablation systems. See Figure 2 for Arctic Front™ cryoablation system.

Cryoballoon ablation procedure. All procedures were done by two primary operators who both performed more than1,000 Arctic Front cryoballoon each. Procedures were performed under general anesthesia. Under TEE guidance, an 8.5-Fr transeptal sheath (SL-0, Abbott) with a Brockenbrough needle (BRK-1, Medtronic) was advanced to the LA and exchanged for the cryoballoon steerable sheath. The cryoballoon and ILMC were advanced in each PV ostium to obtain baseline electrical information. The cryoballoon was inflated and gently advanced to occlude each PV. Pulmonary vein occlusion was assessed with contrast injection. Optimal vessel occlusion is when contrast injection showed total contrast retention inside the PV with no backflow to the LA. Activated clotting time was maintained at 250 seconds by an initial intravenous bolus of heparin with supplemental heparin boluses as required. Protamine was administered after the procedure and manual pressure was applied on the access site after removal of sheath and catheters.

Assessment of electrical isolation. Pulmonary vein electrical isolation was recorded with the ILMC positioned at the proximal site in the ostium before cryoablation of each PV. If PV potentials were visible during cryoablation, time to isolation (TTI) was recorded when PV potentials disappear or were dissociated from LA electrical activity. If PV potentials were not visible during ablation due to a distal positioning of the ILMC, the latter was retracted after completion of the cryoablation to a more proximal position to examine the PV potentials.

Duration of cryoenergy application. A single 180-second application was delivered for each vein with TTI or temperature of less than -40 ºC within one minute of cryoablation, otherwise a bonus freeze was delivered. Cryoablation was immediately terminated if there was weakening of diaphragmatic contraction.

Phrenic nerve monitoring. Right phrenic nerve function was monitored during right-sided PV cryoablation by locating and pacing the right phrenic nerve with a 1200-ms cycle and 20-mA output. The diaphragmatic capture was monitored by the operator's hand on the patient's abdomen for both Arctic Front™ and Polarx™ cryoablation and through the diaphragmatic movement sensor (DMS) accelerometer attached on the patient's right upper abdomen for the Polarx™ cryoablation. Cryoablation was terminated when weakness

Table 1: Description and difference between Polarx™ and Arctic Front™ cryoablation system

	Polarx™	Arctic Front™
Cryoballoon	Polarx™ Diameter: 28mm	Arctic Front Advance Pro™ Diameter: 28mm
Steerable sheath	PolarSheath™ 155° deflection	FlexCath™ 135° deflection
Mapping Catheter	Polarmap™ Diameter: 20mm Electrode: 8	Achieve Advance™ Diameter: 25mm Electrodes: 10
Console	SmartFreeze™ Foot pedal option Diaphragm movement sensor	CryoConsole™

Table 2: Baseline characteristics

	Polarx™ (N, 30)	Arctic Front™ (N, 30)	P value
Gender, male	20 (66)	18 (60)	0.5
Age, years	57.47 ± 15.24	53.53 ± 16.24	0.3
Hypertension	10 (33)	9 (30)	0.7
Dyslipidemia	9 (30)	8 (26)	0.7
Diabetes	1 (3)	2 (6)	0.5
Heart failure	3 (10)	1 (3)	0.3
Coronary artery disease	1 (3)	3 (10)	0.3
Prior embolic event	0	1 (3)	0.3
Left atrium volume index	31.5 ± 8.23	31.87 ± 7.31	0.8
CHA_2DS_2VASc score	1.27 ± 1.33	1.13 ± 1.40	0.7

Data presented as N (%) or mean ± SD; AF, atrial fibrillation

of diaphragmatic movement was noted.

Post ablation management. Patients were admitted in the intensive care unit and continuously monitored with electrocardiogram (ECG) telemetry for at least 18 hours. Post-procedure lower extremity ultrasound and TTE were performed the day after the procedure to assess complications such as pseudoaneurysm, hematoma, cardiac structural damage, or pericardial effusion. If without complication, patients were discharged the day after the procedure. Oral anticoagulation was resumed on the evening of the procedure and continued for at least 3 months.

Statistical analysis. Continuous variables were expressed as mean ± standard deviation (SD) and significant differences were analyzed by Student t-test. Categorical data were expressed as number and percentages and compared by Chi square test. Propensity-score matching was performed in order to compare the outcome between Arctic Front™ group and Polarx™ group. Patients were matched in a 1:1 ratio based on propensity scores calculated for each patient using multivariable logistic regression based on age, gender, CHA_2DS_2VASc score, and presence of LA dilatation (LAVi>34 ml/m2) as covariates. A 2-tailed probability value of <0.05 was deemed significant. Statistical analyses were conducted using SPSS software (SPSS version 27, Armonk, NY, USA).

Results

Baseline characteristics. A total of 202 consecutive patients with paroxysmal A Funderwent cryoablation and were included in our study. Thirty patients who underwent cryoablation using Polarx™ and 172 using Arctic Front™ were included in the matching process. Of that cohort, all the 30 Polarx™ patients were matched to 30 Arctic Front™ patients in a 1:1 ratio based on propensity scores which resulted in two balanced groups. Table 2 shows baseline characteristics of the matched patients.

Procedural characteristics. The matched 60 patients underwent PV isolation by cryoablation using either Arctic Front™ cryoablation system or Polarx™ cryoablation system. Acute PV isolation was achieved in all veins (100%) without the need for additional focal catheter application. No significant difference was found in total cryoballoon applications with Polarx™ and Arctic Front™(1.09 ± 0.3 vs 1.19 ± 0.5, p = 0.6).Significant differences were found in procedure and fluoroscopy time when comparing Polarx™ and Arctic Front™ (60.5 ± 14.23 vs 73.4 ± 13.26 mins, p = 0.001; 12.83 ± 6.03 vs 17.23 ± 7.17 mins, p = 0.01). There was no significant difference in amount of contrast used with Polarx™ and Arctic Front™ (62.17 ± 7.84 vs 60.17 ± 8.03 mL, p = 0.9).There was also significant difference in cumulative freeze duration in both groups (203.38 ± 72.03 vs 224.9 ± 79.35, p = 0.02). For all PVs that underwent cryoballoon applications between Polarx™ and Arctic Front™, there were significant differences in time to reach 0°C (13.76 ± 2.11 vs 10.69± 1.66 secs,p< 0.001), time to reach -40°C (30.43± 12.53 vs 47.96± 16.91 secs, p<0.001), temperature at 60 seconds (-51.57 ± 5.09 vs -42.87 ± 4.41 °C, p<0.001), nadir temperature (-58.13± 6.26vs -49.63± 6.19 °C, p<0.001), thaw time to 0°C (19.31± 7.9vs 10.0± 4.13 secs,p<0.001) and isolation temperature (-35.5 ± 13.36 vs-29.58± 11.27 °C,p< 0.002). There was no significant difference in isolation time between the two groups (34.47 ± 21.23 vs 34.18 ± 26.79 secs, p = 0.9).When performing head-to-head analysis using Student t-test, comparing the Polarx™ and Arctic Front™ for each vein, no significant differences were found for isolation temperature of the left inferior pulmonary vein (LIPV) (-29.52 ± 11.83 vs -25.28 ± 11.17 °C, p = 0.2), right superior pulmonary vein (RSPV) (-31.71 ± 12.07 vs -26.75 ± 10.65 °C, p = 0.1) and right inferior pulmonary vein (RIPV) (-35.64 ± 14.21 vs -30.35 ± 7.88 °C, p = 0.1).Electrical activity visualization enabling real time isolation was significantly different between Polarx™ and Arctic Front™ (84% vs 70%, p = 0.009). Tables 3 and 4 show procedural and cryoablation characteristics of the matched patients.

Complications. There was no significant difference between Polarx™ and Arctic Front™ groups in terms of complications. The most frequent complication noted was transient right-sided phrenic nerve palsy, with incidence of 3% in the Polarx™ group and 3% in the Arctic Front™ group(p = 1.0). Diaphragm weakness was noted in 1 RSPV application in the Polarx™ group, and 1 RSPV application in the Arctic Front™ group. Diaphragm contraction completely recovered during the same procedure. No lower extremity hematoma, pericardial effusion, cerebrovascular accident, or cardiac structural damage were noted.

Discussion

To the best of our knowledge, this is the first study comparing the acute efficacy and safety outcome of Polarx™ cryoablation system with

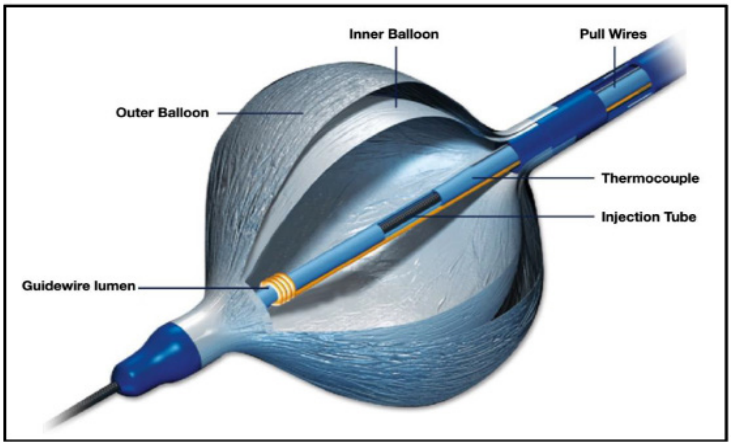

Figure 2: Cross section of the Arctic Front™ cryoballoon catheter, showing integral parts of the balloon catheter. Image courtesy of Medtronic.

Table 3: Procedural characteristics

	Polarx™ (N, 30)	Arctic Front™ (N, 30)	P value
Procedure duration, minutes	60.50 ± 14.23	73.43 ± 13.26	0.001
Fluoroscopy duration, minutes	12.83 ± 6.03	17.23 ± 7.17	0.01
Contrast used, mL	62.17 ± 7.84	60.17 ± 8.03	0.9
Phrenic Nerve Injury	1 (3)	1 (3)	1.0

Data presented as N (%) or mean ± SD

Arctic Front™ cryoablation system. The main findings were: (1) PV isolation with either Polarx™or Arctic Front™ cryoablation system provided acute isolation in 100% of all PVs, (2) Polarx™ was associated with shorter procedure and fluoroscopy time, (3) in all PVs, Polarx™ showed slower time to reach 0º, faster time to reach -40ºC, lower temperature at 60 seconds, lower nadir temperature, longer thaw time to 0 ºC, shorter cumulative freeze duration,and no significant difference in time to isolation, and (4) there were no difference in procedure-related complications between the 2 groups.Optimal placement and contact with the PV ostium are important in creating a well-defined cryothermal lesion. Diminished contact between the cooling zone and PV ostium can lead to gaps and PV electrical reconnection. Several modifications in Arctic Front™'s cryoballoon design over the years have led to a larger ablation area [10-16]. In our study, adequate occlusion during contrast administration and eventual isolation were achieved in all PVs (100%) with no significant difference between the number of cryoballoon applications per vein between Polarx™ and Arctic Front™. While Polarx™ theoretically presents with more stable balloon positioning due to its uniform size and pressure throughout all cryoablation phases (inflation, freezing, thawing), there was no significant difference with the number of occlusions per vein to achieve isolation when using either Polarx™ or Arctic Front™ cryoablation system. In assessing number of occlusions as a measure of learning curve, the insignificant difference is probably due to the large experience accumulated during the years by our operators in performing cryoballoon ablation with the Arctic Front™. Duration of procedure and fluoroscopy time was significantly shorter with Polarx™ when compared to Arctic Front™. Shorter procedure time may be partly due to the inherent set-up of the Polarx™ console where the main steps of inflation, freezing, and deflation are all controlled by the primary operator through the foot pedal attached to the console or through the slide switch on the cryoballoon catheter. This precludes the need for the primary operator to instruct a console operator to inflate, freeze, or deflate the cryoballoon. More importantly, the Polarx™ cryoballoon catheter's body is made of an innovative semi-elastic, thermoplastic material that eases balloon delivery and placement in different PV anatomies, possibly contributing to the shorter procedure and fluoroscopy time as well. Cryothermal energy causes vasoconstriction with a consequent reduction in blood circulation and ischemia. Simultaneously, as the catheter reaches a temperature of -40 ºC, irreversible cell damage is observed due to formation of intracellular and extracellular ice. Furthermore, with subsequent rewarming, endothelial damage occurs which leads to microthrombi formation [17]. Cryoballoon temperature during freezing provides reliable information on balloon-tissue contact, highlighting the relationship between low temperatures and ablation efficiency. The study by Ciconteet al [18] and Watanabe et al [19] showed that nadir temperature reached during freezing (< -51 ºC) represents an independent predictor of absence acute PV reconnection. Furthermore, failure to reach -40 ºC in the first minute of application of cryoenergy represents an independent predictor for late reconnection. Scala et al [20] identified that PV reconnection was associated with longer time to -40 ºC and to reach this temperature in the first minute represents an independent predictor for late reconnection. Warmer temperature at 60 seconds and warmer nadir temperature was associated with PV reconnection. Chierchia et al [21] illustrated that early PV reconnection was associated with a significantly longer TTI. Similarly, Chun et al [22] showed that TTI associated with a durable PV isolation was significantly shorter than in those with electrical reconnection. A recent multicenter study has shown that thaw temperature to 0 ºC of >10 seconds significantly predicts PV isolation [23]. Ghosh et al showed that predictors of PV reconnection include shorter warming time [24]. In the Polarx™ group, the time to reach 0 ºC compared to the Arctic Front™ group was slower, time to reach -40 ˚C was faster, temperature reached at 60 seconds and the nadir temperature were lower, and thaw time to 0 ˚C was longer. Also, there was a significant difference in the isolation temperature between Polarx™ and Arctic Front™. In our study, the nadir temperature and thaw time to 0˚C in Polarx™ met the most marked predictive criteria for successful PV isolation. Furthermore, there were no significant differences in time to isolation between Polarx™ and Arctic Front™.We could infer that these temperature differences might be due to a number of technical factors. The difference in time to reach 0˚C, with Polarx™ being significantly slower than Arctic Front™, is due to the gradual increase in N_2O flow over approximately 10 seconds at the start of cryoablation, enabling the cryoballoon to maintain its size and shape (and therefore occlusion) as therapy is delivered. During this period, there is cryoballoon cooling, but no significant temperature drop until the desired N_2O flow is reached, after which the temperature drops quickly. We could also infer that these temperature differences might be due to different freezing kinetics of the system. Measuring temperature at probe-tissue interface or impedance drop during cryoablation may enhance assessment on the ability of both cryoballoon catheters to create lesions within the ostium for PV isolation.Despite having shorter time to reach -40 ˚ C in Polarx™,both groups reached -40 ˚ C within 60 seconds. This not only represents an acute indicator of PV isolation but also a significant predictor of permanency of PV isolation on the long term. Cumulative freeze duration was also significantly lower with Polarx™. This again might be the result of the adaptable and compliant semi-elastic, thermoplastic material the Polarx™ is made of; therefore facilitating its placement and occlusion in PV ostia despite varying PV drainage patterns. Visualization of PV electrical activity and real time PV isolation was significantly higher in the Polarx™ group than in the Arctic Front™ group. Inner-lumen mapping catheter must be positioned in a proximal portion of the PV in order to maximize the likelihood of visualizing real time recordings without sacrificing cryoballoon stability. Once more, the very nature and design of the Polarx™ played a pivotal role in this setting. Phrenic nerve (PN) palsy is the most common complication of cryoballoon ablation [25] with an incidence of 0.37 - 1.61% [26]. The course of the PN varies from each patient and it is difficult to assess each prior to the procedure. A larger RSPV diameter, a deeper balloon position outside the cardiac silhouette, and rapid temperature drops are known predictors of PN injury [27-30]. In our study, there is no significant difference with the rate of PN injury between Polarx™ and Arctic Front™. All patients who had transient PN injury defined by decrease or abrupt cessation of

Table 4: Cryoablation characteristics

	Polarx™ (N, 30)	Arctic Front™ (N, 30)	P value
LSPV			
Number of occlusion	1.17 ± 0.46	1.07 ± 0.25	0.3
Cumulative freeze duration	225.13 ± 112.86	214.0 ± 78.28	0.65
Time to 0°C, seconds	15.0 ± 1.53	11.93 ± 1.68	< 0.001
Time to -40°C, seconds	30.7 ± 4.35	44.17 ± 10.71	< 0.001
Temperature at 60 secs, °C	-52.33 ± 4.17	-45.0 ± 4.25	< 0.001
Nadir temperature, °C	-57.7 ± 5.42	-52.8 ± 4.57	< 0.001
Real time isolation	27 (90%)	22 (73%)	0.09
Isolation time, seconds	43.81 ± 19.30	48.43 ± 39.98	0.6
Isolation temperature, °C	-44.3 ± 10.6	-35.50 ± 12.59	0.01
Thaw time to 0°C, seconds	19.34 ± 6.92	11.50 ± 4.01	< 0.001
LIPV			
Number of occlusion	1.0 ± 0	1.27 ± 0.64	0.02
Cumulative freeze duration	180.43 ± 19.76	249.07 ± 91.78	< 0.001
Time to 0°C, seconds	13.27 ± 2.28	10.47 ± 1.54	< 0.001
Time to -40°C, seconds	33.30 ± 14.0	54.93 ± 22.37	< 0.001
Temperature at 60 secs, °C	-49.90 ± 5.24	-41.0 ± 4.22	< 0.001
Nadir temperature, °C	-55.33 ± 5.96	-45.37 ± 6.86	< 0.001
Real time isolation	25 (83%)	18 (60%)	0.04
Isolation time, seconds	26.24 ± 9.65	26.11 ± 18.56	0.9
Isolation temperature, °C	-29.52 ± 11.83	-25.28 ± 11.17	0.2
Thaw time to 0°C, seconds	17.71 ± 5.99	8.63 ± 3.8	< 0.001
RSPV			
Number of occlusion	1.13 ± 0.34	1.23 ± 0.62	0.4
Cumulative freeze duration	205.9 ± 71.31	214.27 ± 78.5	0.6
Time to 0°C, seconds	13.4 ± 2.41	10.07 ± 1.31	< 0.001
Time to -40°C, seconds	30.53 ± 13.7	43.74 ± 15.0	0.001
Temperature at 60 secs, °C	-52.47 ± 5.72	-43.83 ± 4.52	< 0.001
Nadir temperature, °C	-59.67 ± 6.83	-51.77 ± 5.66	< 0.001
Real time isolation	24 (80%)	24 (80%)	1.0
Isolation time, seconds	32.83 ± 28.64	24.96 ± 13.97	0.2
Isolation temperature, °C	-31.71 ± 12.07	-26.75 ± 10.65	0.1
Thaw time to 0°C, seconds	20.81 ± 10.36	10.36 ± 4.76	< 0.001
RIPV			
Number of occlusion	1.07 ± 0.25	1.20 ± 0.4	0.1
Cumulative freeze duration	202.07 ± 45.13	222.27 ± 65.38	0.1
Time to 0°C, seconds	13.37 ± 1.69	10.33 ± 1.51	< 0.001
Time to -40°C, seconds	27.2 ± 14.91	49.28 ±16.0	< 0.001
Temperature at 60 secs, °C	-52.0 ± 4.92	-41.57 ± 3.62	< 0.001
Nadir temperature, °C	-58.83 ± 6.17	-48.60 ± 4.73	< 0.001
Real time isolation	25 (83%)	20 (66%)	0.1
Isolation time, seconds	34.16 ± 20.58	36.95 ± 20.38	0.6
Isolation temperature, °C	-35.64 ± 14.21	-30.35 ± 7.88	0.1
Thaw time to 0°C, seconds	19.41 ± 7.93	9.52 ± 3.52	< 0.001
Total			
Number of occlusion	1.09 ± 0.3	1.19 ± 0.5	0.6
Cumulative freeze duration	203.38 ± 72.03	224.9 ± 79.35	0.02
Time to 0°C, seconds	13.76 ± 2.11	10.69 ± 1.66	< 0.001
Time to -40°C, seconds	30.43 ± 12.53	47.96 ± 16.91	< 0.001
Temperature at 60 secs, °C	-51.67 ± 5.09	-42.87 ± 4.41	< 0.001
Nadir temperature, °C	-58.13 ± 6.26	-49.63 ± 6.19	< 0.001
Real time isolation	101 (84%)	84 (70%)	0.009
Isolation time, seconds	34.47 ± 21.23	34.18 ± 26.79	0.9
Isolation temperature, °C	-35.5 ± 13.36	-29.58 ± 11.27	0.002
Thaw time to 0°C, seconds	19.31 ± 7.9	10.0 ± 4.13	< 0.001

Data presented as N (%) or mean ± SD. LSPV, left superior pulmonary vein; LIPV, left inferior pulmonary vein; RSPV, right superior pulmonary vein; RIPV, right inferior pulmonary vein

diaphragm muscle contraction during the cryoablation had resolution of PN function after cryoablation was discontinued.

Limitations

This study compares the novel Polarx™ cryoablation system with the standard Arctic Front™ cryoablation system. This study was conducted in a small cohort of patients and was retrospective in nature. Larger studiesare needed to compare the safety and efficacy of the Polarx™ cryoballoon catheter on a longer follow-up period.

Conclusion

The novel Polarx™ cryoablation system showed similar efficacy in vein occlusion and isolation and safety profile when compared to Arctic Front™ cryoablation system. Procedure time, fluoroscopy time, and cumulative freeze duration were significantly lower with Polarx™ cryoablation system.

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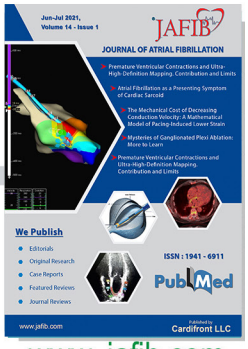

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Endocrine and Mechanical Cardiacfunction Four Months after Radiofrequency Ablation of Atrialfibrillation

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Abstract

Background: Radiofrequency ablation (RFA)is an important treatment option for patients with atrial fibrillation (AF). During RFA, a significant amount of energy is delivered into the left atrium (LA), resulting in considerable LA-injury. The impact of this damage on mechanical and endocrine LA-function, however, is often disregarded.We therefore aimed to evaluate the endocrine- and mechanical function of the heart 4-months after RFA of AF.

Methods: In total 189 patients eligible for RFA of AF were studied. The levels of the N-terminal pro-B-natriuretic peptide (NT-proBNP) and the mid-regional fragment of the N-terminal pro-atrial natriuretic peptide (MR-proANP)were measured. The maximum LAvolume (LAVmax),the LAejection fraction (LAEF) and the LA peak longitudinal strain (PALS), were measured usingtransthoracic echocardiography. The measurements were performed before and 4-months after the intervention.

Results: 87 patients had a recurrence during a mean follow-up of 143±36 days.NT-proBNPand MR-proANPdecreased significantly at follow-up. This reduction was greater in patients who did not suffer any recurrence after RFA.
The LAVmax decreased significantly, whereasthe PALS only improved in patients who did not suffer from any recurrence. On the other hand, LAEF did not change significantly after RFA of AF.

Conclusions: Despite extensiveablation during RFA of AF, the endocrine function of the heart improved 4-months after the index procedure. Patients with no arrhythmia recurrence showed a more pronounced improvement in their endocrinal function. Mechanically, the LAVmax was reduced, and the LA strain improved significantly.

Introduction

Atrial fibrillation (AF) is the most common arrhythmia [1], with an increased riskof embolic stroke and mortality [1,2]. During atrial fibrillation, thecomplex endocrine functions of the heartare activated, including cardiacnatriuretic peptides. These peptides are synthesized and secreted from atrial and ventricular myocardium [3,4]. The mid-regional fragment of the prodromal molecule of atrial natriuretic peptide(MR-proANP) and N-terminal pro B-type natriuretic peptide (NT-proBNP)are elevated in patients with AF, even so in patients without overt HF [5,6]. The key stimuli of production and secretion of natriuretic peptides is the increase of myocardial wall tension [5]. However, data support that local inflammation due to high-frequency contraction of atrial myocytes could constitute a stimulus for synthesis in patients with persistent AF [7].

There are also extra-cardiac neurohormonal systems that play a role in cardiovascular endocrine metabolism. The c-terminal pro-vasopressin (copeptin) and arginine vasopressin (AVP) are both produced in the hypothalamus and released from the neurohypophysis in response to hypervolemia and changes in plasma osmolality [8]. The plasma

Key Words

Atrial Fibrillation, Radiofrequency Ablation, Natriuretic Peptides, Left Atrial Ejection Fraction, Left Atrial Strain.

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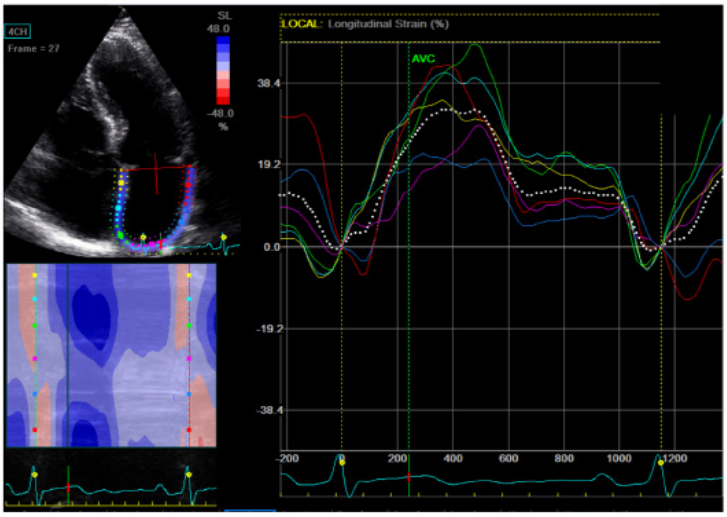

Figure 1: Measuring peak longitudinal atrial strain using speckle tracking echocardiography from apical four chambers view. The dotted curves represent global longitudinal left atrial strain.

concentration of copeptin and AVP increases in patients with HF attributed to inadequate cardiac output, low blood pressure, or increased vascular resistance [9]. Another example of extra-cardiac peptide is the mid-regional portion of pro-adrenomedullin (MR-proADM). MR-proADM is a product of the parental molecule of adrenomedullin. Adrenomedullin is a peptide with vasoactive and natriuretic properties. It is secreted mainly from the adrenal medulla and endothelial cells in response to several hormonal agents and physical stimulants, such as shear stressin blood vessels [10].Studies have also shown that ADM exists and is actively secreted by cardiac cells [11,12], a finding that makes ADM an interesting biomarker for cardiac diseases such as AF.

From a mechanical standpoint, left atrial (LA) remodelling and enlargement is a powerful predictor of several cardiovascular events, including stroke and death.The maximum LA volume (LAVmax) and the LA emptying fraction (LAEF) are usually measured to assess LA remodelling. Two-dimensional speckle tracking echocardiography is a method for quantifying myocardial wall deformation using tracking of acoustic speckles [13], and as suchprovides a more comprehensive assessment of LA function [14].

For patients with symptomatic AF, radiofrequency ablation (RFA) is an important treatment option [1,15]. There is, however, a large variation regarding reportedsuccess rates after a single RFA procedure [16,17]. During the RFA procedure, a significant amount of energy is delivered into the LA, resulting in considerable LA-injury [18]. Nevertheless, the impact of this damage to endocrine and mechanical atrial function has not been widely studied.

Therefore, the aim of this study wasto evaluate the endocrine- and mechanical function of the heart 4-months after RFA of AF.

Methods

Study design and population

The present study is an observational longitudinal study based on the SMURF-study cohort (Symptom burden, metabolic profile, ultrasound findings, rhythm, neurohormonal activation, hemodynamics, and health-related quality of life in patients with AF). The SMURF-study wasconducted between January 2012 and April 2014 [19].

Patients with AF referred for RFA atthe University Hospital in Linköping, Sweden, were screened. The selection criteria for candidates were: 1) Patients≥ 18 years old with paroxysmal or persistent AF, 2) Referred for first time RFA, and 3) With sufficient knowledge of the Swedish language.

Exclusion criteria were: 1) Previous catheter or surgical AF ablation, 2) Previous or planned heart surgery, 3) Severe heart failure (HF) with left ventricular ejection fraction (LVEF) <35%, or 4) Acute coronary syndrome during the past three months.

The full study protocol has been published previously [19].

Subject measurements

The subject measurements and the ablation procedure have been described previously [19,20].

Table 1: Baseline characteristics of the total population and follow up population. The follow up population is also divided in patients with and without AF recurrence after 4 months of follow up

	All patients	All patients with follow up	AF recurrence	No AF recurrence	p-value
Number of pts	189	119	53 (44%)	66 (56%)	
Female	55 (29.1%)	41 (35%)	21 (40%)	20 (30%)	NS
Age	60.5±10.3	61±10.4	63±8	58.7±11.7	NS
Hypertension	80 (42.3%)	51(43%)	24 (45%)	42 (41.2%)	NS
Diabetes	16 (8.5%)	9 (8%)	3 (6 %)	6 (9%)	NS
BMI kg/m²	27.4 (22.6, 34.2)	26.7 (24.7, 29.4)	27.5 (24.6, 29.1)	27.7 (24.9, 29.9)	NS
CKD (GFR < 60mL/ min/1.73 m²)	40 (21.2%)	21(18%)	9(17%)	12 (18%)	NS
Stroke/TIA	11 (5.8%)	6 (5%)	3 (6%)	3 (5%)	NS
IHD	16 (8.5%)	12 (10 %)	4 (8 %)	8 (12 %)	NS
CHA_2DS_2VASc	2 (0, 5)	2 (0, 3)	2 (0, 3)	1 (0, 2.25)	NS
Beta blocker	139 (73.5%)	86 (72%)	40 (76%)	46 (70%)	NS
AAD	98 (51.9%)	64 (54%)	29 (55%)	35 (53%)	NS
AAD follow up	36 (19 %)	21 (18%)	16 (30%)	5 (8%)	0.001
LVEF < 50%	49 (25.9%)	29 (24%)	13 (25%)	16 (24%)	NS
Paroxysmal AF	71 (37.6%)	42(35%)	20 (37%)	22 (33%)	NS
Atrial fibrillation in admission	53 (28%)	34 (29%)	16 (30%)	18(27%)	NS
Procedural time (min)	188±50	187±49.4	189±47	185±52	NS
Complications	7 (4%)	4 (3%)	3 (6%)	1(2%)	NS
Extra ablation lines	28(15%)	18 (15%)	5 (10%)	13 (21%)	NS

Note 1: Normally distributed continuous data are presented as means with standard deviation. Differences between patients who experienced recurrences and those without recurrences were examined with t-test. Non-parametric data are presented as median values with 25th and 75th percentiles within brackets and tested with Mann-Whitney U test. Categorical data are presented as counts with percent values within brackets and tested with chi-square test.
Abbreviations: AAD: antiarrhythmic drugs; AF: atrial fibrillation; BMI: body mass index; CHA_2DS_2VASc: congestive heart failure, hypertension, age ≥ 75, diabetes, stroke, vascular disease, gender; CKD: chronic kidney failure; LVEF: left ventricular ejection fraction; GFR: glomerular filtration rate; IHD: ischemic heart disease.

Table 2: Lines performed during radiofrequency ablation, in addition to pulmonary vein isolation

Additional lines	Total
RA isthmus	11 (5.7%)
LA isthmus	1 (0.5%)
LA roof	15 (7.8%)
CS line	1 (0.5%)
No additional line	164 (85.4)

Note: Data are presented as counts with percent values within brackets.
Abbreviations: RA: right atrium, LA: left atrium, CS: coronary sinu

In short, all patients underwent a full baseline evaluation the day before the procedure, including medical history andtransthoracic echocardiographic examination (TTE).

The day of the procedure the patients were catheterized, and blood samples were retrieved from the femoral vein for biomarker analysis [19,20].

Follow-up and definition of recurrence

Patients underwent a follow upfour months after RFA and whenever otherwise required due to symptomswith 12-lead electrocardiograms and 24-h Holter ambulatory electrocardiograms. Of note, there was no blanking period after the RFA procedure. Episodesof atrial tachyarrhythmia or AFlasting >30 seconds during the follow up period on ECG, 24-h Holter ambulatory monitoring or on pacemaker/ implantable defibrillator interrogation were registered as clinical recurrences [21]. At the follow-up, blood samples were retrieved from a peripheral veinfor biomarker evaluation,and TTE was performed in patients who were residents of the County of Östergötland [19,22]. The period of four months was chosen on the assumption that the changes made by the RFA would be mainly healed, and that a stable biomarker situation was acquired.

Echocardiography

TTE measurements

All participants underwent TTE prior to RFA and a subgroup of patients underwent acontrol TTE at 4-months follow up [20].

The Simpson's biplane method was used to calculate LVEF. TheLAVmax and the minimum LA volume (LAVmin) were measured according tothe biplane area-length methodand were corrected for body surface area (BSA) [23]. LAEF was calculated according to the following equation ((Vmax - Vmin)/ Vmax) x100 [22-24].

The measurements and evaluations were performed according to the guidelines of the European Society of Echocardiography [25].

Speckle tracking echocardiography

Two-dimensional images of the LA were obtained from the apical 4 chamber (C)(figure 1) and 2C view for speckle tracking evaluation.The frame rate was between 55 and 100 frames/s. The endocardial border of the LA wastraced, and a region of interest (ROI) was generated (Echo PAC version BT 12,GE Healthcare, Horten, Norway). Manual adjustments were performed when necessary. The ROI was divided into 6 segments and if these were of good quality further analysis was performed. Segments of poor quality wererejected from furtherprocessing. Finally, strain curves were generated.The LA peak longitudinal strain (PALS) during the entire cardiac cycle lengthwas calculated from all LA segments obtained from 4C and 2C views.If some segments were excluded from the analysis, the calculation was made by averaging the remaining segments [19,26].

Laboratory tests

The concentrations of NT-proBNP were analyzed on the Elecsys 2010 platform (Roche Diagnostics, Mannheim, Germany). The total coefficient of variation (CV)was 4.6% at 426.5 pg/ml, (n=487) and 3.2% at 2308 pg/ml (n=495). The Kryptor platform (Brahms AG, Hennigsdorf Germany) was utilized for the analysis of the MR-proADM, the MR-proANPand copeptin. The intra assay CV for MR-proADM, was ≤ 10% for concentrations between 0.2 and 0.5 nmol/l, < 4% for concentrations between 0.5 nmol/l and 2 nmol/l, <2% for concentrations between 2 nmol/l and 6 nmol/l, and < 3.5% for concentrations over 6 nmol/l according to the manufacturer. The intra assay CV for MR-proANP was ≤ 5% for concentrations between 10 pmol/l and 20 pmol/l, < 3.5% for concentrations between 20 pmol/l and 1000 pmol/l, and < 3.5% for concentrations over 1000 pmol/l. Copeptin's CV was 4% at a concentration of 15 pmol/l (n=18) and 3.5% at concentrations of 100 pmol/l (n=18)[20,27].

Endpoint

The primary endpoint of the study was changes in MR-proANP, NT-proBNP, MR-proADM, and copeptin concentrations, as well as LAVmax, LAEF and PALS measurements following RFA of AF depending on possible recurrences and after adjustment for covariates such as age, gender, type of AF, rhythm and LVEF (baseline vs 4 months follow-up).

Statistical methods

For baseline data, categorical data were presentedas counts with

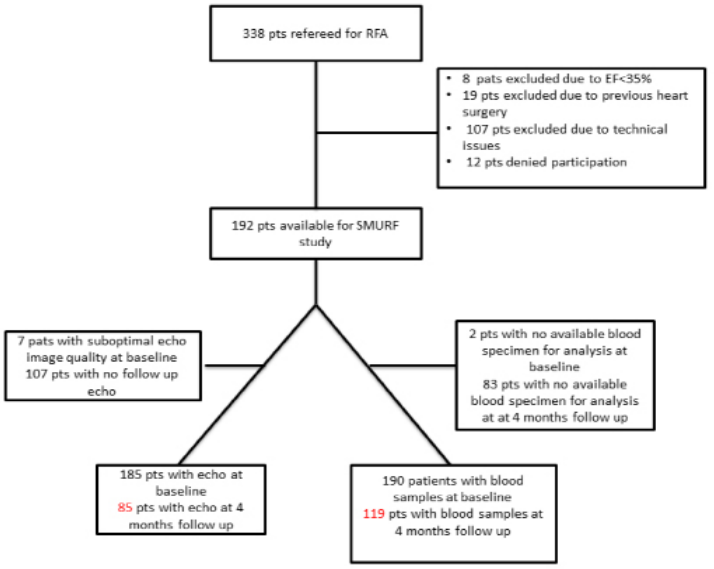

Figure 2: Flow chart of the study participation inclusion

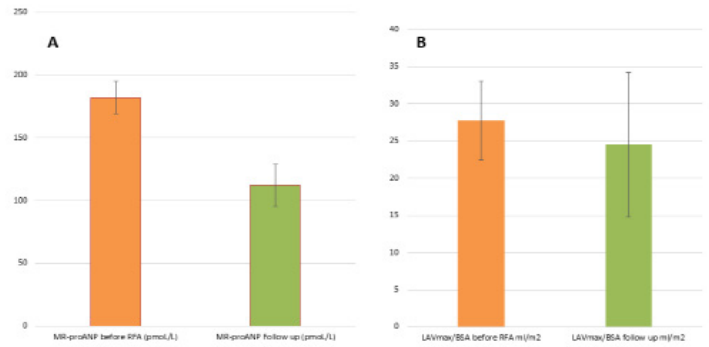

Figure 3: Effect of radiofrequency ablation on; A. MR-proANP, B. LAVmax/BSA Note: $P_{MR\text{-}proANP}$<0.001; $P_{LAVmax/BSA}$ <0.001.

percentages within brackets, continuous variables were expressed as means ± standard deviation (SD) andvariables not normally distributed were presented as medians with 25th and 75th percentiles within brackets. The normality of the samples was checked by the Kolmogorov-Smirnov test. The two-sample Student t-test, Mann-Whitney Utest, and x^2 test were used for comparison of normalcontinuous, not normally distributed, and categoricaldata, respectively.

As there was a substantial number of missing data in the primary study end points, statistical evaluation using mixed linear model was used.MR-proANP, NT-proBNP, copeptin, MR-proADM, LAEF, LAVmax and PALS were used as dependent variables in different mixed models' analyses. Time (baseline and at 4 months follow-up) was used as repeated variable. Unstructured repeated covariance type was chosen (in order to avoid the need for normally distributed data),and the presence of AF or any other atrial tachyarrhythmia during the follow-upperiod was used as fixed factorwith patient indicatoras a random intercept. The analyses were adjusted for covariates: age>65 years, gender, BMI > 30 kg/m2, type of AF (paroxysmal or persistent), rhythm at the time of blood sample retrieval or TTE(sinus rhythm (SR) or AF) and at the time of follow up, LVEF < 50 % and glomerular filtration rate of <60 ml/min/1.73 m2 (calculated by using a previously described cystatin-C formula) [28],hypertension, diabetes,additional ablation lesionsand cumulative delivered energy. Moreover, a sensitivity analysis was performed for the main outcome excluding patients with no follow up data.

The models were fit by an enter method, where all variables were entered into the original model stepwise. Variables with p values of >0.1 were thereafter removed.

Analysis of residuals and multicollinearity diagnostics were performedin order to validate the mixed model analyses.

All reported p values were two-sided and a p-value <0.05 was considered statistically significant. The analyses were performed using the SPSS 24.0 (SPSS, Chicago, IL, USA).

Results

In total, 192 patients with AF were included in the SMURF study (56 women and 136 men), whilethreewere lost from follow up. Blood samplesfrom119 patients were available for biomarker analysis and 85 patients underwent TTE at the 4-month follow-up(figure 2). The baseline characteristics are presented in detail in table 1.

The RFA procedural time was 188±49 min, the total RFA time was 40±13 min and the median cumulative energy delivery was 67280J (38088J, 96472J). Additional ablation lines were performed in 27 participants (table 2).

The complication rate was 3.7%. In total, three patients suffered from pericardial effusion, two of them requiring pericardiocentesis. Moreover, fourpatients developed peripheral vessel complication three patients suffered frompseudoaneurysm, and another patient developed a larger than normal hematoma of the groin [22].

A total of 87 (45 %)patients had a recurrence after a single RFA procedure during a follow up period of 143±36 days. At 4 months follow up,4 patients (3%) were in AF at the time of blood sampling and TTE, whereas 19 % of patients remained on antiarrhythmic drugs and75% onbetablockers.

RFA effect on biomarkers

The main finding was that a highly statistically significant reduction of all four biomarkers (MR-proANP, NT-proBNP as well as copeptin and MR-proADM) was demonstrated four months after RFA compared to baseline concentrations (MR-proANP: p<0.001(figure3); NT-proBNP p=0.019; copeptin p<0.001; MR-proADM p=0.008; table 3, table 4).

RFA effect on biomarkers depending on recurrences

It is interesting to note that patients who did not suffer any recurrence after RFA had lower concentrations of three of the biomarkers (MR-proANP, NT-proBNP and MR-proADM) at 4 months follow up compared to those who had recurrences (MR-proANPp<0.001 (figure

Table 3: Effect of RFA on the endocrine and structural function four months after RFA compared to baseline for the whole population; and for patients without recurrences compared to those who suffered recurrences 4 months after RFA, with their combined loading vectors

	Whole population	Patients without recurrences compared to patients with recurrences 4months after RFA
MR-proANPpg/mL	↓	↓
NT-proBNPpmol/L	↓	↓
Copeptinpmol/L	↓	N
MR-proADMpmol/L	↓	↓
LAVmax/BSA ml/m²	↓	N
LAEF %	N	N
PALS %	N	↑

Arrows pointing down are biomarkers or echocardiographic markers that lower their levels 4 months after RFA compared to baseline (or lower levels in patients without recurrences compared to patients with recurrences 4 months after RFA in the last column). Arrows pointing up are biomarkers or echocardiographic markers that showed higher levels 4 months after RFA compared to baseline (or higher levels in patients without recurrences compared to patients with recurrences 4 months after RFA in the last column). 'N' stands for no change after the RFA.
Abbreviations: AF: atrial fibrillation; BSA: body mass index; LAEF: left atrial ejection fraction; LAVmax: maximum left atrial volume; LVEF: left ventricular ejection fraction; PALS: peak atrial longitudinal strain; MR-proADM: mid-regional portion of pro-adrenomedullin; MR-proANP: mid-regional fragment of the N-terminal precursor of atrial natriuretic peptide; NT-proBNP: N-terminal pro B-type natriuretic peptide; RFA: radiofrequency ablation; SR: sinus rhythm.

Table 4: RFA effect on the endocrine and structural cardiac function

	N	Mean baseline (95% CI)	N	Mean follow up (95% CI)	Mean difference (95% CI)	P value
MR-proANPpg/mL	189	182.2 (169.5-194.8)	119	129.1 (112.2-154.7)	40.2 (29.3-51.1)	<0.001
NT-proBNPpmol/L	189	390.7 (330.4-451.1)	119	294 (221.5-366.6)	96.7 (16.2-177.1)	0.019
Copeptinpmol/L	189	17.04 (12.6-21.5)	119	9.02 (7.82-10.21)	8.02 (3.59-12.45)	<0.001
MR-proADMpmol/L	189	0.798 (0.77-0.826)	119	0.766 (0.734-0.798)	0.032 (0.009-0.056)	0.008
LAVmax/BSA ml/m²	180	27.7 (22.4-33.1)	81	24.5 (14.8-34.2)	3.23 (1.9-4.5)	<0.001
LAEF %	180	0.29 (0.25-0.34)	81	0.3 (0.25-0-35)	-0.007 (-0.03-0.02)	0.651
PALS %	185	16.9 (14-19.8)	85	15.5 (12.4-18.7)	1.4 (-0.2- 2.9)	0.08

Note 1: Data are presented in estimated means with 95% CI
Note 2: Analyses were performed via a mixed linear model method. Time (baseline and at 4 months follow up) was used as repeated variable. Unstructured repeated covariance type was chosen and the presence of any recurrence during the follow up was used as fixed factor with patient indicator as a random intercept. The analyses were adjusted for various covariates including age>65 years, BMI > 30 kg/m², type of AF, gender, rhythm at the time of blood sample retrieval or TTE(SR or AF), in respect to the dependent variable, LVEF < 50 % and glomerular filtration rate of <60 ml/min/1.73 m² (calculated by using a previously described cystatin-C formula). The potential statistical significances of those analyses are presented with P-values. Statistical significance in bold font
Abbreviations: AF: atrial fibrillation; BMI: body mass index; BSA: body mass index; CI: confidence interval; LAEF: left atrial ejection fraction; LAVmax: maximum left atrial volume; LVEF: left ventricular ejection fraction; PALS: peak atrial longitudinal strain; MR-proADM: mid-regional portion of pro-adrenomedullin; MR-proANP: mid-regional fragment of the N-terminal precursor of atrial natriuretic peptide; NT-proBNP: N-terminal pro B-type natriuretic peptide; RFA: radiofrequency ablation; SR: sinus rhythm; TTE: transthoracic echocardiogram.

4); NT-proBNP: p=0.01; MR-proADM: p=0.03; table 3, table 5))

However,the copeptin concentration at 4 months follow up did not differ between patients who suffered a recurrence and those who did not(copeptin: p=0.116; table 4).

RFA effect on echocardiographic parameters

LAVmaxcorrected for BSA was significantly lower at the 4 months follow up visit after RFA compared to baseline (p<0.001; table 3, table 4, figure 3).However, in the total group, LAEF and PALS showed no significant change 4 months after the RFA compared to baseline(LAEF: p=0.651; PALS: p=0.08; table 3, table 4).

Patients undergoing only pulmonary vein isolation (PVI) had higher LAEF and PALS, compared to those with PVI and additional lesions (LAEF p= 0.043, PALS p=0.044).

The interobserver variation for PALS using speckle tracking echocardiography was not statistically significant (Supplementary figure 1).

RFA effect on echocardiographic parameters depending on recurrences

Interestingly, PALS in patients with no documented recurrences was higher compared to those who had episodes of AF or AT (p=0.02; table 3, table 5, figure 4). However, no differences were observed in LAEF or LAVmaxcorrected for BSA between patients who suffered a recurrence and those who did not (LAEF: p=0.867; LAVmax /BSA: p=0.222; table 3, table 5).

Sensitivity Analysis

The sensitivity analysis excluding patients with no follow-up data did not result in any noteworthy change compared to the main analysis. The results of this analysis are presented in the supplement (Sensitivity analysis in the supplement).

Discussion

Given the amount of radiofrequency energy that is delivered during RFAof AF, it is important to studythe endocrine and mechanical cardiac function, due to the tissue injury that is produced through the procedure, and to evaluate the response to the healing process in the heart. We report the endocrine and mechanical consequences of the RFA procedure after four months of follow-up, which is a time window when it could be expected that the tissue damage has healed.

We assessed the cardiac endocrine function with two known ¨cardiac peptides¨MR-proANPand NT-proBNP. Furthermore, we analyzed copeptin and MR-proADM, which have intimate relation to both volume changes, but also to cardiac function. After adjusting for various well-known clinical covariates that might influence the level of the biomarkers evaluated, we found an improved endocrine function 4 months after RFA as appraised from changes in the concentration of the four biomarkers evaluated.

The atrial mechanical function was determined with LAVmax/BSA, LAEF and PALS by use of specle tracking methodology. The evaluation demonstrated a decrease of the LAVmax, andan improved LA strain in the patients without AF recurrences, a method more sensitive compared to volumetric measures [29]. As expected, we could not demonstrate any improvement of the LAEF after a follow-up period of four months, in concurrence with results from the literature [30].

Given previous reported results in the literature, and the size of thestudy population, this study providesa more detailed information about the effect of RFA on the endocrine and mechanical functions of the heart.

Effect of RFA on natriuretic peptides

Restoration of sinus rhythm leads to a sustained decrease in natriuretic peptides, a fact observed following electrical cardioversion [30, 31]. The

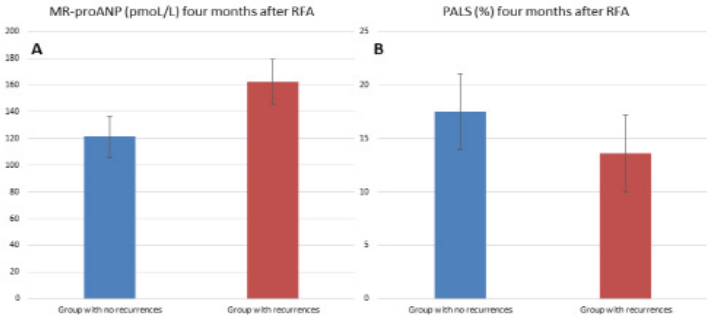

Figure 4: Effect of radiofrequency ablation on; A. MR-proANP, B. PALS depending on recurrences
Note: $P_{MR\text{-}proANP}$<0.001; PPALS=0.02

Table 5: RFA effect on the endocrine and structural cardiac function depending on possible recurrences

	N	Mean follow up (patients without recurrences) (95% CI)	N	Mean follow up (95% CI)	Mean difference (95% CI)	P value
(patients with recurrences)	Mean difference (95% CI)	P value	119	129.1 (112.2-154.7)	40.2 (29.3-51.1)	<0.001
MR-proANPpg/mL	66	121.4 (105.8-137)	53	162.5 (145.7-179.2)	-41.1 (-60.7 - -21.5)	<0.001
NT-proBNPpmol/L	66	197.1 (99.8-294.3)	53	391 (282.7-499.4)	-193.9 (-340 - -47.9)	0.01
Copeptinpmol/L	66	9.68 (8.28-11.1)	53	8.36 (6.86-9.87)	1.31 (-0.32 – 2.96)	0.116
MR-proADMpmol/L	66	0.738 (0.7-0.777)	53	0.793 (0.751-0.835)	-0.06 (-0.10 - -0.006)	0.03
LAVmax/BSA ml/m2	46	24.3 (5.3-43.4)	35	24.6 (3.7-45.5)	-0.25 (-3.18 – 2.68)	0.867
LAEF %	46	0.32 (0.26-0.38)	35	0.28 (0.23-0.34)	0.04 (-0.02-0.09)	0.222
PALS %	49	17.5 (14-21.1)	36	13.6 (10-17.2)	3.96 (0.645-7.29)	0.02

Note 1: Data are presented in estimated means with 95% CI
Note 2: Analyses were performed via a mixed linear model method. Time (baseline and at 4 months follow up) was used as repeated variable. Unstructured repeated covariance type was chosen and the presence of AF or any other atrial tachyarrhythmia during the follow-up was used as fixed factor with patient indicator as a random intercept, presence of any recurrence during the follow up period was used as fixed factor with patient indicator as a random intercept. The analyses were adjusted for various covariates including: age>65 years, BMI > 30 kg/m^2, type of AF gender, rhythm at the time of blood sample retrieval or TTE(SR or AF), in respect to the dependent variable, LVEF < 50 % and glomerular filtration rate of <60 ml/min/1.73 m^2 (calculated by using a previously described cystatin-C formula). The potential statistical significances of those analyses are presented with P-values. Statistical significance in bold font
Abbreviations: AF: atrial fibrillation; BMI: body mass index; BSA: body mass index; CI: confidence interval; LAEF: left atrial ejection fraction; LAVmax: maximum left atrial volume; LVEF: left ventricular ejection fraction; PALS: peak atrial longitudinal strain; MR-proADM: mid-regional portion of pro-adrenomedullin; MR-proANP: mid-regional fragment of the N-terminal precursor of atrial natriuretic peptide; NT-proBNP: N-terminal pro B-type natriuretic peptide; RFA: radiofrequency ablation; SR: sinus rhythm; TTE: transthoracic echocardiogram.

decrease in the concentration of the natriuretic peptides four months after RFA is most prominent in those with SR. However, regardless of arrhythmia recurrence, a decrease in biomarker concentration can be demonstrated, which is in accordance with previouspublished data. This can be attributed to the decrease of total arrhythmia burden in patients with recurrences [32]. Furthermore,improvement of the diastolic heart function [33] and LA reverse remodelling post AF ablation [34] can contribute to the improvement of the endocrine function of the heart due toa decrease of atrial myocardial wall tension.

RFA effect on copeptin and MR-proADM

Copeptin reveals information regarding volume, but also in cardiac wall tension. This has also been reported in a recent study from our group showing immediately increased levels of copeptin after RFA due to myocardial damage, fluid volume administration and endocrinestress response during RFA [20]. The decrease in copeptin concentration could possibly beattributed to the improvement of both systolic and diastolic heart function [33] after restoration of sinus rhythm, even though copeptin is not produced in the myocardium as far as we know today [20].

MR-proADM is a product of the parental molecule of adrenomedullin. In patients with HF,a ventricular-derived production of adrenomedullin is observed [35]. MR-proADMis also found to predict arrhythmia recurrence after RFA [36].

An increase in adrenomedullin usually reflects an overflow from local sites of production besides hemodynamic alterations and volume overload [12].Thus, increased levels of MR-proADM are found in patients with more severe cardiac disease [37]. Hence, we assume that decreased levels of MR-proADMafter RFA of AF found in this study reflect structural atrial reversed remodeling and atrial hemodynamic improvement. Finally, both copeptin and MR-proADM are sensitive biomarkers for volume changes in the body, something positively influenced by the restoration of SR.

RFA effect on mechanical function of LA

An important finding in our study was an improvement of PALS, and a reduction in LAV max/BSA, four months after RFA.

It has been reported that RFA can cause LA scarring that can influence LA structure and function negatively [18]. At the same time, RFA is a method designed to remove the underlying electrophysiological mechanism of AF, which leads to structural and functional LA remodeling, including changes in LA size, strain and LAEF [38].Previous studies have shown that enlargement of LA can be reversed after a successful catheter ablation. Thus, LA reverse remodeling after RFA may be an indicator of successful RFA[21,39].

Studies have reported that atrial scarring and loss of myocardial mass caused by ablation prevent further LA dilatation.[40] However, LA systolic function can be impairedunder such circumstances [30]. Furthermore, Kim et al. reported that during a follow-upperiod of 12 months,40-70% of patients who underwent ablation for AF showed a decrease in LAEF [41], whereas one third of patients with electrocardiographic p wave restoration was not accompanied by hemodynamic evidence of effective atrial systole [30].These findings concur with the reduction of LAV with no concomitant increase of LAEF found in our study.

However, PALS might represent an earlier index of atrial function, and was improved in this evaluation.

Patients with AF have decreased global longitudinalstrain,possibly because of theatrial remodeling process [42]. During peak positive deformation (when PALS is measured), the LA is stretched, mainly due to venous return from the pulmonary veins, and functions as a reservoir. Therefore,higher PALS suggests better LA reservoir function [43]. Furthermore, LA strain has been shown to correlate with the progression of LA wall fibrosis in patients with AF. Hence, the improvement of PALS in patients without arrhythmia recurrence after RFA can be a marker of reverse remodeling of LA after ablation, even though the LAEF does not improve [44]. The pre-RFA fibrosis is a potentially important factor that is discussed by Packer as a possible variable to prevent an increased LAEF function post-RFA[30].

Additionally, PALS depends on the longitudinal movement of the LA wall while LAEF is more dependent on the LA contraction (i.e.,

radial movement). This can explain theobserved discrepancy between PALS and LAEF changes after RFA.

In conclusion, the mechanical parameters improved, and the tissue injury caused by the RFA process seems to be healed after four months of follow-up, as can be noted from the results above.

Limitations

This is a single-centre cohort study with a moderate sample size. Our cohort consists of patients with both paroxysmal and persistent AF, presenting in both SR and AFas well as normal and reduced EF. Additionally, weneitherrandomizedthe patients nor used a control groupwhere no ablation was carried out, thus our study can show association but not causality. Nevertheless, using a control group in such an occasion (invasive procedure)cannot constitute an alternative from an ethical point of view. Furthermore, we were not able to follow up all patients with TTE and blood sampling due to geographical and logistical difficulties as the patients were recruited from a large geographical area. This issue can raise some concerns regarding therisk of selection bias and hence, the robustness of our results.In order to address this issue, a mixed model analysis was chosen to deal with missing values, as all the data obtained were included in the analysis. Furthermore, no differences in baseline characteristics were observed between the group that we have followed up and those with no follow up data (supplementary table 1) and the sensitivity analysis excluding patients with no follow-up data did not result in any significant change compared to the main analysis (Sensitivity analysis in the supplementary)

In total, 87 patients (48 %) suffered a recurrence during the 4-months follow up. This constitutes a high percentage of recurrence in our population. This finding can be attributed to 1) our patients were subjected to a thorough follow up which,in clinical routine, is not as rigorous, 2)in similar studies, the first 3 months after the ablation procedure are considered 'blanking period' and the recurrences are not counted during this period. We choose four months as an appropriate follow-up time since the healing process to a large extent is completed at that time point. Thus, we regard the obtained results as relevant and informative.

Perspectives

In order to provide an optimal treatment, the effects of the treatment to target organs and the resulting mechanisms due to the treatment is fundamental. This study provides additional knowledge of both endocrine and mechanical changes after RFA of AF. The combination of data from cardiac, and, for the first time, extra-cardiac endocrine systems as well as the presentation of the mechanical function of the LA with a reproducible technique provide a clearer picture of the effect of RFA. Furthermore, the size of the population of this study and the broader inclusion criteria compared to previous studies further strengthens the results.[32,34]

Taken together, we argue that the endocrine and mechanical function as assessed by natriuretic peptides, MR-proADM, LAVmax and strain before and after the ablation could be valid instruments to assess the impact of RFA of AF on the LA function.

Conclusions

In the present study, we demonstrate that despiteextensive atrial ablation during RFA of AF, the endocrine function of the heart, assessed by different biomarkers, is significantly improved four months after the index procedure. Patients with no arrhythmia recurrence showed a more pronounced improvement in their endocrinal function.

As a result of the RFA procedure a reduction of LAV could be demonstrated, as well as an improvement of LA strain four months after the index procedure. However, the LAEF did not increase during the follow-up period.

Statements

Informed consent and ethical considerations

The protocol of this study has been approved by the Regional Ethical Review Board of the Faculty of Health Sciences, Linköping, Sweden, (Dnr 2011/40-31, 2012/226-32). Written informed consent was obtained from all patients. The study complies with the Declaration of Helsinki[45].

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

EC, LK, UA and HW designed the study. EC analysed the data and drafted the manuscript. EC, LK, C-JC, IL, AHJ, HW and UA interpreted the results and edited the manuscript critically. All the co-authors have read and accepted this version of the manuscript.

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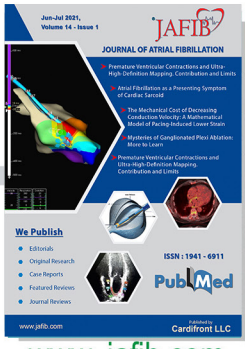

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The Mechanical Cost of Decreasing Conduction Velocity: A Mathematical Model of Pacing-Induced Lower Strain

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Abstract

Purpose : To simulate the effect of decreasing conduction velocity (Cvel) on average segmental myocardial strain using mathematical modeling.

Method: The simulation was run using MatLab version 7.4 (The MathWorks, Inc. Natick, Massachusetts). A normal strain-time curve pattern was sampled from a normal human echo study using the 2D strain imaging software (GE Healthcare, Milwaukee, Wisconsin). Contraction was simulated from simultaneous segmental activation (Cvel=∞) through normal activation (Cvel=400cm/sec) to pacing Cvel (100 to 10cm/sec). The simulation generated average segmental strain-time waveforms for each velocity and peak strain as a function of Cvel and time to peak strain as a function of Cvel curves.

Result: With decreasing Cvel, average peak segmental strain was found to be decreased and delayed. The following correlation equation represents the correlation between peak strain and Cvel : strain= $-20.12+27.65 \times e^{(-0.29 \times Cvel)}$. At the highest pacing Cvel (100cm/sec) average peak segmental strain dropped by 10%, at 50cm/sec by 30% and at the lowest pacing Cvel (10cm/sec) peak strain dropped by >90%. Time to peak segmental strain was minimally longer with decreasing Cvel down to 70cm/sec (pacing velocity range). Further decreased velocity dramatically increased time to peak strain of the simulated segment.

Conclusion: The simulation yielded a predictive correlation between slower conduction velocities and decreased and delayed segmental strain.

Introduction

Cardiac resynchronization therapy (CRT) has proven helpful in patients with heart failure (HF) and ventricular dyssynchronization [1-4]. The major concept being an attempt to resynchronize early and delayed opposing wall contraction. It is easily understandable how dyssynchronized wall contraction results in lower average function . Right ventricular pacing has been shown to adversely affect left ventricular systolic and diastolic function [5,6]. However, biventricular pacing has not been universally successful and even detrimental in some patients [7,8].

Conduction velocity (Cvel) in the Purkinje system is 2 to 4 M/sec, while the Cvel in muscle is 0.5 to 1 [9]. As the Cvel during pacing is reduced by 4-10 fold, the electrical impulse propagates sequentially via myocardium causing intra-segmental delay. By applying similar reasoning that correlates reduced left ventricular function due to delayed wall contraction, sequential myocardial cell activation and contraction may result in less average shortening compared to the normal simultaneously activated segmental shortening. We used mathematical modeling to simulate average segmental strain to Cvel correlation.

Methods

The simulation was run using MatLab version 7.4 (The Math Works, Inc. Natick, Massachusetts). A normal strain-time curve pattern was sampled from a normal human echo study using the Echo PAC PC 2D strain imaging software (GE Healthcare, Milwaukee, Wisconsin). It was generated from 10 healthy volunteers in sinus rhythm at a heart rate of 60-70 beats per minutes. Long axis echocardiographic views were analyzed using Siemens Velocity Vector Imaging (Mountain view, CA, USA) and generated 18 segments strain curves per subject.

Key Words

Strain, Pacing, Conduction Velocity.

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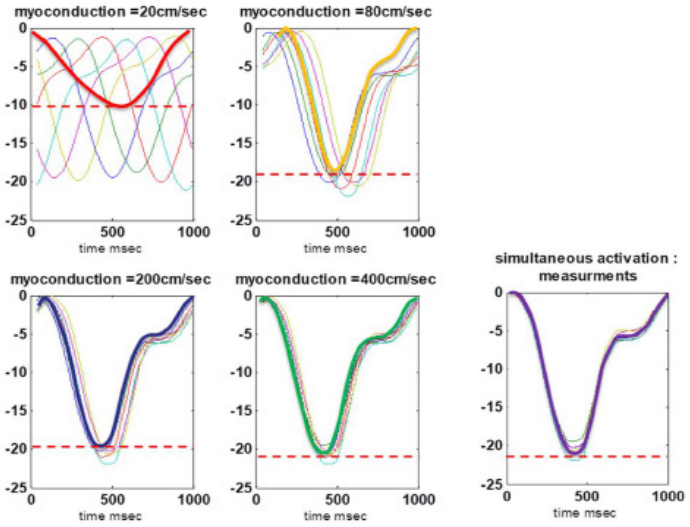

Figure 1: **Strain-time waveforms within a segment in different conduction velocities (Cvel) are showed. With low Cvel of the pacing range (less than 100 cm/sec), the waveforms (dashed lines) within a segment were sequentially generated, while with increasing Cvel (≥200 cm/sec), the waveforms became more and more overlapped until being simultaneously generated when the velocity is within or above the range of normal Cvel (≥400 cm/sec). The bold curve generated from the summation of the strain-time waveforms within a segment represents the average strain-time waveform of the segment in each Cvel.**

All 180 segmental curves were normalized to cycle length to generate an average strain curve for the model. This pattern was set as the single sarcomere (oscillator) shortening waveform. The following parameters were entered for segmental representation in the simulation : segmental length of 5cm, myocardial cell length 120μm, 50% longitudinal overlap between cells, and 60 oscillators per cell[10]. All oscillators within a single cell were activated simultaneously. Contraction was simulated from simultaneous segmental activation (Cvel=∞) through normal activation (Cvel=400cm/sec) to pacing conduction velocities (100 to 10cm/sec). The simulation generated sequential strain-time waveforms within a segment and average segmental strain-time waveform for each velocity (figure 1). This simulation also generated average peak segmental strain as a function of Cvel and time to average peak segmental strain as a function of Cvel curves.

Statistical evaluation

Strain and time-to-peak strain relationship to Cvel was assessed using curve-fitting quadratic regression analysis.

Results

The strain-time waveforms within a segment are showed in figure 1. With low Cvel of the pacing range (less than 100 cm/sec), the waveformswithin a segment were sequentially generated, while with increasing Cvel (≥200 cm/sec), the waveforms became more and more overlapped until being simultaneously generated when the velocity is within the range of normal Cvel(≥400 cm/sec) .

With decreasing Cvel the average peak segmental strain decreased and was increasingly delayed (Figure 1,2). The decrease in average peak segmental strain followed the following correlation equation (Figure 3): strain= -20.12+27.65 x $e^{(-0.29 \times Cvel)}$. The first part of the formula (-20.12) represents normal peak strain and the second part (27.65 x $e^{(-0.29 \times Cvel)}$) represents a negative exponential function. Maximal average peak strain plateaued at Cvel conduction of 400 cm/sec. Increasing the velocity above 400 cm/sec did not further increase strain. However, decreasing Cvel caused an exponential reduction in strain. At the highest pacing Cvel (100cm/sec) the average peak segmental strain dropped by 10%, at 50cm/sec it dropped by 30% and at the lowest Cvel (10cm/sec) strain dropped by more than 90%.

Figure 4 represents time-to-average peak segmental strain correlation with Cvel, following the equation: time-to-peak strain = 360+ 406 x $e^{(-0.04 \times Cvel)}$. Time to peak strain was minimally longer with decreasing Cvel down to 70cm/sec (within the pacing velocity range). Further decreased velocity dramatically elongated time-to-peak strain of the simulated segment.

Discussion

Simulation and experimental results

The simulation yielded a predictive correlation between slower conduction velocities and decreasing peak segmental strain and increasing delay in its timing, resulting from intra-segmental, or microscopic dyssynchrony. This is very similar to wall (macro) dyssynchrony found in some of the dilated cardiomyopathy patients. It is easily understandable how misaligned wall peak contractions cause a decrease in global strain, forming the basis for resynchronization therapy. Our simulation demonstrates that the same phenomenon may happen microscopically within a single segment, adversely affecting its potential maximal strain in a predictable way related to Cvel. Pacing reduces Cvel to levels that would reduce peak segmental strain in the range of 10% to 90%. As the simulation is not linear an average pacing velocity of 50 cm/sec would be expected to decrease strain by 30%.

Reduced Cvel and dyssynchrony may cause molecular changes including ion channels and electrical alterations that are similar in

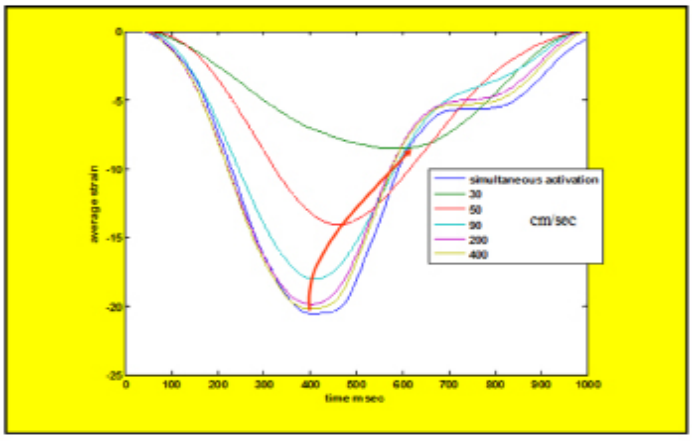

Figure 2: **Average longitudinal segmental strain-time curve patterns at various conduction velocities from simultaneous segmental activation (conduction velocity =∞) through normal activation (400cm/sec) to pacing conduction velocities (<100cm/sec). With decreasing conduction velocity, the average peak longitudinal segmental strain decreased and delayed.**

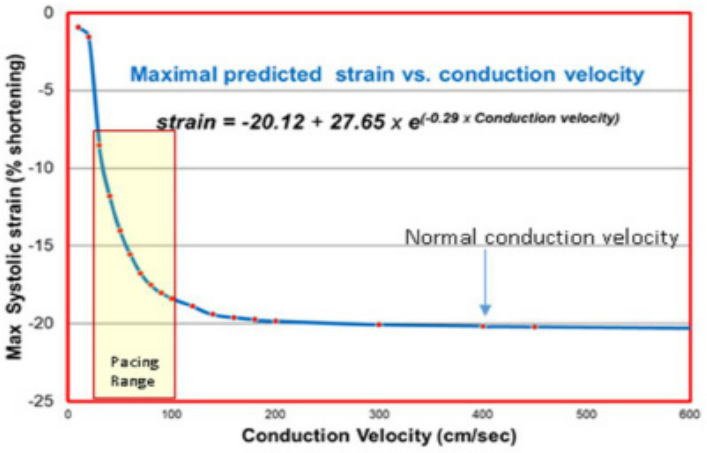

Figure 3: Average peak longitudinal segmental strain (max systolic strain) to conduction velocity correlation. The decrease in average peak strain with decreasing conduction velocity followed the following correlation equation : strain (%)= -20.12+27.65 x e [-0.29 x conduction velocity (cm/sec)]

some aspects to those in HF and reduced ejection fraction. Chronic left ventricular dyssynchrony due to regionally delayed electrical activation can induce regional and global molecular signalling that alters excitation –contraction coupling, energetics, arrhythmia susceptibility, and myocardial survival [11]. Moreover electrical conduction delay and mechanical dyssynchrony can trigger complex biomolecular changes beyond the known changes in HF [11]. Spragg et al [12] found in animal model that left ventricular dyssynchrony in failing hearts generates myocardial protein dysregulation concentrated in the late-activated, high-stress lateral endocardium. Such molecular polarization within the left ventricle creates transmural and transchamber expression gradients of calcium handling and gap junction proteins that may worsen chamber function and arrhythmia susceptibility.In another study [13], it was demonstrated that left ventricular dyssynchrony induces regional differences in potassium and calcium currents, which increased action potential duration in the lateral wall. Early after depolarizations were increased in the dyssynchronous failing heart.

Significance of the results

The understanding that pacing has a contractility cost may be very important to decision making related to pacemaker implantation in various indications, weighing mechanical cost vs. benefit of pacing. Moreover, as our simulation does not simulate pacing per-se, but rather the effect of decreasing Cvel, it can be generalized to the effect of native conduction defects. Thus, bundle branch blocks would be assumed to decrease contractility at segmental level above and beyond the creation of overall left ventricular dyssynchrony. Importantly, average Cvel at pacing sites adjacent to the conduction system (the conduction system could be early invaded by the electrical impulse generated by the pacing site and thus activates directly part of the myocardium) could be higher than at sites far from the conduction system. This may explain the differences that could be in contraction in different pacing sites and different forms of fascicular blocks and intraventricular conduction delays.

Specifically in patients candidates for biventricular pacing, higher baseline lateral strain would seem important to identify as pacing may decrease it beyond the power gain from realigning dyssynchronized walls. Moreover, the Cvel at the pacing segment can be measured during implantation to try to predict the mechanical cost of pacing. Finally this predictable loss of contractility could be used in situations where it me be desirable as in obstructive cardiomyopathy.

Beyond the understanding that pacing may reduce myocardial function and work efficiency, the results of this model support contemporary trends of engaging the conduction system in pacing. This may be especially important in patients with reduced ejection fraction before pacing to avoid further functional impairment. This could be assessed during lead positioning by echocardiographic strain imaging to assure best activation patterns with the least impact on contraction. However, the clinical benefit of this strategy should obviously be validated in a clinical trials. Recently, conduction system pacing (His bundle pacing or left bundle branch pacing) has been suggested to restore and retain normal electrical activation of the ventricles or to achieve electrical synchrony of the left ventricle [14,15]. His bundle pacing and left bundle branch area pacing have emerged as alternative method for CRT in patients with HF and left bundle branch block [16,17]. Our simulation suggests yet another advantage for that procedure maximizing contraction and timing of the paced segments. It may help selecting patients for this new procedure.

Theoretically, this model can be applied to atrial myocardium. Pacing at different sites in the atria may cause to different strains as the Cvel is not similar on all parts of atria. For example, Cvel along Crista Terminalis and Bachmann's bundle is relatively higher compared to other sites, and Cvel may be lower at fibrotic sites compared to normal sites. The clinical significance of pacing from different sites is not clear. Indeed, small studies have previously indicated that atrial pacing may precipitate atrial fibrillation [18,19]. Two large randomized studies have shown that low inter atrial septal pacing is superior to right atrial appendage pacing in preventing persistent or permanent atrial fibrillation in patients with sinus node dysfunction and intra-atrial conduction delay [20,21].In the other hand, no association between the

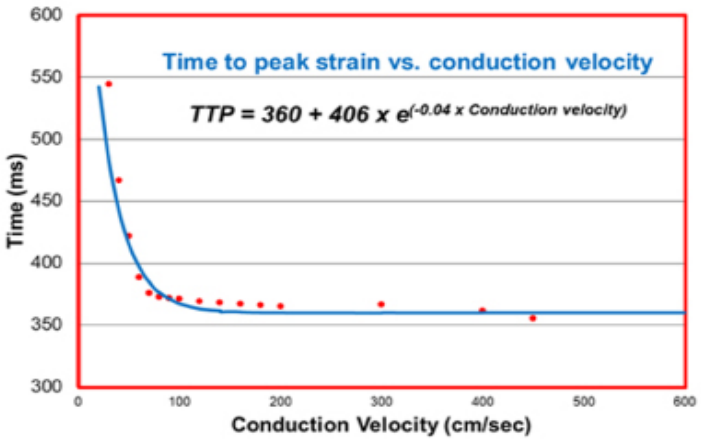

Figure 4: Time to average peak longitudinal segmental strain (TTP) to conduction velocity correlation. The correlation followed the equation: TTP (msec)= 360+ 406 x e [-0.04 x conduction velocity (cm/sec)].

percentage of atrial pacing and the development of atrial fibrillation was found in patients with sick sinus syndrome in other study [22].

Limitations

The simulation does not incorporate cellular pre-stretching by earlier activated cells. This is hard to account for, as it is dependent on tissue compliance that may vary according to left ventricular dysfunction etiology. Pre-stretching would adversely affect strain even more, thus the simulation may underestimate the effect of conduction velocity on strain.

In Summary

The simulation yielded a predictive correlation between slower conduction velocities with a decreasing segmental strain and with increasing delay in its timing, resulting from intra-segmental, or microscopic dyssynchrony. Clinical studies are needed to confirm the clinical significance of this model

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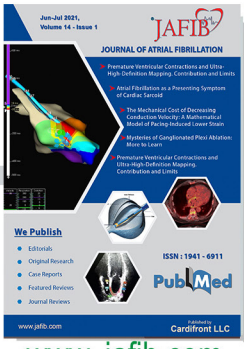

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Atrial Fibrillation as a Presenting Symptom of Cardiac Sarcoid

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Abstract

We submit an unusual presentation of spontaneous atrial fibrillation in a young, fit, active-duty U.S. military African-American male without evidence of structural heart disease. His atrial fibrillation was refractory to several ablation treatments over the course of 3 years. Subsequently he was diagnosed with extracardiac sarcoidosis and a fluorodeoxyglucose-positron emission tomography (FDG-PET) scan identified bi-atrial hypermetabolic lesions, concerning for cardiac sarcoidosis. Given the low incidence of atrial fibrillation in patients < 45 years-of-age, this case report aims to underscore consideration of cardiac sarcoidosis as a subclinical contributor towards developing atrial fibrillation in the appropriate patient population. Broadly more investigations are needed to explore the role of cardiac sarcoidosis with atrial involvement and the likelihood of developing atrial arrhythmias.

Learning objectives:

1) Atrial fibrillation (AF) in the absence of overt cardiac disease may be the first indication of another underlying disease. Therefore, AF in patients < 45y, which is refractory to catheter ablation should prompt further work-up for an underlying cause.

2) Cardiac sarcoid (CS) is known to cause congestive heart failure and a fatal complication, ventricular arrhythmias (VAs). Supraventricular arrhythmias (SVAs) in CS are infrequently described in literature, are less common than VAs, and include atrial tachycardia, atrial ectopy, atrial flutter, and AF.

Introduction

Sarcoidosis is a multi-organ chronic granulomatous disease of unknown etiology, characterized by non-caseating granulomas. Relatively uncommon, the annual incidence of sarcoidosis in the United States is estimated to be 0.011% among Caucasians and 0.036% among African-Americans, and is slightly more common in women than in men.[1] Clinical cardiac involvement in sarcoidosis has a prevalence of 5% and subclinical cardiac involvement is approximated to be 25%.[2] In the setting of cardiac sarcoidosis (CS), atrial arrhythmias are thought to be less common (19%) in comparison to ventricular arrhythmias (23%) and most commonly, complete heart block (30%).[3] The pathophysiology of atrial arrhythmias in CS remains unclear, but is thought to be less commonly either due to (1) sarcoid granulomatous deposition in the left atrium leading to inflammation and scarring or more commonly due to (2) elevated atrial pressures secondary to ventricular dysfunction and/or pulmonary hypertension.[4] Outside the setting of sarcoidosis, atrial fibrillation (AF) is the most common cardiac arrhythmia. In the United States, the 5 most common characteristics of patients with AF include female gender, age > 65years-of-age (y), hypertension, dyslipidemia, and obesity. However, the incidence of AF in patients < 45y, is only 3%.[5]

Key Words

Atrial Fibrillation, Atrial Arrhythmia, Cardiac Sarcoidosis, Cardiology, Internal Medicine

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Case report

A fit active-duty U.S. military African-American male with no significant past medical history initially presented with AF at age 40. His symptoms were a 3-day history of "racing heart," palpitations, and intermittent episodes of shortness of breath. He denied chest pain, diaphoresis, exercise intolerance, dyspnea on exertion, or any limitations in his activities of daily living. He maintained a vigorous physical fitness regimen, and was able to consistently score highly on his bi-annual military physical fitness test, which included running 2-miles within 13 minutes. Family history was negative for premature cardiovascular disease and AF.

Objectively, he was afebrile, normotensive with a blood pressure, 108/77 mmHg, heart rate, 89 beats-per-minute (BPM), respiratory rate, 20 breaths-per-minute, and had a normal body mass index, 24. Cardiovascular examination noted irregularly irregular rate and rhythm with normal first and second heart sounds. No murmurs, bruits, pulsating masses, or edema were observed. Jugular venous pressure was within normal limits. Peripheral pulses were normal in all extremities. Pulmonary examination was within normal limits. ECG (Figure 1) was notable for AF. Transthoracic and transesophageal echocardiogram (TEE) both demonstrated left ventricular ejection fraction (LVEF) 60-65% with normal sized ventricles, normal sized atria, no septal

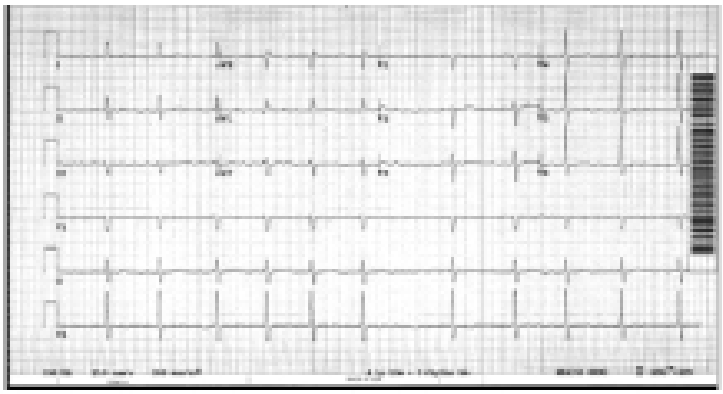

Figure 1: ECG demonstrating AF.

defects, trace mitral regurgitation, and otherwise normal valves. TEE was indicated to rule out left atrial thrombus prior to cardioversion. Left heart catheterization demonstrated no evidence of atherosclerotic cardiovascular disease. Polysomnography was obtained and was within normal limits. Patient underwent his first radio frequency ablation at age 40 and was successfully converted to normal sinus rhythm.

The following year, he developed symptomatic paroxysmal AF once again with heart rates up to 150 beats per minute. In the ensuing months, he failed beta-blocker rate control therapy and a rhythm control strategy with flecainide was chosen. Subsequently, he underwent 3 more ablations at ages 41, 42, and 43 over the course of 3 years respectively but his AF continued to be refractory. Fourteen-day ambulatory event monitoring was obtained after his latest ablation, which now confirmed persistent AF and identified rare episodes of non sustained ventricular tachycardia (NSVT) and ventricular ectopy (Figure 2). Ultimately, he was medically optimized on a combination of rate control (metoprolol succinate 25mg daily) and rhythm control (flecainide 100mg twice daily). Given that his CHA_2DS_2-VASc score was 0, he did not qualify for permanent anticoagulation. A defibrillator was not indicated at the time because NSVT burden was < 1% and the patient was still undergoing further work-up.

Shortly thereafter, patient (age 43) presented with right sided, non-exertional, non-dyspneic, non-radiating, non-traumatic chest pain localized to the ribs. Further work-up and imaging revealed bilateral hilar lymphadenopathy, small right sided pleural effusion, and several smaller bilateral pulmonary nodules. Right lower lobe endobronchial biopsy demonstrated chronic inflammation and noncaseating granulomas, confirming a diagnosis of sarcoidosis. FDG-PET scan noted hypermetabolic lesions within both atria, more prominent in the left atrium than in the right atrium (Figure 3) as well as a hypermetabolic lesion at the base of the cardiac septum (Figure 4). Maximum standardized uptake value (SUV) was 4.15, 3.8, and 4.21 in the left atrium, right atrium, and at the base of the cardiac septum respectively. Repeat echocardiogram noted diminished LVEF of 44%, left atrial dilation, left ventricular dilation, without wall motion abnormalities. Nuclear medicine myocardial perfusion scan demonstrated normal perfusion imaging of the heart without evidence of ischemia. Brain Natriuretic Peptide (BNP) was mildly elevated at 125 pg/mL, not consistent with heart failure (HF). Notably patient did not meet Framingham heart failure criteria and had no symptoms of HF. Steroid therapy was initiated with prednisone 20 mg daily and 3 months later, repeat FDG-PET scan noted resolution of hypermetabolic atrial lesions (Figure 3). Patient continued to be in AF, which had now progressed to permanent AF, CHA_2DS_2-VASc score stable at 0. Patient refused any further cardioversions and ablations. After extensive patient-physician discussion, rhythm control strategy with flecainide was abandoned and he was continued on rate control therapy with beta-blockade with good efficacy.

Discussion

Organs commonly involved in sarcoidosis include lungs, lymph nodes, skin, eye and central nervous system. Clinical cardiac involvement occurs in as few as 5% of sarcoid patients, although autopsy studies have demonstrated subclinical cardiac involvement in up to 25% of sarcoid patients. Notably in Japan, the leading cause of death in sarcoid patients is CS (up to 85%).[6] CS is known to cause congestive heart failure and a fatal complication, ventricular arrhythmias (VAs). Supraventricular arrhythmias (SVAs) in CS are infrequently described in literature, are less common than VAs, and include atrial tachycardia, atrial ectopy, atrial flutter, and AF.[3,7] Rarely, atrial arrhythmias (AAs) are caused by direct granulomatous involvement of the atria. Typically AAs are due to LV dysfunction or cor pulmonale.[7]

Our patient was clinically diagnosed with cardiac sarcoidosis based on the Heart Rhythm Society Consensus Statement for the Diagnosis of CS and the Japanese Ministry of Health and Welfare Criteria for Diagnosis of CS.[6] Specifically, he had (A) biopsy proven extracardiac sarcoidosis, (B) abnormal FDG-PET scan with notable bi-atrial and cardiac septal hypermetabolic lesions, (C) abnormal ECG (NSVT), and (D) abnormal echocardiogram demonstrating reduced LVEF< 50% without evidence of ischemia. The wide complex tachycardia noted on ambulatory monitor (Figure 2A) was thought more likely to be NSVT rather than supraventricular tachycardia with aberrancy (Ashman phenomenon) due to presence of an additional example of NSVT without the long-short sequence (Figure 2B), ventricular ectopy (Figure 2C), and presence of hypermetabolic lesion within the cardiac septum (Figure 4). Taken together, these findings were fundamentally diagnostic of CS.

In the setting of CS, LV dysfunction was thought to be secondary to infiltrative granulomatous myocardial disease. CHA_2DS_2-VASc score was utilized for anticoagulation, which was 0, therefore patient did not qualify for long-term anticoagulation. Beta-blockade for AF without treating the underlying cause (CS) was insufficient but beta-blocker

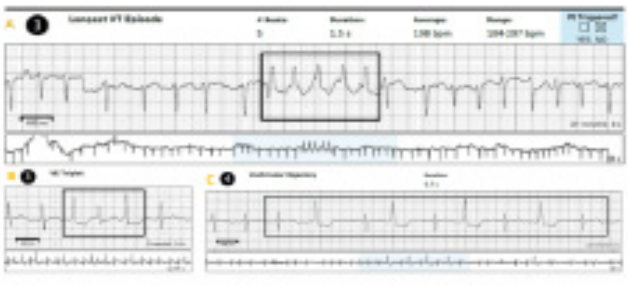

Figure 2: Ambulatory event monitor demonstrating asymptomatic NSVT lasting 5 beats (A), asymptomatic NSVT lasting 3 beats (B), and ventricular bigeminy (C).

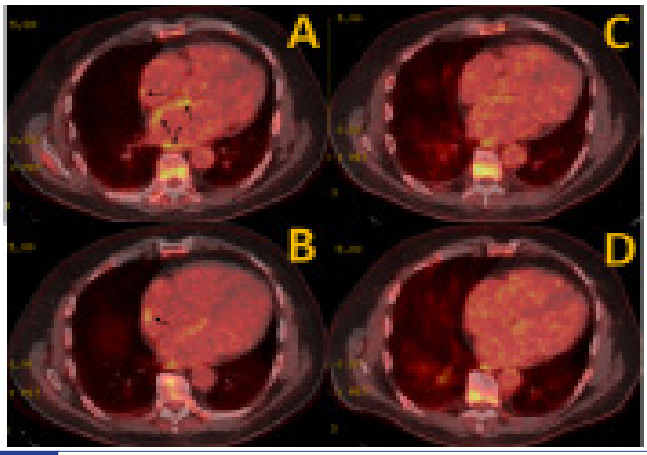

Figure 3: FDG-PET scan demonstrating bi-atrial hypermetabolic lesions (A and B), which resolved with steroid therapy (C and D). Hypermetabolic lesions are more prominent in the left atrium than in the right atrium (A and B). Left atrial maximum SUV was 4.15 and right atrial maximum SUV was 3.8 (A and B).

therapy following steroid therapy for systemic sarcoid was an effective rate-control strategy. Evident by improvement in conduction disease following steroid initiation as reported by Mehta et al.[1]

Initially, the patient presented with AF at age 40 without any evidence of structural heart disease or ischemia. His AF was refractory to 4 radiofrequency ablation treatments. Probable atrial sarcoid involvement was not identified till 3 years later via FDG-PET scan. The role of infiltrative cardiomyopathies like CS and the probability of developing SVAs in patients < 45y remains unclear. This case raises 2 questions, which require further investigation. (1) Predicting which young patients are at risk for developing SVAs with evidence of structural heart disease on echocardiography (left atrial enlargement and/or diastolic dysfunction). (2) More elusive and arguably more interesting is predicting which young patients are at risk for developing SVAs with no evidence of structural heart disease on echocardiography. Our case exemplifies the latter.

AF is primarily a disease of the elderly. The prevalence of AF in patients < 40y is as low as 0.5% and data on patients < 35y are scant. The pathophysiology of AF in young patients is broad and includes genetic factors, cardiomyopathies, and ion-channelopathies, and life-style factors (e.g. alcohol).[8] AF in the absence of overt cardiac disease may be the first indication of another underlying disease, or more rarely termed lone AF if no extracardiac cause can be identified.[9] Therefore AF in patients < 45y, which is refractory to catheter ablation should prompt further work-up for an underlying cause.

In patients with CS, development of AF is thought to be due to remodeling of the tricuspid annulus from elevated ventricular diastolic pressure. Uncommonly, however AF can be from inflammation, myocardial granulomatous involvement, and scarring. Deposition of sarcoid granuloma may occur more commonly and with greater density in the left atrium than in the right.[4] Due to these hypothesized structural changes, atrial ablation can offer a high, short, and intermediate post-procedural AF abortion rate. Saguner et al. estimated the efficacy of AF catheter ablation in young adults (mean age: 31) to be 84%.[10] Even after successful ablation, patients should be anticoagulated with warfarin or novel oral anticoagulant for at least 2 months, with continuation based on patient's current stroke risk profile rather than the clinical outcome of the procedure.[11]

In patients with AF with concomitant CS, the underlying granulomatous disease should be treated. However, there is limited data to guide therapeutic management in CS alone.[12] In our patient, with both cardiac and systemic sarcoid disease, the mainstay of treatment are corticosteroids to suppress granuloma formation and inflammation, as it has been shown to improve clinical and radiological findings. The survival benefit of steroids is unknown. Although there is some data to suggest improvement in cardiac magnetic resonance imaging findings at 12 months with steroid doses greater than 20 mg per day, more data are needed to determine the ideal dose for treatment. Steroid sparing agents such as methotrexate and azathioprine may also be used for refractory cases, although there is no consensus regarding ideal treatment regimen among non-steroidal options.[13] CS should be considered in the appropriate patient population presenting with AF. These include patients without a readily identifiable cause for AF who remain at an elevated risk for developing Sarcoidosis. Individuals at higher risk include those who are modestly female predominant, have age < 55y, are African-American, lack a history of hypertension, dyslipidemia, obesity, diabetes, tobacco use, and evidence of structural heart disease to include coronary artery disease and valvular disease.[14,15,16] CS should always be on the differential for patients presenting with new complete AV block, heart failure, and/or ventricular tachycardia without an apparent cause. Similarly, all patients with extracardiac sarcoidosis should be evaluated for CS.[17]

Acknowledgments

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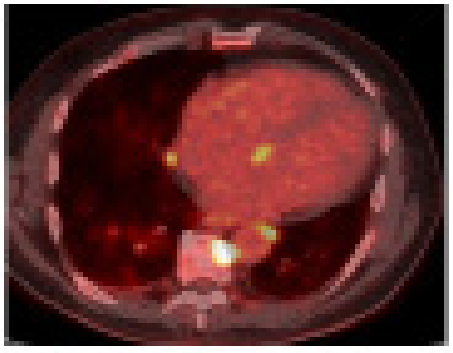

Figure 4: FDG-PET scan demonstrating hypermetabolic lesion within the base of the cardiac septum with maximal SUV 4.21.

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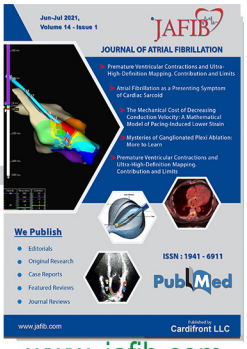

Hemoptysis post Radiofrequency Ablation of Atrial Fibrillation

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Abstract

Left atrial appendage (LAA) exclusion is the cornerstone of stroke prevention in surgical treatment of atrial fibrillation (AF).Still, little is known about the direct hemodynamic consequences of LAA closure. In the current pilot study, where we aimed to evaluate these consequences in patients undergoing hybrid AF ablation with LAA exclusion by an atrial clip, seven patients were included. Hemodynamic and intracardiac pressure measurements such as systemic, pulmonary artery (PA), central venous and LA pressure, cardiac output and indexed left ventricular stroke volume (LVSVi) were measured directly before (T0) and after (T1), and 10 minutes after (T2) LAA closure. We found no differences between all timepoints for LA pressure, PA pressure and LVSVi. As such, this is the first study describing the direct hemodynamic consequences of LAAexclusion. LAAexclusion by use of an atrial clip is safe and does not directly affect hemodynamic and intracardiac pressures.

Case Description

A 41-year-old female with symptomatic paroxysmal atrial fibrillation (AF), intolerant to antiarrhythmic drugs, was referred for catheter ablation. The patient had an elevated body mass index with no other significant comorbidities. She underwent an elective radiofrequency (RF) pulmonary vein isolation under general anesthesia Intravenous unfractionated heparin was administered during the procedure, The procedure was well tolerated, Anticoagulation was partially reversed with protamine at the end and Apixaban was restarted 4 h after removal of sheaths. The patient was discharged the following morning.

Six days post-ablation, the patient presented with dyspnea on minimal activity, cough, and blood in her sputum. Computed tomography (CT) of the chest with contrast revealed multifocal groundglass opacities surrounding the perihiliar pulmonary vasculature within the upper and lower lobes bilaterally, suggestive of alveolar hemorrhage (Figure, upper panel). The pulmonary arterial phase ruled out acute pulmonary embolism and there was no evidence of pulmonary vein stenosis. She was admitted to Intensive Cardiac Care for monitoring. Anticoagulation was temporarily discontinued. A complete rheumatology panel was negative. The hemoptysis gradually resolved within the next 24 h and she was discharged home after 3 days with only occasional dry cough. Anticoagulation was restarted 48 hours post discharge without recurrence of hemoptysis. A repeat CT scan, 3 weeks following initial imaging, revealed complete resolution of the pulmonary infiltrates (Figure, lower panel).

Hemoptysis is a rare complication of AF ablation. The differential diagnosis includes conditions such as pulmonary embolism or pulmonary vein stenosis, but the latter typically develops weeks to months post procedure1. Hemoptysis has also been described post cryoballoon ablation due to bronchial trauma or cryoinjury to the lung parenchyma2. Only a few cases of alveolar hemorrhage related to RF ablation have been reported3. Possible etiologic factors that have been postulated include mechanical ventilation-induced lung injury, the effect of high-dose intraprocedural anticoagulation, idiosyncratic lung injury related to anesthetic agents, and negative pressure pulmonary hemorrhage due to acute upper respiratory obstruction during extubation.

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Key Words

Pulmonary Hemorrhage, Catheter Ablation, Atrial Fibrillation

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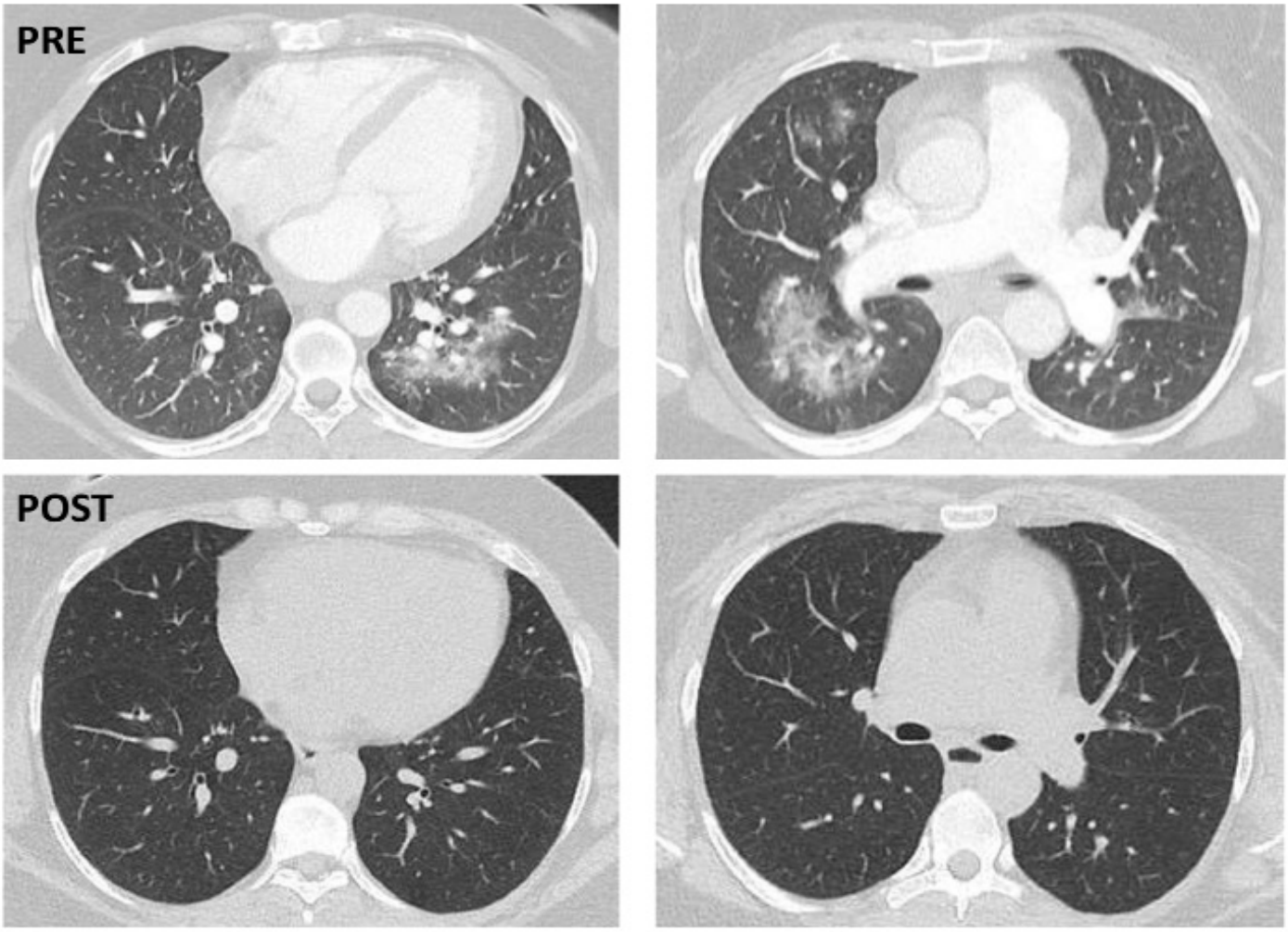

Figure 1: Upper Panel, Lower Panel

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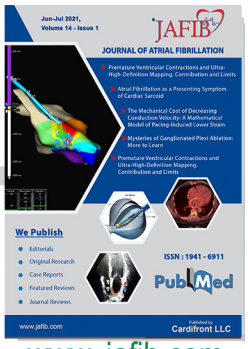

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Does Left Atrial Appendage Exclusion by an Epicardial Clipinfluence Left Atrial Hemodynamics? Pilot Results of Invasive Intra-Cardiac Measurements

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Abstract

Left atrial appendage (LAA) exclusion is the cornerstone of stroke prevention in surgical treatment of atrial fibrillation (AF).Still, little is known about the direct hemodynamic consequences of LAA closure. In the current pilot study, where we aimed to evaluate these consequences in patients undergoing hybrid AF ablation with LAA exclusion by an atrial clip, seven patients were included. Hemodynamic and intracardiac pressure measurements such as systemic, pulmonary artery (PA), central venous and LA pressure, cardiac output and indexed left ventricular stroke volume (LVSVi) were measured directly before (T0) and after (T1), and 10 minutes after (T2) LAA closure. We found no differences between all timepoints for LA pressure, PA pressure and LVSVi. As such, this is the first study describing the direct hemodynamic consequences of LAAexclusion. LAAexclusion by use of an atrial clip is safe and does not directly affect hemodynamic and intracardiac pressures.

Introduction

The left atrial appendage (LAA) is the most common site of thrombus formation in patients with non-valvular atrial fibrillation (AF).[1] Therefore, LAA exclusion, either through amputation, stapling or clipping, is the corner stone in the surgical treatment of AF to reduce stroke risk.[2] It is known that LAA closure can result in lower systolic blood pressure on the long term[3] and it is suggested that it can induce volume overload by neuro-hormonal modulation on the longer term asthe LAA is the predominant site of atrial natriuretic peptide (ANP) production in the heart.[4] However, the acute direct hemodynamic effects of its closureremain unknown.Therefore, the aim of the current pilot study was to report on the direct hemodynamic consequences of LAA closure evaluated by hemodynamic and invasive intracardiac pressure measurements during hybrid AF ablation.[5]

Key Words

Atrial Fibrillation, Radiofrequency Ablation, Natriuretic Peptides, Left Atrial Ejection Fraction, Left Atrial Strain.

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Materials and Methods

Patient population

Seven patients undergoing hybrid AF ablation were included in the current study (see Table 1). Patient were referred for paroxysmal or persistent AF. Our local ethics committee approved the prespecified study protocol (METC 14-5-078, dated October 10th, 2014).

Surgical procedure

The surgical procedure was described in detail elsewhere.6 Before incision, the absence of LAA thrombus is confirmed by trans-esophageal echocardiography (TEE). After surgical AF ablation consisting of bilateral pulmonary vein isolation with use of a biparietal bipolar radiofrequency (RF) ablation clamp (OLL2/OSL2 Isolator Synergy Access Clamp, Synergy System, AtriCure), and superior and inferior connecting lesions (so-called 'box-lesion') with use of unidirectional bipolar RF device (Coolrail, Atricure) via bilateral thoracoscopy, the LAA is excluded using the Atriclip Pro device (Atricure, Mason, OH, USA). Hereafter, endocardial validation of epicardial lesions and touch-up ablation, if needed, is performed. The creation of additional lesions is left at the discretion of the electrophysiologist (EP).

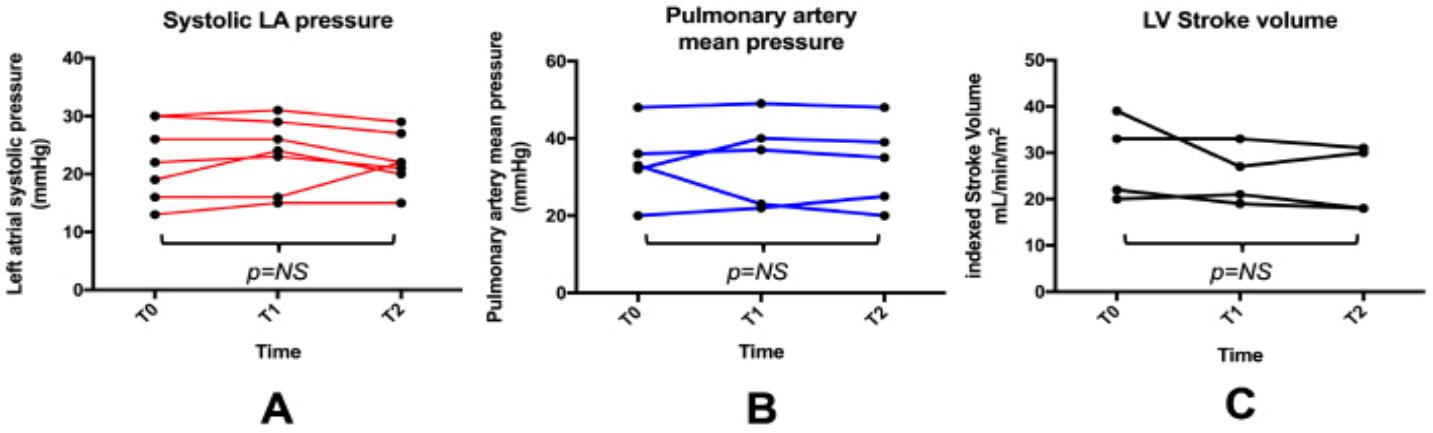

Figure 1: Graphical representation of the different invasive pressure and hemodynamic measurements

NS: non significant.

Echocardiographic evaluation

All patients underwent pre-operative trans-thoracic echocardiography with extensive atrial and ventricular function and dimension evaluation (Table 1). Per-procedural echocardiographic evaluation was performed with TEE (Epiq 5, Philips, Eindhoven, the Netherlands).

General anesthesia

General anesthesia was provided by total intravenous anesthesia (TIVA) using propofol (diprivan, hypnoticum) and sufentanil (opioid) with a low dose of norepinephrine (in the range of 0.05 mcg/kg/min). Before LAA exclusion, it was important to maintain a steady and stable hemodynamic condition (in terms of heart rate, blood pressure and cardiac output (CO)). Therefore, hemodynamic parameters were observed during a 10 minute period, and when stable, we proceeded with LAA exclusion. During LAA exclusion and intracardiac pressure measurements, no interventions such as volume-loading (preload) or administration of additional vasoactive medication (afterload) were necessary.

Pressure and hemodynamic measurements

Systemic arterial pressure was registered by a left radial artery catheter (Arrow, Teleflex, Athlone, Ireland), central venous pressure by a central venous catheter in the right jugular vein. Pulmonary artery (PA) pressuresweremeasured by a Swan-Ganz PA catheter (Edwards Lifesciences, Irvine, CA, USA). Cardiac output (CO)and left ventricular stroke volume (LVSV) were assessed based on arterial pressure derived monitoring (MostCareUp, Vygon, Padua, Italy). The pressure analytical method used to derive the LVSV has been described extensively elsewhere.7 Cardiac output was calculated from LVSV and heart rate using the formula: CO(liters per minute)=LVSV (liters)× heart rate (beats per minute).

For the intra-cardiac pressure measurements, transseptal puncture was performed by a flexible introducer and needle, through the right femoral vein (Agilix NXT, Abott, Lake Bluff, IL, USA). Intra-atrial location of the pressure wire allowed for precise and direct LA pressure measurements.All measurements were performed just before LA exclusion(T0), 1 minute after LA exclusion(T1) and 10 minutes after LA exclusion(T2). All patients were in sinus rhythm (without need of cardioversion) at the time of LAA exclusion and intra-cardiac pressure measurements.

Statistical analysis

Given the small study population, all data were presented as median and corresponding ranges. Testing for differences at the different prespecified timepoints was performed by use of the Wilcoxon-signed rank test. A two-sided p-value of <0.05 was considered statistically significant. Testingwasperformed for T_0 versus T_1, T_1 versus T_2 and T_0 versus T_2. Due to the sample size, data were also presented in graphs at the different timepoints for visual assessment. All statistical analyses were performed in SPSS for Mac (SPSS version 27, Armonk, NY, USA). Graphs were realized using GraphPad Prism version 7

Table 1: Baseline and surgical characteristics

	Sex	Age (years)	BSA (m2)	LVEF (%)	LAvol (mL)	LAVI (mL/m²)	Rhythm at incision	Clip size (mm)
Patient 1	M	68	1.96	56	127	65	AF	35
Patient 2	M	62	2.02	58	102	60	AF	35
Patient 3	M	66	2.31	43	89	39	SR	40
Patient 4	M	55	2.20	58	66	30	AF	35
Patient 5	M	69	1.94	60	95	49	AF	35
Patient 6	F	68	1.77	66	81	46	AF	35
Patient 7	M	66	2.08	56	78	38	SR	35

AF: atrial fibrillation, BSA: body surface are, LAVI: indexed left atrial volume, LAvol: left atrial volume, LVEF: left ventricular ejection fraction, SR: sinus rhythm

Table 2: Pressure measurements and hemodynamic parameters

	T0	T1	T2	p-value
Systolic LA pressure	22 mmHg [13-30]	24 mmHg [15-31]	22 mmHg [15-29]	0.865
Mean PAP	33 mmHg [20-48]	37 mmHg [22-49]	35 mmHg [20-48]	1.000
Indexed LVSV	28 mL/m² [20-39]	24 mL/m² [19-33]	24 mL/m² [18-31]	0.066
Systemic MAP	83 mmHg [74-90]	88 mmHg [72-104]	88 mmHg [73-100]	0.345
CVP	19 mmHg [7-27]	23 mmHg [6-24]	23 mmHg [6-24]	0.496
SvO2	73% [64-77]	78% [72-78]	76% [72-78]	0.368

Data is presented as median and corresponding [ranges], p-value presented for T0 versus T2. CVP: central venous pressure, LA: left atrial, LVSV: left ventricular stroke volume, MAP: mean arterial pressure, PAP: pulmonary artery pressure, SvO2: central venous oxygen saturation

(GraphPad software, La Jolla, CA, USA).

Results

Patients

Median age of the patient population was 66 years (range 55-69), and included one female (14%). All patients underwent stand-alone hybrid ablation without concomitant procedures. Clip size was determined intra-operatively by assessing the LAA size with the bipolar linear RF device (Atricure). All but one patientreceived a size 35mm clip (86%). All patients were referred for paroxysmal or persistent AF, 5 patients were in AF at the beginning of the surgery (72%), 2 in sinus rhythm (SR, 28%). At the time of LAA exclusion and intra-cardiac pressure measurements, all patients were in SR.

Invasive measurements

Systolic LA pressure

Median systolic LA pressure at baseline (T0) was 22mmHg (range 13-30), 1 minute after LAA exclusion(T1) 24mmHg (range 15-31mmHg) and 10 minutes after LAA exclusion(T2) 22mmHg (range 15-29mmHg). There were no significant differences in LA pressure between the different timepoints T0 versus T1, T1 versus T2 or T0 versus T2 (p=0.131, p=0.339 and p=0.865 respectively, Figure 1A, Table 2).

Mean PA pressure

Mean PA pressure at T0 was 33mmHg (20-48mmHg), at T137mmHg (22-49mmHg) and at T235mmHg (20-48mmHg). There were no differences in mean PA pressures between the timepoints (p=0.498, p=0.414 and p=1.000 respectively, Figure 1B, Table 2).

Indexed LV stroke volume

LVSV was measured and corrected for body size (LVSVi) by use of the body surface area (BSA). At baseline, LVSVi was 28mL/m² (20-39mL/m²), at T1 24mL/m² (19-33mL/m²), and at T2 24mL/m2 (18-31mL/m²). There were no significant differences in LVSVi at the different timepoints and overall (p=0.285, p=0.581, p=0.066 respectively, Figure 1C, Table 2).

Other measurements

Other hemodynamic measurements, such as mean systemic arterial pressure (p=0.345), central venous pressure (p=0.496) and central venous oxygen saturation (p=0.368) did not exhibit a statistical difference between T0 and T2 (Figure 1, D-F, Table 2).

Discussion

In the setting of hybrid AF ablation, we have the unique possibility of simultaneous measurement of intracardiac pressures, without adding risk to the procedure.[6] As such, the current pilot study is the first to perform intracardiac pressure measurements intra-operatively. We aimed to evaluate the direct hemodynamic consequences of LAA exclusion in these patients. Surprisingly, we did not observe any significant changes in hemodynamic parameters or intracardiac pressure measurements just before, directly after, and 10 minutes after release of the atrial clip.

Neurohormonal, the LAA is the main site of ANP production, and as such, it is perceived that its exclusion can lead to volume overload in the days following surgery. In addition, the LAA also has a contractile function and takes part in the LA contraction process, especially in patients in SR. In patients in SR, LAA ejection fraction (EF) was measured to be 46%, while in the same patients in AF, EF was 26%, demonstrated in an elegant study by Akosah et al.[8].

Potentially, as LAA contractile function is already diminished in patients in AF – five of seven patients in this study were in AF at the time of surgery – its exclusion does not significantly affect LA contractile function in general. Still, our findings seem in line with a previous study by de Maat et al.[9], where LA function was measured only by echocardiographyin patients with paroxysmal AF, undergoing this procedure.

Limitations

The current pilot study included a modest number of patients, which were predominantly in AF. Therefore, it cannot be ruled out that LAA exclusion in larger patient cohorts in SR, does affect hemodynamics. Furthermore, the LAA comes in different sizes and variations, which was not assessed in the current study. It might be possible that its exclusion does have consequences in larger sized LAA's.

Conclusion

This is the first study demonstrating the direct hemodynamic consequences of LAAexclusion by intracardiac pressure measurements. Although this pilot study population was modest in numbers, LAAexclusion by use of an atrial clip appeared to be safe, without affecting hemodynamic and intracardiac pressures. Future studies with larger patient cohorts are warranted to corroborate these findings.

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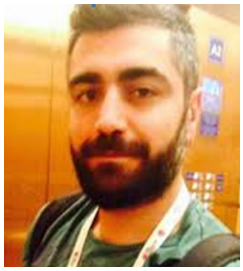

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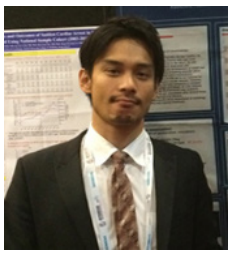

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