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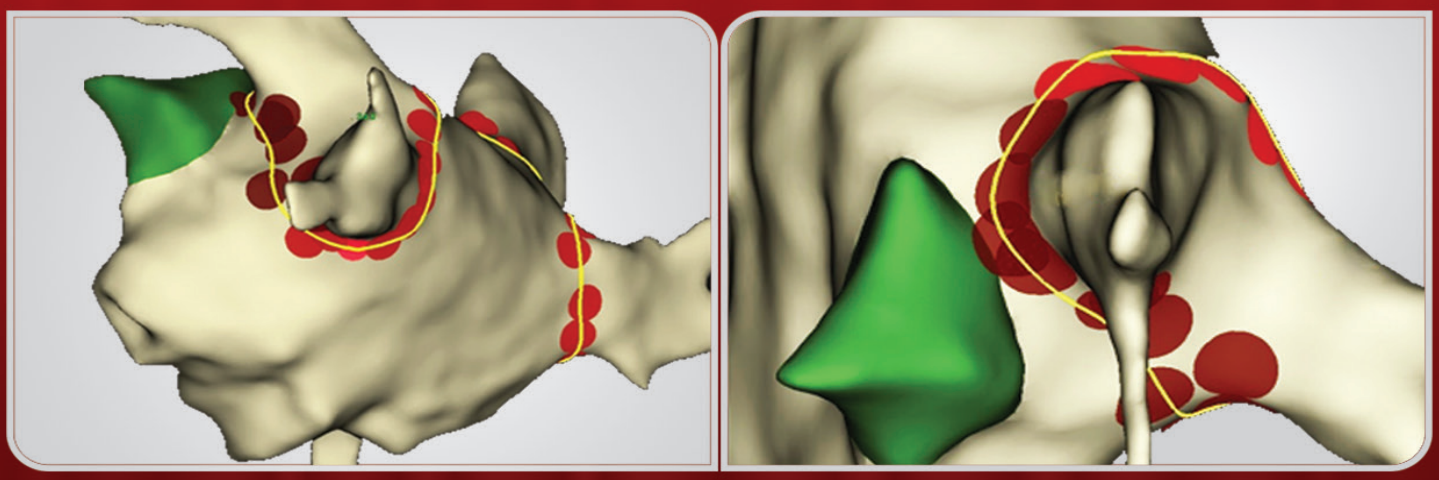

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Editorial

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MAVERIC, CABANA and more.....

Dear Colleagues

Welcome to the May issue of the Journal of Atrial Fibrillation. Somehow Spring totally skipped North America this year. We jumped straight from Winter to a Toasty Summer already with record 3-digit temperatures by the end of May. Untimely tropical storms in the Southeast and volcanic eruptions in the Hawaii island all of it can point to some sinister climatic changes that we may want to think twice about. Or may be its all fake news!!

Heart Rhythm Society (HRS) successfully completed the 39th annual sessions in Boston with another great turnout from all around the world. We want to congratulate George Van Hare MD, the immediate past president of HRS for his contributions to the society and his leadership. Hearty welcome to Thomas Deering MD on his new assignment to be the current President of HRS. Tom in his acceptance speech has laid out his vision for the society's grass roots level engagement and global outreach.

There were several thought-provoking studies and many more exciting ideas presented at the HRS, that will continue to advance the field of Electrophysiology. Of the several late breaking clinical trials presented some are worth talking about. There was a late breaking clinical trial that summed the cumulative data on device related thrombus from the Watchman experience. This opened several important questions about the need for extended surveillance in the post implant phase and whether we should understand the factors that drive this. Or newer devices could potentially address this issue by making some structural changes. May be epicardial left atrial appendage excluders are better choices! The MAVERIC registry from our group looked at the potential etiopathogenesis of high burden- symptomatic premature ventricular contractions. It is sobering to know that more than 50% of these patients may actually have underlying myocarditis as an inciting cause. Systematic use of Fluorodeoxy Glucose mediated Positron Emission Tomography (FDG-PET) and Magnetic Resonance Imaging with delayed hyperenhancement (MRI-DHE) may help identify these patients who may represent the early phase of the initiation of non-ischemic cardiomyopathic process. Perhaps, aggressive upstream therapy of myocarditis may have some several important implications that are worth taking into consideration. Steroids were helpful only marginally and use of real immunosuppressants like methotrexate, mycophenolate etc, was successfully in treating the myocarditis associated with excellent clinical response. This we believe is the first step towards our understanding of the non-ischemic cardiomyopathies.

Then the most anticipated study of the last decade – CABANA! Doug Packer and co-investigators presented the results of a randomized controlled trial that looked at the difference between catheter ablation and medical therapy with antiarrhythmic drugs. A total of 2204 patients were enrolled. 9% of patients randomized to the ablation arm never got it and 28% of patients randomized to the drug arm moved on to get an ablation before the completion of the 5 year follow up. Even though the intention to treat analysis showed no significant difference in the primary outcomes, we still believe that CABANA still revealed several important positive attributes of therapeutic ablation. Patient who had CA have 47% higher chance staying in sinus rhythm and those who actually received CA have improved mortality (40%). The primary end points of death, strokes, bleeding, and cardiac arrests of this study was dramatically lowered with ablation. In fact, those patients who actually got an ablation in this study experienced a 33% lower risk of death, strokes, bleeding, or cardiac arrest. While it is disappointing for puritan trialists it is win for patients who continue to show significant improvement in their quality of life. This is a perfect example of how intention-to-treat analysis may not be the end all approach to analyze and understand the impact of therapeutic strategies. While the debate continues, for those who oppose catheter ablation what other real options do you have – Angiotensin receptor blockers, statins and magnesium supplements? It was interesting that in a recent debate a famous CA

contrarian agreed that he will consider ablation if he were to develop symptomatic AF. While meaningful scientific discourse is important, pragmatic approaches to cure diseases is our responsibilities as the takers of the Hippocratic Oath. The full manuscript on this study will hopefully come out soon and address the many unanswered questions.

Have a great summer.
Best wishes

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Prospective Evaluation of Lesion Index-Guided Pulmonary Vein Isolation Technique in Patients with Paroxysmal Atrial Fibrillation: 1-year Follow-Up

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Abstract

Background: Pulmonary vein isolation (PVI) using contact force (CF) sensing ablation catheters currently relies on CF and force-time integral (FTI) guidelines. Such measurement of lesion effectiveness still lacks information on current delivery to the tissue, influenced by system impedance and power. Lesion Index (LSI) is a multi-parametric index incorporating CF and radiofrequency current data across time. We aimed to prospectively assess the efficacy of an LSI-guided approach to PVI in patients with paroxysmal atrial fibrillation (PAF).

Methods and Results: The study prospectively enrolled 28 consecutive patients with PAF undergoing PVI with a CF sensing catheter (TactiCathTM, Abbott). LSI-guided ablation target was adapted according to the mean regional thickness of pulmonary vein antra (PVA): LSI range 5.5-6 was pursued in the anterior and septal portions of PVA, 5-5.5 elsewhere. Data from 32 consecutive PAF patients who underwent PVI ablation with a non-CF guided approach (NCF-group) were retrospectively collected for comparison of procedural and clinical outcome.

AF-free survival rate at follow-up (17±6 months) was higher for LSI-guided group than NCF-group (89.3% vs 65.6%, p=0.037), with no increase in periprocedural complication rate (no tamponades or other major adverse events reported). Among 1126 lesions with LSI within target range (5-6), average CF was >10g and <30g for 976 lesions (86.7%). Moreover, 1015 lesions (90.1%) had FTI>400gs, but with wide distribution: 30.2% within 400-500gs, 30.0% within 501-600gs, 29.9% over 600gs.

Conclusions: In this first prospective study, LSI-guided PVI improved clinical outcome without any increase in complication rate when compared with standard, non-LSI-guided approach.

Introduction

The The cornerstone of radiofrequency (RF) catheter ablation of paroxysmal atrial fibrillation (PAF) is pulmonary vein (PV) isolation (PVI)[1,2], which is achieved by creating contiguous, transmural lesions around the ostia of the PV. When AF recurs after PVI, it is frequently associated with the reconnection of conduction between PVs and the left atrium (LA)[3] due to inadequate lesions. Using standard irrigated catheters, parameters such as RF power, catheter tip temperature, impedance drop, and modification of the intracardiac signal are commonly exploited during RF delivery. However, these provide limited accuracy in assessing lesion quality.

The use of contact force (CF)–sensing catheters enables stability and lesion depth to be controlled more precisely during point-by-point PV encircling, since no effective lesion is formed without adequate CF, and excessive CF is associated with excessive tissue heating and an increased risk of steam pop occurrence[4,5]. The feasibility and efficacy of CF monitoring during AF ablation have already been demonstrated in terms of reductions in procedural time, radiation exposure and the incidence of PV reconnection (PVR), and of increased success rates[6-8].

The formula combining CF and RF time - identified as the Force-Time-Integral (FTI) - can provide better real-time information on lesion depth and diameter than CF alone, thereby increasing the efficacy and safety of RF ablation[9,10]. However, FTI does not incorporate the important role of power delivery.

Lesion Index (LSI) is a proprietary multi-parametric index that aggregates CF and RF current data across time during ablation. It could predict the extent of myocardial tissue lesions more accurately than FTI[11] and guide AF ablation, thereby achieving better acute and long-term success rates. Retrospective studies on the correlation between procedural outcome and compliance with CF guidelines including LSI demonstrated a strong correlation of the index with PV durable isolation[12,13].

In clinical practice, differences in the frequency of PVRs and in clinical outcomes after PVI with and without CF monitoring have not yet been fully investigated. Acute and late PVRs still occur, and data on 1-year outcome are not consistent across studies.

Key Words

Radio Frequency Ablation, Contact Force, Lesion Index

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In the present study, we aimed to assess prospectively the efficacy of the LSI-guided approach to PVI in patients with PAF. Rates of acute PVI and 1-year success (defined as freedom from AF recurrence) using this approach were then compared with those recorded in a similar group of patients, retrospectively but consecutively recruited from our database of patients who had undergone a non-LSI-guided PVI procedure for PAF.

Material and Methods

Study Population

In accordance with current guidelines, patients with symptomatic PAF (defined as ECG-proven episodes of AF which are self-limiting and last up to 7 days on each occurrence or which are electrically or pharmacologically cardioverted within 7 days) refractory to or intolerant of at least one antiarrhythmic drug were scheduled to undergo circumferential PVI. The exclusion criteria were: age under 18 years, previous AF catheter ablation, severe structural cardiac abnormalities and less than 6 months of follow-up after PVI.

LSI-Guided Group

From June 2015, all patients undergoing PVI for PAF with a CF sensing catheter were followed up prospectively. All patients provided informed consent. The local institutional review committee approved the study protocol.

Non-Contact Force (NCF) Group

Data from consecutive patients who had undergone PV ablation for PAF from October 2014 to June 2015, by means of a non-CF ablation catheter, were retrospectively collected and compared with those of the LSI-guided group.

Ablation Protocol

Prior to the ablation procedure, a transesophageal echocardiogram was routinely performed to assess the left atrial appendage (LAA) for thrombus, chamber size and dimensions and anatomical structures. Antiarrhythmic drugs (AAD) were discontinued at least five half-lives before the procedure.

PVI was performed under conscious sedation. Intravenous heparin was administered at the time of trans-septal puncture, the target being an activated clotting time > 300 sec during the procedure.

A deflectable multi-electrode catheter was positioned inside the coronary sinus (CS) via the left femoral vein. Access to the LA was obtained by means of a single trans-septal puncture. Via the right femoral vein access a circular decapolar catheter, Reflexion Spiral™ (Abbott) was then positioned in the LA through a 8.5-French long sheath (SL0, Abbott) and the irrigated ablation catheter (using either a fixed SL0 long sheath or a steerable AgilisTM, Abbot, sheath). All procedures were carried out with the aid of the EnSiteTM VelocityTM/PrecisionTM mapping system (MS), by using the One ModelTM software. In all patients, the geometry of the LA was reconstructed by alternately using both the circular and the ablation catheters.

Continuous circumferential lesions were then created by using either a point-by-point (where RF energy was interrupted after the ablation target was achieved and before to move the catheter tip over the next LA antral segment) or a drag technique (where the catheter tip was moved to the next position after the ablation target was achieved but without interrupting RF delivery), guided by the circular mapping catheter and 3D MS. Lesion lines were created about 5 mm outside PV ostia, and all RF sites were tagged onto the 3D left atrial geometry on the MS.

The ablation targets were to eliminate local near-field PV signals on the circular diagnostic catheter and to achieve bidirectional conduction block between the LA and PVs when standard pacing maneuvers were implemented.

LSI-Guided Group

A 7-French 3.5 mm open-tip irrigated ablation catheter was used: TactiCathTM Quartz (Abbott). This catheter has a force sensor incorporated into its distal part; the sensor consists of a deformable body and 3 optical fibers that use infrared light to measure micro-deformations caused by forces applied to the tip of the catheter.

Real-time CF, FTI and LSI values were monitored on the MS.

LSI is a novel ablation index that incorporates CF between the ablation tip and target tissue, applied current and duration of RF delivery, expressing the non-linear lesion formation due to the heterogeneity of concurring factors: resistive heating during the early phase and conductive heating during a later phase.

The equation describing the LSI model is:

$$LSI\ (F, I, t) = k_I * (f_2(1-e^{-F/f_1}) + f_0)*i_2(1-e^{-(I/i_1)2})*\{(1-k_0)+k_0\,[(1-e^{-t/\tau})/(1-e^{-60/\tau})]\}$$

Where f_0, f_1, f_2 are force parameter coefficients, i1 and i2 are electrical current coefficients, k_0 is a diffusive heating coefficient and τ is a characteristic time value. The equation comprises a resistive heating component $(1-k_0)$ that is independent of time: resistive heating occurs in the first 3 to 5 seconds of RF delivery and accounts for a lesion maximum depth up to 4 mm. The diffusive heating component, $k_0\,[(1-e^{-t/\tau})/(1-e^{-60/\tau})]$ in the equation, is time-dependent, slower (30-50 s), reaches a maximum depth of 6-9 mm and reflects heat conduction from the initial resistive lesion[11].

The CF target ranged from 10 g to 30 g, in keeping with the recommendations that were established and validated after the EFFICAS I and II studies[10,14]. The LSI target was 5-5.5 in the posterior wall, roof and floor of PV antra, and 5.5-6 between the left PVs and LAA and in the septal portion, in accordance with reported data from a subgroup of TOCCASTAR12 and EFFICAS I patients13 and specific LA wall thickness15,16 (Figure 1).

AutoMarkTM lesion color scale by LSI value is also shown on the left column. RF energy was delivered in a temperature-controlled mode (upper limit 42°C).

The RF power output was limited to 25 W in the posterior wall and roof segments, and was set to 30 W during ablation of the anterior segments of the left PVs and the septal segments of the right PVs.

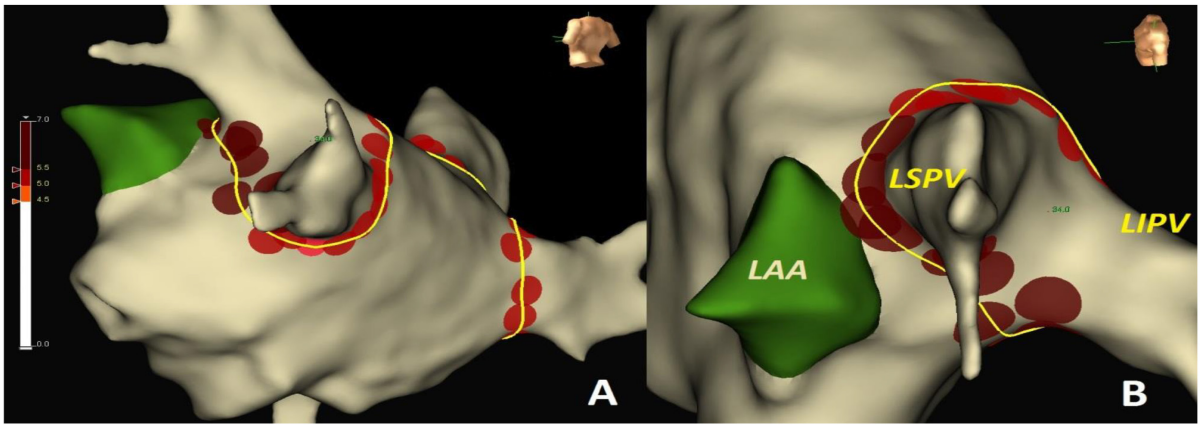

Figure 1A & 1B: **1A: In the posterior wall, roof and floor of PVs, where the expected wall thickness was lower, LSI level ranging from 5 to 5.5 were targeted (bright red dots).**
1B:In the LA segments with thicker walls, such as the carina between the left PVs and the LAA and in the septal segments, the target LSI values ranged from 5.5 to 6 (brown dots).

These power sets were chosen to achieve an optimal safety profile and in accordance with the recommendations on the use of the TactiCathTM Quartz catheter.The location of each RF application along the isolation line was assigned to 1 of 4 predefined positions around each PV: posterior and anterior wall, roof and floor.

All RF sites were tagged automatically onto the 3D left atrial geometry on the MS by means of the EnSite™ AutoMark™ module (Abbott), which is able to simultaneously record the catheter position, CF, FTI, LSI, start time of ablation, RF power, the number of ablations and the sequence of lesion deployment.

The catheter tip stability was automatically addressed by the AutoMark™ module using three stability indexes: Average Contact Force, Constant Force and Stable Contact Force (where Average Contact Force is the average force to be considered as acceptable; Constant Contact represents the minimum force to be considered for contact versus no contact, providing feedback on the degree of intermittent contact; Stable Contact Force provides feedback on the degree of contact force variation over time, the time interval over which the stability of the force is analyzed: 3sec).

RF lesions were deployed in a given segment only when all the three indicators target values were simultaneously reached (average CF > 10 grs, constant contact > 2 grs and stable CF < 7.5 grs).

A new lesion tag was added by the MS to the ablation map when the automatically measured distance from the previous lesion was 5.5 mm or more (Marker Spacing was set > 5.5 mm), while the precise distance from the previous lesion was not available.

NCF Group

A 3.5 mm tip (Thermocool™ Biosense Webster) or 4 mm tip FlexAbility™ (Abbott) irrigated ablation catheter was used with a SL0 sheath. Catheter stability before each RF application was confirmed by means of fluoroscopy. The RF power output ranged from 30 W, in posterior and roof portions, to 35 W in the anterior line of the left PVs and septal portion of right PVs. Each application of RF energy was delivered for 40 to 60 s, based on both impedance drop and modification of local intracardiac electrogram, with a maximum temperature of 42°C.

PV check

We confirmed acute PVI in both groups by demonstrating entry and exit block by means of a 10-pole circular mapping catheter placed sequentially in each of the PVs. At least 30 minutes after electrical isolation of each PV, we performed a check to confirm bidirectional conduction block between the LA and PVs during sinus rhythm. In the event of reconnection, touch-up ablation was performed at the presumed site of the gap until PVI was obtained. Only in the LSI-guided group the locations of touch-up lesions were tracke.

Follow-up

AF recurrence was defined as any episode lasting at least 30 seconds that was documented by ECG during scheduled visits and by 24-h Holter, when available, or by reports from the emergency room when medical intervention was required. After a blanking period of 3 months following the procedure, antiarrhythmic therapy was resumed at the discretion of the treating physician. ECG Holter monitoring was performed after 3, 6 and 12 months and then every 6 months.

Statistical Analysis

Continuous variables were expressed as mean ± SD when normally distributed, while non-normally distributed data were reported as medians and interquartile ranges. For normally distributed data, comparative analyses were performed by means of Student's t test for equal and unequal variances when appropriate. Statistical analyses on CF data were based on the analysis of variance tests (ANOVA and Kruskal-Wallis). Categorical variables were expressed as counts and percentages and were compared by means of the Chi-square test or Fisher exact test. A probability value (p) of < 0.05 was considered to be statistically significant. The statistical analyses were made by means of STATA 13.1 statistics software (StataCorp LP, College Station, TX, USA).

Results

Twenty-eight consecutive patients were enrolled in the LSI-

Table 1: Characteristics of the patients and procedural details in non-contact force (NCF) and LSIguided groups.

	All patients (N = 60)	NCF (N=32)	LSI-guided (N= 28)	p-value
Age, mean ± SD [years]	60.0 ± 10.2	58.9 ± 10.0	61.2 ± 10.6	0.40
Gender, male, n (%)	38 (63.3)	19 (59.4)	19 (67.9)	0.50
BMI, mean ± SD [kg/m^2]	26.3±4.1	26.9 ± 4.7	25.5 ± 3.2	0.20
History of Heart Failure, n (%)	0	0	0	—
Hypertension, n (%)	24 (40.0)	13 (40.6)	11 (39.9)	0.92
Cardiomiopathy, n (%)	12 (20.0)	9 (28.1)	3 (10.7)	0.09
NYHA Class: I, n (%)	60 (100)	32 (100)	28 (100)	—
CHADS2-VASC:				
0, n (%)	16 (26.7)	10 (31.2)	6 (21.4)	
1, n (%)	16 (26.7)	8 (25)	8 (28.6)	
2, n (%)	21 (35.0)	10 (31.2)	11 (39.3)	0.38
3, n (%)	5 (8.3)	4 (12.5)	1 (3.6)	
4, n (%)	2 (3.3)	0	2 (7.1)	
5, n (%)	0	0	0	
Left atrial AP Diameter, mean ± SD [mm]	40.1±5.4	40.0 ± 5.6	40.1 ± 5.2	0.96
History of paroxysmal AF, mean ± SD[months]	54.2 ±55.0	57.9 ±67.2	49.8 ± 36.4	0.56
Failed AADs, mean ± SD [n]	1.2 ± 0.6	1.4 ± 0.7	1.1 ± 0.5	0.09
Ejection Fraction, mean ± SD [%]	64.4±5.8	63.7 ± 6.6	65.4 ± 4.6	0.26
PVs anatomy:				
4 PVs, n (%)	50 (83.3)	29 (90.6)	21(75.0)	0.22
LCPV, n (%)	9 (15.0)	3 (9.4)	6 (21.4)	
LCPV+RCPV, n (%)	1 (1.7)	0	1 (3.6)	
Ablation Count, mean ± SD [Adim]	35.2 ±12.4	30.2 ± 9.8	40.3 ± 12.8	0.002
RF Time, mean ± SD [min]	37.7 ±8.6	38.7 ± 9.5	36.7 ± 7.5	0.38
Procedure Time, mean ± SD [min]	191.1 ±39.9	200 ±28.3	180.9 ±48.7	0.07
Fluoroscopy Time, mean ± SD [min]	24.9 ±10.6	29.1±11.2	20.1 ± 7.4	<0.001
Acute Complications, n (%)	3 (5)	1 (3.1)	2 (7)	0.6

guided group and compared with 32 historically treated patients (NCF group).

Patient Characteristics

[Table 1] summarizes the general demographics of the study population. There were no significant differences between the two treatment groups.

LSI-Guided Group : Description of Contact Force Parameters (Figure 2,Table 2)

In the LSI-guided group, 1909 ablation records were available, 1797 (94.1%) of which were used for analysis; 112 RF applications (5.9%) lasting less than 6 seconds were excluded owing to poor catheter stability and tissue contact. An accurate description of the topographic distribution of CF, FTI and LSI parameters was obtained, as each RF application was assigned to one of the 4 specific anatomic locations around each PV (anterior, posterior, roof and floor), as previously mentioned. In line with the protocol, higher LSI values were reached in the anterior and septal segments (median LSI = 5.7 [5.3-6]) than in the posterior wall (median LSI = 5.3 [4.9-5.6], p <0.001) and roof (median LSI 5.5 [5-5.9], p = <0.001).

Among the total number of analyzed lesions, 1126 had an LSI

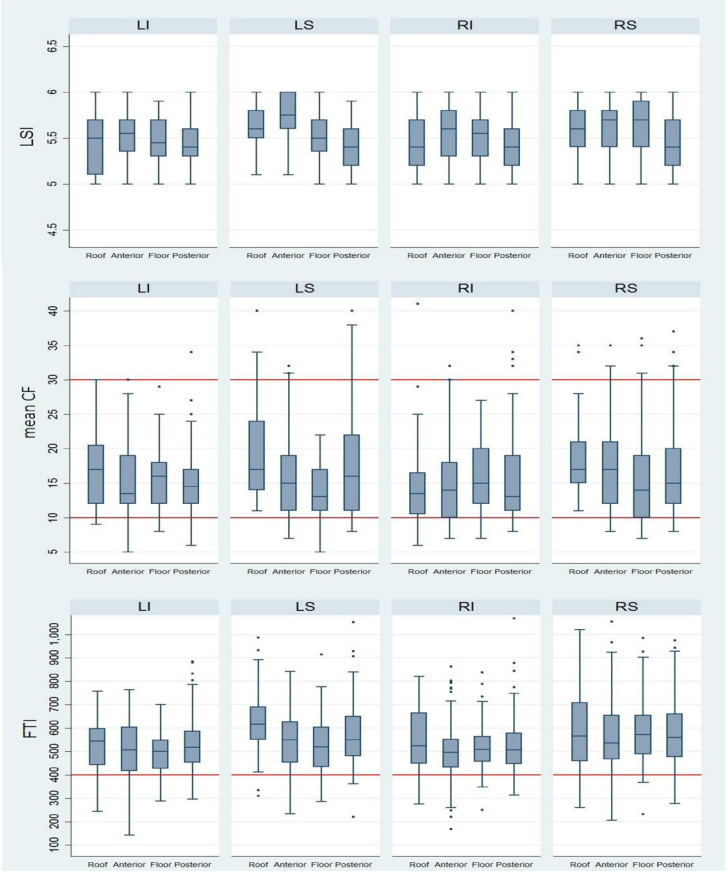

Figure 2: Box-plots by pulmonary vein for LSI (upper panel), CF (middle panel), FTI (lower panel).

value within the target range (5-6). Considering each vein separately, average LSI still depended on the specific target for each segment, as expected per-protocol (Figure 2, upper panel). Average CF was > 10 g and < 30 g for 976 lesions (86.7%) and in by-vein analysis it ranged 10 to 20 g in all segments (Figure 2, middle panel). Moreover, 1015 out of 1126 lesions (90.1%) had an FTI > 400 gs, but a wide distribution was noted: 30.2% of the lesion had a FTI between 400-500 gs, 30.0% in the range 501-600 gs and 29.9% over 600 gs (Figure 3).

FTI values recorded during RF ablation of the same segment of

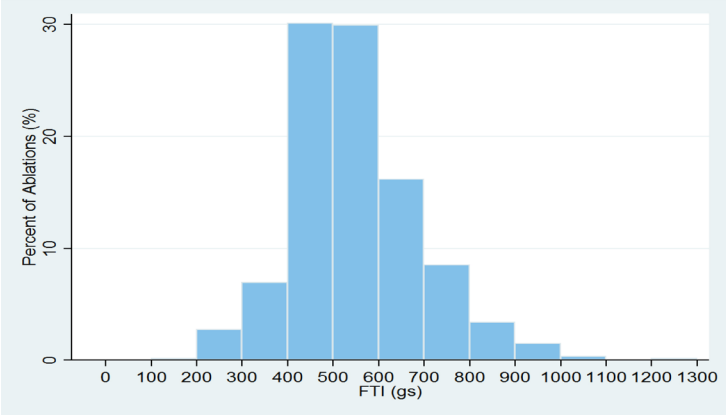

Figure 3: Histogram of FTI values of the 1126 lesions with the same LSI target range between 5 and 6.

Table 2: Regional mean, median and interquartile range (IQR) values of CF, FTI and LSI.

	PV segment	Mean ±SD	Median	(IQR)
CF (g)	Roof	17.0 ± 7.9	16	12-21
	Anterior	16.3 ± 7.1	15	11-21
	Floor	14.4 ± 6.1	13	10-18
	Posterior	15.8 ± 7.7	14	11-19
FTI (gs)	Roof	516 ± 227	535	381-669
	Anterior	500 ± 218	502	408-614
	Floor	477 ± 198	488	394-593
	Posterior	480 ± 212	495	370-603
LSI	Roof	5.3 ± 0.9	5.5	5-5.9
	Anterior	5.5 ± 0.9	5.7	5.3-6
	Floor	5.3 ± 0.8	5.4	5-5.8
	Posterior	5.1 ± 0.8	5.3	4.9-5.6

the PV antra varied significantly between the four veins (Figure 2, bottom; roof FTI values comparison between LSPV, LIPV, RSPV and RIPV: p = 0.02; anterior segment FTI: p = 0.03; floor FTI: p = 0.02; posterior segment FTI: p = 0.02).

Acute PV reconnection

All PVs were checked for bidirectional block at least 30 minutes after successful isolation. Acute reconnection data were available only in the LSI-guided group; in 24 patients (85.7%), no gap was detected on remapping. In the remaining 4 cases (14.3%), PVs were re-isolated. Of 104 PVs targeted, 5 (4.8%) required a touch-up ablation at the end of the procedure: 3 right superior PVs, 1 left inferior PV, 1 right inferior PV. Gaps were found in 4 types of segments: septal RSPV antra (in 2 patients), anterior portion of LIPV, floor of RIPV and posterior wall of RSPV. The roof region of PV antra never showed early reconnection. No significant differences were found in average values of CF, FTI or LSI values in areas of reconnection compared with sites of successful one-shot RF. The number of RF lesions in each area and the continuity of lesion deployment were not considered in this analysis.

Procedural Findings

The mean procedure time was similar in both groups (180.9 ± 48.7 min. in the LSI-guided group vs. 200 ± 28.3 in the NCF group, p = 0.07). Although total RF time was similar (see Table 1), the number of RF applications was higher in the LSI-guided group (40.3 ± 12.8 vs 30.2 ± 9.8, p = 0.002). Fluoroscopy time was significantly shorter in the LSI-guided group (20.1 ± 7.4 min vs 29.1 ± 11.2, p < 0.001).

Adverse events

No tamponades or other major adverse events related to catheter ablation were reported. A groin hematoma occurred in one NCF group patient; in LSI-guided group, one arteriovenous fistula and one mild pericardial effusion not requiring pericardiocentesis were reported.

Follow-up

Clinical outcomes were evaluated in both groups after a mean follow-up (FUP) of 72 ± 28 weeks (mean FUP of 71.1 ± 29.7 weeks in the NCF group vs. 73.1 ± 26.5 weeks in the LSI-guided group, p = 0.78, maximum FUP of 120 weeks for both groups).

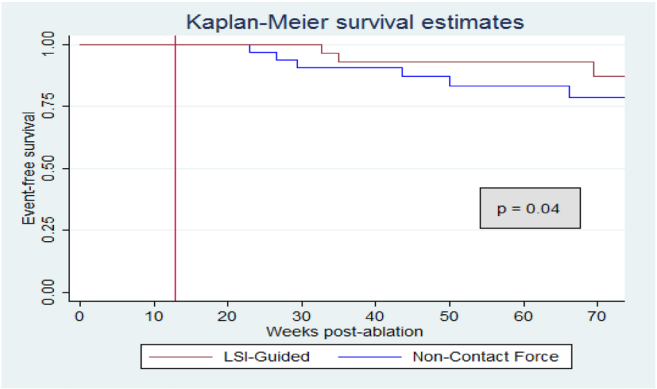

Figure 4: Kaplan–Meier curves of the two groups' AF-free survival and Log-Rank test p-value.

Global AF-free survival on follow-up differed significantly between the two groups (NCF: 65.6%; LSI-guided: 89.3%; p = 0.037). Kaplan-Meier survival curves are shown in [Figure 4]. Time-to-event was comparable (65.6 ± 32.1 weeks in the NCF group; 45.8 ± 20.6 weeks in the LSI-guided group, p = 0.34). In the NCF group, 21 (65.6%) patients were off any AAD at the latest follow-up visit vs. 24 (85.7%) in the LSI-guided group (p = 0.073). Among these, 18 patients (85.7%) in the NCF group and 22 (91.7%) in the LSI-guided group were in sinus rhythm on FUP (p = 0.65).

Discussion

The main finding of our study is that, in PAF ablation, a LSI-guided approach is safe and effective, with a 89.3% success rate after a mean FUP of over 17 months.Current guidelines on the use of fiberoptic CF-sensing catheters for PVI indicate a minimum FTI target value of 400 gs for each RF application[14]. Other authors advocate lower FTI values for PVI[17], but these data were derived using electromagnetic CF-sensing ablation catheters. As demonstrated by Bourier et al, fibertoptic and electromagnetic CF sensing catheter may show different accuracy in CF measurement, with the latter technology being possibly less accurate in measurements of 90° degrees acting forces (parallel contact, which is often required when creating linear lesion as in the case of PVI)[20,21].

Therefore, since FTI is derived from a simple multiplication of CF by time, data obtained using electromagnetic CF-sensing catheters should be compared with caution with data derived using fiberoptic catheters.

However, the use of FTI as an index of lesion efficacy suffers several limitations since it does not take into account multiple factors, such as the power delivered to the tissue, the impedance of the system and the complexity of lesion formation.

LSI is a complex metric that combines RF current, RF duration and CF applied to cardiac tissue into a non-linear formula, thus providing a comprehensive description of lesion quality. In-vitro testing showed not only a good correlation between LSI and lesion depth and width, but also suggested that LSI could be considered as an objective and absolute index of lesion size, since its reliability is consistent across different values of CF and RF[11]. The LSI

clinical significance was initially evaluated in the EFFICAS I study: its correlation with PVR and lesion gaps 3 months after PVI was 10 times stronger than that of FTI[13]. Limited data are available regarding which LSI values should be targeted in order to achieve a permanent lesion without any increase in complication rates. In a subgroup study of TOCCASTAR patients, Mansour et al. found the greatest improvement in PVI rate (80% vs. 46%, p = 0.004) in subjects treated with LSI > 5, combined with CF > 20g and FTI > 400gs[12]. As the transmural thickness of the LA is not uniform[15] and since it has been demonstrated that the posterior wall and roof are significantly thinner than the anterior and septal walls[16], setting different LSI targets (higher for anterior wall and lower for posterior wall) is reasonable and justified, in order to ensure both safety and efficacy.

Consequently, considering the few data available on the influence of LSI parameter on PV reconnection, we established an optimal LSI target range between 5 and 6, according to each specific anatomical location. In the present study, higher LSI values were targeted in the anterior and septal segments (target 5.5-6) than in the posterior wall and roof (target 5-5.5) (Figure 1). This choice is further justified by the results of EFFICAS II[10], where more gaps were reported in the anterior portions of PVs, in a scenario in which only CF and FTI guidelines were observed.

In this study, CF remained between 10 and 20 g in the vast majority of RF applications. In standard ablation procedures, by contrast, the available literature reports high variability in the applied CF,

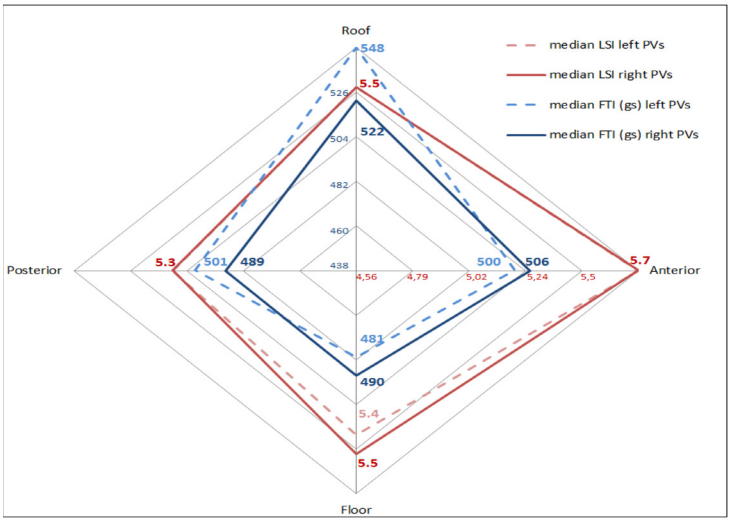

Figure 5: **Radar chart to represent the distribution of average LSI and FTI values per PV segment.**

depending on the accessibility of the ablation site[8]. Moreover, most of the LSI-guided lesions fulfilled the criterion of FTI > 400 gs, but with a wide range of distribution, to the point that 29.9% of lesions required FTI values > 600 gs to achieve the target LSI (Figure 3).

The FTI > 400 gs criterion alone, as in EFFICAS II study protocol, is not precise enough to define lesion quality, since it does not provide any indication about a maximum target value. LSI values distribution was not similar to that of FTI, either around the left or right PV antra (Figure 5). This finding may be explained considering that, as previously mentioned, LSI reflects the amount of RF energy delivered to the cardiac tissue, which is in turn influenced by power, adequately titrated according to the area. However, it is also influenced by other factors, which cannot be directly measured in a complex and varying clinical scenario, e.g. the overall impedance of the ablation system. Therefore, as shown in vitro[11], LSI should constitute a more reliable predictor of lesion width and depth, regardless of the amount of delivered RF power.

Ideally, the local LSI target value should be customized to the patient-specific LA wall thickness in each PV segment, if such information was routinely available with adequate precision (e.g. by means of cardiac MRI or CT scan imaging techniques).

In our study RF energy was delivered in a temperature-controlled mode (upper limit 42°C) because the LSI equation, unlike other multiparametric lesion indexes, takes into account instantaneously the precise amount of RF energy delivered to the tissue in every moment of the lesion deployment, both in the in the first period of RF delivery (when power ramps up and resistive heating mainly occurs) and the subsequent diffusive heating phase of lesion creation.

A 33% reconnection rate after successful PVI is reported[2]. Das et al. reported a 26% rate of acute recurrence of electrical conduction after ipsilateral PVI when adequate CF was achieved[17].In the present study, in the LSI-guided group, touch-up lesions 30 minutes after successful isolation were necessary in 4.8% of the veins. The low incidence of acute reconnection did not allow in-depth statistical analysis on the influence of average CF, FTI and LSI values on the presence of gaps. However, considering reconnection rates reported by the literature, LSI may provide an aid to achieving one-shot transmurality more effectively than non-CF parameters or CF alone.

The number of RF applications delivered was higher in the LSI-guided group, while the total RF duration was similar in both groups. This could be explained primarily by the fact that accurate monitoring of LSI values may have encouraged the adoption of a point-by-point ablation technique. Secondly, while RF time was comparable between the two groups, lower power settings were adopted in the LSI-guided group, thereby ensuring greater safety without affecting efficacy, as previously reported[11].

In line with other experiences[6,7] fluoroscopic exposure time resulted significantly lower in the CF group, since the use of fluoroscopy to confirm catheter contact and stability could often be avoided.

These results broaden the growing body of literature supporting CF-guided ablation[18,19].They also extend the comparison of technologies, potentially improving the current CF guidelines by promoting an objective and absolute method of ensuring the effectiveness of RF lesions deployment. LSI incorporates multiple variables, such as current, time and CF, and delivers this complex information in one intuitive index, which is both applicable and reliable in clinical practice.

Study Limitations

The small study sample does not allow to draw definite conclusions about the safety of an LSI-guided PVI approach. Although no

tamponades or other major complications were reported, further studies are needed to assess the potential safety improvement.

The limited ECG monitoring during follow-up and the use of 24-h instead of 7-day Holter or other continuous monitoring devices might have failed to detect asymptomatic AF recurrences; consequently, ablation success rates might have been overestimated. However, as there was no difference in the monitoring protocol between the two study groups, any potential bias would have been small.

The comparison between the two groups is neither randomized nor parallel and several other biases may have influenced outcomes: contact force information alone, operator experience and learning curve.

Moreover, a steerable sheath was used almost exclusively in patients of the LSI-guided group: it is the authors opinion that the use of such a stiff sheath in the absence of any contact-force feedback in the NCF group would have result harmful.

The aim of the comparison between the two ablation strategies was to investigate whether an LSI-guided ablation strategy using a CF ablation catheter, could improve the procedural outcome of PAF ablation in a single center. More robust data on the safety and effectiveness of LSI-guided PVI in patients with PAF should be obtained from larger randomized trials with longer follow-up in order to confirm our results.

Conclusions

LSI is a multi-parametric index which incorporates time, current and CF data during RF ablation. This is the first study to prospectively evaluate the LSI-guided approach to PVI. This approach improved clinical outcome and was not associated with any increase in complication rate when compared with standard, non-LSI-guided PVI.

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Abnormal Atrial Activation at Surface Electrocardiogram Examination in Born Underweight Young Adults

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Abstract

Introduction: Recent published data demonstrated how subjects born preterm are at higher risk of developing early atrial fibrillation (AF).

Materials and Methods: The surface ECG of twenty-four adults, former preterm infants born with an extremely low birth weight (ex-ELBW; mean age at study: 23.2±3.3 years; mean gestational age: 27.8±2.3 weeks; mean birth weight: 840±120.1 grams), were compared with those of 24 healthy counterparts born at term (C). A few parameters known to be capable of predicting a predisposition to develop AF were examined: P wave duration and dispersion, P terminal force, isoelectric interval length, PR interval length, and advanced interatrial blocks.

Results: A shorter PR interval length was found in ex-ELBW compared to C ($p<0.0003$) as well as longer P wave duration and dispersion, p terminal force, and isoelectric interval ($p<0.0001$, $p<0.0001$, $p<0.01$, and $p<0.0004$, respectively). Four cases of advanced interatrial block were detected in ex-ELBW, and none in C ($p<0.0001$). P wave duration, PR interval length, and P wave dispersion were significantly correlated with birth weight ($r=0.51$ $p<0.01$, $r=0.46$ $p<0.02$, and $r=0.42$ $p<0.04$, respectively).

When excluding the possible influence of gestational age on birth weight, P wave duration and dispersion were found to be the only statistically significant determinants of abnormal atrial electrical activation ($p<0.03$ and $p<0.04$, respectively). On the contrary, when excluding the possible influence of birth weight on gestational age, only P wave duration remained statistically significant ($p<0.05$).

Conclusions: Surface ECG findings of abnormal atrial activity in ex-ELBW may explain their previously reported predisposition to developing AF.

Introduction

It has been highlighted how birth weight is associated with an increased risk of early onset of atrial fibrillation (AF), in patients of both genders and with no traditional cardiovascular risk factors, thus suggesting that early life determinants may play a pivotal role in the pathogenesis of AF[1,2]. This relationship was not attenuated even following adjustment for cardiovascular risk factors and ethnicity at multivariate analysis[3].

Abnormal atrial activation, defined as atrial structural change, conduction abnormalities, and sinus node dysfunction, is likely to predispose to the development and progression of AF[4].

The aim of this study was to evaluate a series of signs of atrial activation at surface electrocardiogram (ECG) in a group of young adults born preterm with an extremely low birth weight (ex-ELBW; birth weight <1,000 grams), and to compare the findings with results obtained in a group of healthy counterparts born at term[5,6], in order to identify a potential correlation between these electrocardiographic signs and perinatal factors including birth weight and gestational age[7].

Key Words

Surface Electrocardiogram, Atrial, Atrial Fibrillation, Gestational Age, Birth Weight, Intrauterine Growth Restriction.

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Materials and Methods

A comparison was carried out between 24 ex-ELBW (4 males and 20 females) ranging between about 20 and 30 years (mean age±SD, 23.2±3.3 years; mean gestational age±SD, 27.8+2.3 weeks ; mean birth weight±SD, 840+120.1 grams) and a control group (C) comprising 24 healthy subjects born at term, matched for sex, age and BMI. All subjects were contacted in alphabetical order from the Records of the Neonatal Intensive Care Unit (NICU) of the University of Cagliari, Italy. Subjects represent the first surviving ex-ELBW assisted in the sole NICU present in Cagliari (Italy).

Exclusion criteria were as follows: patients suffering from conditions and/or assuming compounds known to predispose to the onset of AF (for example, hypertension, mitral valve disease, caffeine and alcohol addiction)[8]. In this respect, nine patients were excluded.

Arterial blood pressure was measured by auscultatory method. A standard 12-lead surface ECG was performed (Cardioline ar2100 view 12-channel electrocardiograph, Italy) in order to evaluate several parameters of atrial activation (P wave duration, dispersion, P terminal force (in precordial lead V1), isoelectric interval length, and

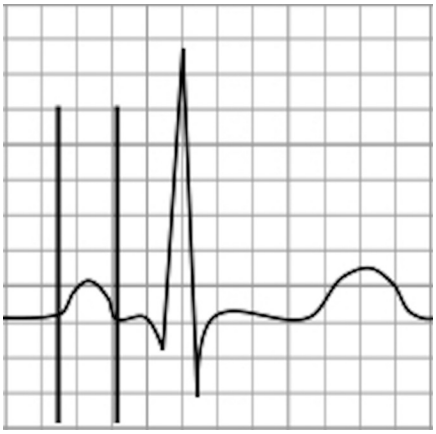


Figure 1: P wave duration, defined as the first onset and the last offset of the P wave

PR interval length). They were measured manually by the same trained cardiologist with expertise in electrophysiology (98.5%intraobserver reproducibility rate)[5]. For the sake of precision in measuring, a magnifying glass was used.

Specifically, P wave duration [Figure 1] is defined as the first onset and the last offset of the P wave (at three standard leads), while P wave dispersion is the difference between the maximum and the minimum P wave duration detected in a 12-lead standard ECG. P terminal force [Figure 2] is defined as the duration (in seconds) of the terminal part (negative) of the P wave in lead V1 multiplied for its depth (in millimeters). If the P wave terminal part is positive, then the interval extending from the first notch to the wave end must be considered. Precordial V1 (and V2) leads were corrected displaced in the fourth intercostal space. Isoelectric interval length [Figure 3] is defined as the difference between total P wave duration and maximum P wave duration. PR interval length [Figure 4] is the period that extends from the beginning of the P wave until the beginning of the QRS complex. It was measured in lead V1. Lastly, advanced or third degree interatrial blocks are characterized by a p wave duration >120 msec as well as a p wave bifid morphology in leads D1 and aVL and biphasic in D2, D3, aVF, V1, and V2[5,9].

Three measures were taken for each of the examined parameters and their average used. The data were blinded, so that the examiner did not know if the ECGs belonged to the population in the study or controls.

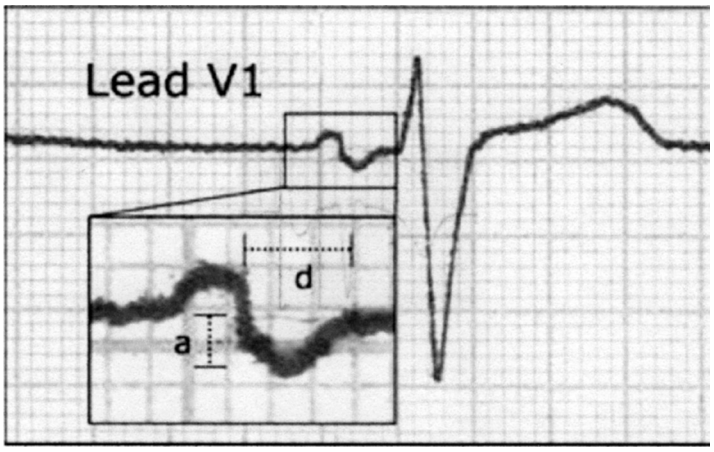


Figure 2: P terminal force, defined as the duration (in seconds) of the terminal part (negative) of the P wave in lead V1 multiplied for its depth (in millimeters)

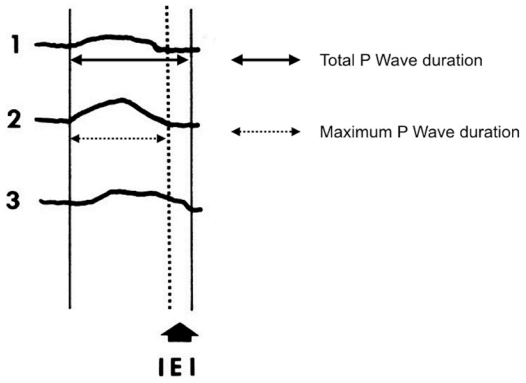
The assessed ECG parameters were subsequently compared to birth weight and gestational age, as reported on clinical records.

A 24-hour Holter ECG registration was performed in both ex-ELBW and controls as well.

Informed written consent for participation in the study was obtained from all ex-ELBW. The research was formally approved by the internal Ethics Committee (PG/2015/1859) and conducted in accordance with the Helsinki declaration.

Statistical Analysis

The results of the entire study population (n=24), which was normally distributed, were first analyzed, and ex-ELBW subjects subsequently compared to C (n=24) using the parametric Student t-test. Relationships between the various parameters studied were



Isoelectric Interval (IEI) = Total P Wave duration — Maximum P Wave duration

Figure 3: Isoelectric interval length, defined as the difference between total P wave duration and maximum P wave duration

assessed by means of univariate analysis. Multivariate analysis was not been applied due to the inadequacy of sample size for this statistic test. However, partial correlation analysis was applied, in order to hive off the possible influence of a variable on another one, when these two are deeply correlated, such as birth weight and gestational age.

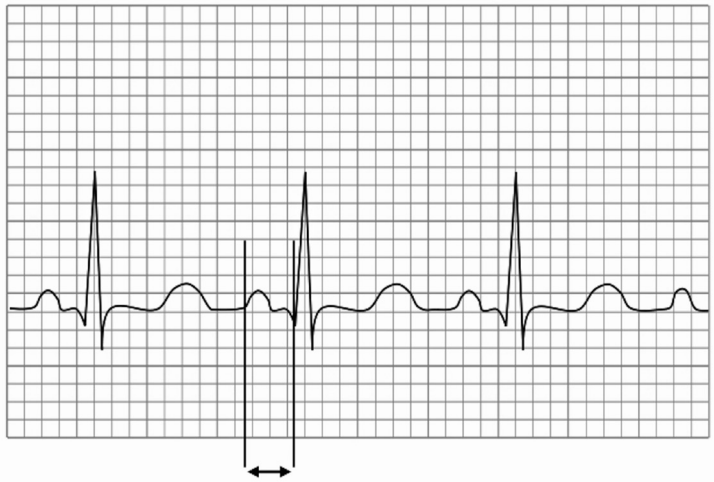


Figure 4: PR interval length is the period that extends from the beginning of the P wave until the beginning of the QRS complex

The presence of a potential correlation between the above stated parameters of atrial activation and both gestational age and birth weight was investigated in accordance with Pearson's correlation coefficients. Values of $p<0.05$ were set as the minimum level of statistical significance throughout the study. For all analyses, commercially available computer software (SPSS version 22.0, SPSS Inc., Chicago, Illinois, USA) was used.

Results

The clinical characteristics of the population investigated (ex-ELBW vs C) are summarized in [Table 1]. The assessed ECG parameters are reported in [Table 2].

A statistically significant difference was detected for PR interval length, which was found to be shorter in ex-ELBW compared to the same values in C ($p<0.0003$). Furthermore, longer P wave prolongation and dispersion, P terminal force, and isoelectric interval were detected in ex-ELBW compared to C ($p<0.0001$; $p<0.0001$; $p<0.01$; and $p<0.0004$, respectively).

P wave duration, PR interval length, and P wave dispersion were significantly correlated with birth weight ($r=0.51$ $p<0.01$, $r=0.46$ $p<0.02$, $r=0.42$ $p<0.04$, respectively). When excluding the possible influence of gestational age on birth weight, P wave duration and dispersion were found to be the only statistically significant determinants of abnormal atrial electrical activation ($p<0.03$ and $r=$ $p<0.03$). On the contrary, when excluding the possible influence of birth weight on gestational age, only P wave duration remained statistically significant ($p<0.05$).

Table 1: Clinical characteristics (patients and control group)

	Ex-ELBW	C	P
Gestational age (weeks)	27.8 ± 2.3	39.4 ± 0.7	0.0001
Birth weight (grams)	840 ± 120.1	3.257 ± 0.391	0.0001

Furthermore, four cases of advanced interatrial block (16.6%) - a strong marker of paroxysmal supraventricular tachyarrhythmias - were detected in ex-ELBW, and none in the control group ($p<0.0001$)[9].

At 24-hour Holter ECG registration the incidence of supraventricular ectopic beats and supraventricular tachycardia runs in ex-ELBW was higher compared with controls (31 premature atrial complexes/hour vs 4/hour, $p<0.0001$; longest supraventricular run /24 hours =12 vs 0, $p<0.0001$).

Table 2 : Examined electrocardiographic parameters of atrial activation that predispose to the onset of atrial fibrillation (patients and control group)

	Ex-ELBW	C	P
HR (beats/min)	78 ± 3	82 ± 3	ns
P dur (msec)	122.4 ± 3.5	79.6 ± 4.1	0.0001
PWD (msec)	44.4 ± 3.5	37.1 ± 1.1	0.0001
PTFV1 (mm x sec)	0,06 ± 0.1	0.04 ± 0.1	0.01
IEI (msec)	39.0 ± 9.9	84.6 ± 19.9	0.0004
PR (msec)	141.4 ± 13.4	164.2 ± 24.0	0.0003
Advanced interatrial Blocks (%)	4/24 (16.6%)	0/24 (0%)	0.0001

Acronyms: HR: heart rate; P dur: P wave duration; PWD: P wave dispersion; PTF: P terminal force in the lead V1; IEI: isoelectric interval; PR: PR tract length

Discussion

Although old age continues to be the strongest predictor for the development of AF, in recent years other factors capable of increasing the risk of incident AF have been identified, including low birth weight[1,3]. Also higher birth weight was associated with an increased risk of AF during adulthood. The two highest categories were associated with a 70% and 71% increased risk after multivariable adjustment[2].

Analysis of atrial activation at surface 12-lead ECG may help to identify subjects with a predisposition to developing this form of arrhythmia[10]. All examined parameters of atrial activation were previously shown to be able to give information about the anatomical substrate predisposing to the onset of AF[5]. In fact, they represent an electromechanical interaction, being the electrocardiographic expression of atrial stretching/enlargement, impaired atrial conduction, and various changes in the atrial activation vector. Accordingly, in our study all these parameters presented significant differences compared to those of the control group, although only P wave duration and dispersion continued to be significantly correlated with birth weight following the exclusion of possible influence of gestational age, and only P wave duration when excluding the influence of birth weight on gestational age. It means that low birth weight (i.e. intrauterine growth restriction) is an atrial fibrillation predisposing factor stronger than gestational age, in accordance with previous reports[1-3].

An excessive prolongation of P wave duration at surface ECG reflects the presence of intra-atrial conduction abnormalities[11]. A slow conduction velocity is crucial in the development of reentrant arrhythmia, since a shortened refractory period makes atrial tissue sensitive to premature atrial depolarization. This would indeed imply the possibility of obtaining a series of important data from analysis of P wave characteristics measured at surface ECG in our patients.

Specifically, the use of different definitions for P wave duration may influence results[11]. In this study, P wave duration was detected manually at three standard leads and the averaged measure used. The cut-off points used were the first (onset) and last (offset) deflections from baseline. Previous reports have shown that an increased P wave duration at 12-lead surface ECG and signal averaged ECG recordings is a reliable predictor of the future onset of AF, featuring a high sensitivity and specificity[12].

On the other hand, P wave dispersion is defined as the difference between the longest and shortest P wave durations recorded from multiple different ECG leads. It represents the inhomogeneity and discontinuation in atrial conduction and has proven to be a marker capable of predicting the development of AF in a number of clinical scenarios[13].

Advanced or third degree interatrial blocks are considered strong markers of paroxysmal supraventricular tachyarrhythmias[9]. They are not uncommon in the general population and associated with ischemic stroke at multivariate analysis, thus strengthening the hypothesis that left atrial disease should be considered an indipendent risk factor for stroke[14,15]. An underlying atrial pathology in term of remodelling

was clearly demonstrated at advanced echocardiography as well as cardiac MRI in those presenting with interatrial blocks[16,17].

A pathophysiological explanation of our findings is likely linked to the fact that prematurity at birth and low birth weight may result just in atrial remodeling, as a consequence of the modifications induced on atrial structure, function, electrophysiological and metabolic activities[18]. Our research group had previously demonstrated an approximately 30% prevalence in ex-ELBW of atrial septal aneurysms at echocardiography, while prevalence of this defect in the general population ranges from 0.2 to 3.2% and was 2.7% in controls[19]. This finding is in agreement with the traditional hypothesis of Hanley et al., according to which extremely mobile atrial septal aneurysms are correlated with the onset of AF in adults[20]. The high prevalence of an aneurismal aspect of the interatrial septum may be induced by the presence of a marked difference in pressure between the two atria (atrial stretching), such as in born preterm subjects with a long time patency of ductus arteriosus and/or the presence of severe respiratory distress at birth[21].

An abnormal electrical remodelling has also been recently described in cardiac ventricles of adolescents born preterm and/or with intrauterine growth restriction[22]. This is likely the underlying cause of reported repolarization abnormalities (QTc and QT dispersion prolongations) at standard ECG in adult individuals meeting either of these criteria[23-25].

This study is undoubtedly hampered by a series of limitations: a) small sample size, which we would enlarge in future studies. It probably explains even the lack of a possible relationship between interatrial advanced blocks and gestational age and/or birth weight. This objective limitation is due to the restricted number of patients available with suitable characteristics at our University; b) definition of P wave duration, owing to the lack of universally accepted cut-off points - although the highest accuracy in detecting P wave points is achieved manually, intra and inter-observer measurement errors continue to confound this method[26,27] ; c) parameters of atrial activation were only investigated at surface ECG, whilst a comparison with results obtained at transoesophageal ECG may have facilitated a more precise evaluation of atrial electrophysiological activity[28]; d) inducibility of AF in ex-ELBW has not been confirmed in electrophysiological studies of the heart. However, the examined patients in the study were decidedly younger compared to those enrolled in the previous studies showing an increased risk of developing atrial fibrillation[1-3]. The follow up was shorter as well. Even though none of the ex_ELBW developed atrial fibrillation, at 24-h Holter ECG the incidence of supraventricular ectopic beats and supraventricular tachycardia runs –which are known to be predictors of AF- was higher compared with controls[29]; e) it may prove beneficial to take other factors that might potentially contribute towards increasing susceptibility of developing AF into consideration, such as the augmented thickness of epicardial fat previously demonstrated in ex-ELBW, which has been hypothesized to exert a local pathogenetic effect on the arrhythmogenic substrate supporting AF[30,31].

Conclusions

Although considerable progress has recently been made in predicting the onset of AF, to date no reliable methods of detection have been proposed. In line with a series of previously established markers, which may be capable of predicting the onset of AF, ex-ELBW seem to display an abnormal atrial activity at surface ECG, possibly explaining the previously reported predisposition of these subjects to develop AF. The findings of this study also provide further confirmation of the arrhythmic vulnerability of this population[1,20,21,32].

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Real-Time Recordings in Cryoballoon Pulmonary Veins Isolation: Comparison Between the 25mm And the 20mm Achieve Catheters

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Abstract

Aims: Real Time Recordings (RTR) of pulmonary vein (PV) activity provide important information in the setting of the 2nd generation Cryoballoon (CB-A), as a funcion of time to isolation. Visualization of RTR with the standard inner lumen mapping catheter (ILMC) 20mm Achieve (AC) is possible in roughly 50% of PVs. A novel 25mm-Achieve Advance (AC-A) has been developed with the aim of increasing the detection of RTR. The purpose of this study is to compare the AC-A with the AC, to feasibility and improvement of RTR.

Methods: We assigned 50 patients with paroxysmal or persistent atrial fibrillation to CB-A PVI, using the AC-A as ILMC. We compared this group with 50 patients, matched for age and left atrial volume, who previously underwent the CB-A PVI using the AC.

Results: RTR were more frequently observed with the AC-A than with the AC (74% vs 49%; p= 0.02). RTR in the left superior PVs was similar in both groups (74% vs 72%, p= 0.8). RTR with the AC-A were equally appreciated in left or right sided, superior or inferior PVs. No significant differences were found in terms of feasibility, procedure fluoroscopy and freezing times, nadir temperatures, and acute PVI.

Conclusions: CB-A PVI with the AC-A is feasible and safe in all PVs. The AC-A has proven significantly superior in visualising RTR if compared to the AC, affording RTR in 74% of PVs.

Introduction

Real Time Recordings (RTR) of pulmonary vein (PV) electrical activity provide important information in the setting of the 2nd generation Cryoballoon (CB-A) pulmonary vein isolation (PVI) for the management of atrial fibrillation (AF)[1-3]. Data available in the literature indicate that RTR, as a function of time to PV isolation, can predict effective isolation of PV in the long term, and they may become the cornerstone to perform the best freeze[2,3]. To date, CB-A PVI is usually documented in real time by the standard 20mm Achieve (AC) (Medtronic, Minnesota, USA) inner lumen mapping catheter (ILMC) during the cryoenergy application. However RTR with the AC is possible only in nearly half of the PVs, as it has been demonstrated in several previous studies and this ILMC cannot be enought reliable to guide real time PVI[4-7]. Consequently, a novel ILMC, the 25mm-Achieve Advance (AC-A) (Medtronic, Minnesota, USA) has been developed to overcome this limitation, incresing the possibility to better detect RTR during PVI. No studies comparing the latter AC-A with the standard AC have been carried out yet.

Key Words

Achieve Advance Catheter, Cryoballoon Pulmonary Vein Isolation, Real Time Recordings, Time To Pulmonary Vein Isolation

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Aim of the Study

The main aim of the study consisted in the assessment of the feasibility of CB-A ablation in conjunction with the novel 25mm AC-A compared to the standard 20mm AC, in terms of the rate of visualisation RTR during ablation, and successful acute PVI.

Methods

Study population

From February 2017 to beginning of April 2017, consecutive patients who underwent PVI as an index procedure with the CB PVI using the novel 25 mm AC-A as mapping catheter consisted in the study population. This group (case group) was subsequently matched for age and left atrial (LA) volume (ml/m2) with patients who underwent the same procedure using the 20 mm AC, during the

previous months (control group). Finally 100 patients were included in the analysis (50 patients in each group).

Pre-procedural management

All patients provided written informed consent prior to the procedure. Inclusion criteria for PVI with the CB were patients with paroxysmal or persistent AF - refractory at least to one anti-arrhythmic drug AAD) – who underwent AF ablation for the first time. To exclude the presence of thrombi in the left atrial appendage (LAA), all patients underwent twodimensional (2D) trans-esophageal echocardiography (TEE) the day before the procedure, along with a trans-thoracic examination (TTE) enabling assessment of LA dimensions, left ventricular, and valvular function. Also, prior to procedure, detailed information on LA anatomy was obtained by computed tomographic (CT) scan. Antiarrhythmic drug therapy was discontinued prior to ablation, according to the pharmacokinetics. Exclusion criteria were the presence of LA thrombus, severe uncontrolled heart failure, contraindications to general anesthesia and LA diameter ≥ 50 mm. The study was in compliance with the principles outlined in the Declaration of Helsinki and approved by the institutional ethics committee of our Institution.

The novel 25 mm Achieve Advance inner lumen circular mapping catheter

The AC catheter is an ILMC specifically designed to be used in conjunction with CB to obtain RTR PV electrograms during cryoenergy application, with the double purpose of being a mapping catheter and a supporting guidewire for the CB-A. The proximal part of the catheter is a 146 cm long stainless steel tube of 3.3.F diameter. The distal part consists of 10 electrodes positioned on a 25 mm circular loop with an intelectrode distance of 6 mm. The latter has been recently developped (2ACH25 Achieve Advance ST Mapping catheter – Medtronic), based on the assumption that a larger diameter and 2 additional electrodes might yield a higher chance of contact with the PV ostium and consequently enhance the possibility of detecting PV potentials (PVPs) and therefore RT isolation. (Figure 1A,Figure 1B and Figure 1C).

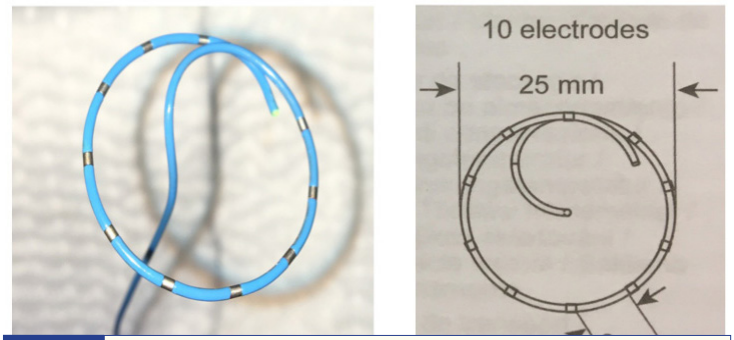

Figure 1A: Novel 25mm Achieve Advance ILMC

Cryoballoon ablation procedure and assessment of PV isolation with the ILMC

The CB-A ablation procedure has been described in detail previously[8,9]. All procedures were performed under general anaesthesia. The operators involved in performing CB-A PVI in the AC group were the same operators who performed the CB-A PVI

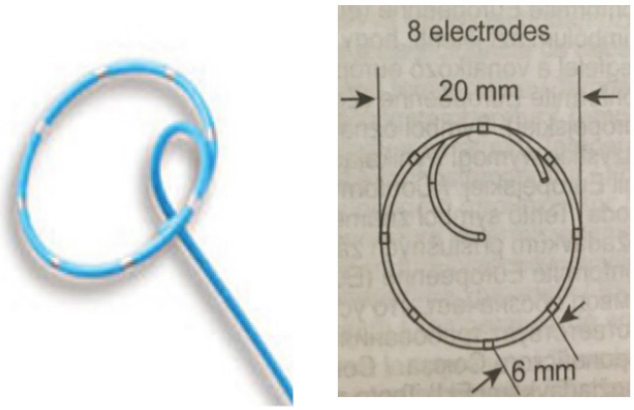

Figure 1B: Standard 20mm Achieve ILMC

in the AC-A group and they were senior-experienced in this field. Briefly, a steerable 15 Fr sheath (Flexcath, Medtronic) was placed in the LA through a single transseptal puncture (TSP). Before introducing the balloon catheter in the sheath, the ILMC was inserted in the lumen of the CB-A. The insertion technique of the ILMC in the inner lumen of the CB-A is identical for both the AC and AC-A catheters.

Then the 28 mm CB-A (Arctic Front Advance, Medtronic) was advanced through the sheath into the LA with the ILMP

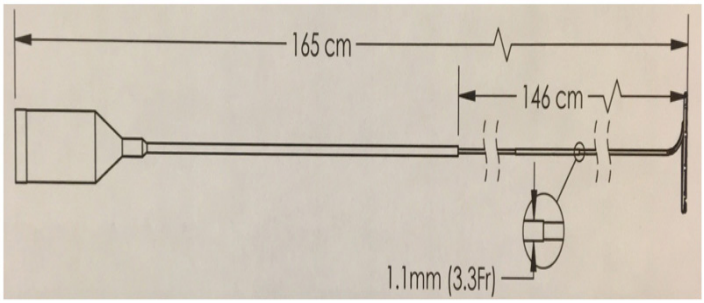

Figure 1C: Shaft of both ILMC

used as a guidewire. Before ablation, for each PVs the ILMC was positioned in the ostium to record baseline electrical activity. Then, the ILMC was advanced more distally similarly to a guidewire and the CB-A was wedged in the ostium to occlude the vein. Optimal vessel occlusion was considered to have been achieved when selective contrast injection showed total contrast retention with no backflow to the atrium. Vessel occlusion was evaluated according to a semiquantitative grading, ranging from grade 0 (very poor occlusion) to grade 4 (perfect occlusion). Once occlusion was documented, cryothermal energy was started delivering a single freeze–thaw cycle of 180 seconds (s) for each vein[10, 21]. Based on previous findings, a second freeze-thaw cycle of 180 s was delivered when at the first freeze RT isolation occured after 60 s (when PVPs were visible) and/or the specific parameter of -40°C within the first 60 s was not reached[2]. Specifically, if a temperature of -40°C was not reached within the first 60 seconds despite very early isolation a bonus freeze was performed, since reaching -40 within 60 seconds it has been proven to be a strong protective factor to increase the probability of long lasting PVI (ß Coefficient -1.13)[2]. However, future studies including larger cohorts of patients based on dosing strategies guided by RTR might lead us to modify our strategy. If PVPs were visible

during energy application, time and temperature to isolation were recorded when PVPs completely disappeared or were dissociated from LA activity. Pacing maneuvers for the differentiation of any potential non-PV sources were applied as mentioned above. If PVPs were not visible during ablation, the temperature-guided approach of – 40°C within first 60 s was taken to assess an effective application[11]. Once the application ended, if PVPs were not visible during the freeze, the ILMC was retracted to a more proximal position in the ostium were electrical information had been recorded prior to ablation. In order to avoid phrenic nerve palsy (PNP), a complication observed during right-sided PVs ablation with CB, a bipolar catheter was inserted in the superior vena cava, and diaphragmatic stimulation was achieved by pacing the ipsilateral phrenic nerve with a 1200 ms cycle at an output of 20 mA. Phrenic nerve capture was monitored both via the femoral venous pressure waveform (VPW) analysis and with tactile feedback by placing the operator's hand on the patient's abdomen. VPW monitoring has been described in detail previously[12]. Refrigerant delivery was immediately stopped if VPW decreased of more than 50% of the peak to peak initial value, and weakening or loss of diaphragmatic movement was noted. After transeptal access, activated clotting time (ACT) was maintained over 250 with supplements of heparin infusion, as required.

Post-procedural management

All patients were dismissed the day following ablation. A 2D TTE was performed in all individuals in order to exclude postprocedural pericardial effusion. Low molecular weight heparine (LMWH) was started the same day following ablation and continued until target international normalized ratio (INR) was between 2-3. Oral anticoagulation (OAC) was started the same evening after the procedure. In patients under NOAC therapy, the latter was restarted the same day following ablation, without LMWH bridging.

Statistical analysis

Statistical differences were calculated using x2 test for discrete variables and t-test for continuous variables (expressed as mean values and standard deviation). All statistical analyses were performed using the SPSS software (SPSS v24, IL, USA). A p value > 0.05 was considered statistically significant.

Results

Baseline population characteristics

Mean age of the total population was 58+13 years (65 male; 65%). There were no statistical differences in the baseline clinical characteristics between both patient groups ("25 mm/AC-A" group and "20 mm/AC" group). All patients underwent preprocedural cardiac CT scan. Left common ostium was identified in 10 patients (20%) of the 25mm-group and in 7 patients (14%) of the 20mm group; 1 right middle vein (2%) was identified in the 25mm group no other accessory vein was identified. Baseline characteristics are shown in Table 1.

Procedural parameters

Procedure, fluoroscopy, and freezing time

A 28 mm CB-A was used in all patients. Mean procedure time, considered from first groin puncture to complete sheath extraction (61.9+-15 min vs. 66.5+-14.6 min, p = 0.126) and fluoroscopic time (14.2+-6.2 min vs. 15.5+-9.2 min, p = 0.386) did not differ significantly between both groups. There was no statistical difference either in the mean freezing time (min), or in the number of veins that required more than 1 freeze. There was no need to switch to a regular guidewire in any procedure in both groups.

Table 1: General population and procedural characteristics

Variable	Overall n° pt = 100	25mm AC-A n° pt = 50	20mm AC n° pt = 50	p-value
Male	65	32	33	1.00
Age (years)	59.4 ± 12.8	61.5 ± 12.8	57.2 ± 12.5	0.09
LV EF (%)	56.9 ± 7.3	56.3 ± 8.3	58.1 ± 4.8	0.30
LA diameter (mm)	40.8 ±8.4	43.2 ± 9.9	39.1 ± 6.9	0.21
Index LA volume (ml/m2)	36.1 ± 8.2	37.5 ± 9.4	34.6 ± 6.7	0.08
BMI (kg/m2)	26.9 ± 4.6	27.5 ± 4.6	26.4 ± 4.7	20.25
Paroxysmal AF	79	37	42	0.33
HTN	58	31	27	0.54
Diabetes	9	6	3	0.49
Heart Failure	7	5	2	0.44
CAD	9	7	2	0.16
Valvular Disease	4	1	3	0.62
TIA/CVA	5	4	1	0.36
Procedure Time (min)	64.2 ± 15.2	61.9 ± 15.2	66.5 ± 14.6	0.13
Fluoroscopy Time (min)	14.8 ± 7.9	15.5 ± 9.2	14.2 ± 6.3	0.39

Continous variable values are expressed as mean ± standard deviation.

Pulmonary vein isolation

At the end of each procedure, all PVs (100%) were confirmed to be isolated. Real time recordings were more frequently observed with the AC-A than with the standard AC (74% vs 49% of all PVs; p= 0.02). Specifically, RTR could be observed in 74% in the AC-A group and in 72% of the AC group (p= 0.8) in the LSPV, in 74% vs 36% - p< 0.001 in the LIPV; in 72% vs 48% - p= 0.024 in the RSPV and in 74% vs 40% - p< 0.001 in the RIPVs. Real time recordings

Table 2: Specific procedural parameters

Variable	Overall	25mm AC-A	20mm AC	p-value
>1 freeze LSPV (n°)	21	8	13	0.33
>1 freeze LIPV(n°)	23	13	10	0.64
>1 freeze RSPV(n°)	19	13	6	0.12
> 1 freeze RIPV(n°)	34	18	16	0.83
Time to isol LSPV (s)	40.5 ± 18.7	40.1 ± 19.3	41.8 ± 17.6	0.81
Time to sol LIPV(s)	40.8 ± 17.1	40.3 ± 18.6	42.1 ± 17.4	0.82
Time to isol RSPV(s)	27.3 ± 14.2	26.3 ± 12.9	28.5 ± 15.4	0.56
Time to isol RIPV(s)	47.5 ± 31.7	43.5 ± 29.1	51.9 ± 34.4	0.34
T°C of isol LSPV (°C)	-32.2 ± 9.4	-31.7 ± 9.9	-32.6 ± 8.9	0.7
T°C of isol LIPV (°C)	-30.8 ± 7.8	-30.2 ± 7.6	-31.5 ± 8.1	0.72
T°C of isol RSPV(°C)	-25.3 ± 12.3	-24.9 ± 12.1	-25.7 ± 12.8	0.79
T°C of isol RIPV(°C)	-30.2 ± 11.6	-28.8 ± 10.7	-31.7 ± 12.6	0.38
Nadir T°C LSPV(°C)	-49.3 ± 5.4	-49.0 ± 5.7	-49.6 ± 5.1	0.58
Nadir T°C LIPV(°C)	-46.8 ± 5.2	-46.7± 5.5	46.8 ± 5.0	0.98
Nadir T°C RSPV(°C)	50.6 ± 5.5	-50.3 ± 6.2	-50.9 ± 4.7	0.56
Nadir T°C RIPV (°C)	-48.5 ± 5.6	-47.8 ± 5.6	-49.1 ± 5.6	0.3

Continous variable values are expressed as mean ± standard deviation.

with the AC-A could be appreciated in equal proportions without significant difference between left or right sided, superior or inferior PVs. Mean time to isolation, mean temperature at isolation and mean minimal temperatures achieved did not differ significantly between both groups, when comparing homologous veins. (Table 2)

Complications

No serious adverse events occurred in any procedure. Transient phrenic nerve palsy was observed in 4 patients (8%) of the AC group and in 1 patients (2%) of the AC-A group (p = 0.36), while freezing in 3 RSPVs and in 2 RIPVs. Diaphragmatic contraction completely recovered in each case before the termination of the procedure.

Discussion

To the best of our knowledge, this is the first study comparing the novel 25 mm AC-A catheter with the standard 20 mm AC, in the context of 2nd generation CB-A. The main findings are that: (1) Overall, the RTR were significantly more frequently observed with the AC-A than with the standard AC. (2) RTR in the LSPVs were observed with similar rates in both groups. (3) RTR with the AC-A can be equally appreciated in left or right sided, superior or inferior PVs, (4) PVI with the CB-A using the novel AC-A is feasible, safe and effective in all veins, and (5) no significant differences were observed between both ILMC in terms of acute successful isolation, procedure-time, fluoroscopy-time and freezing-time. Recent articles have highlighted the importance of temperature attainment as a predictor of successful PV isolation. Deubner et al.[13] interestingly demonstrated that a steeper temperature slope descent in the first instances of the freeze proved to reliably predict acute PV isolation. In addition, Iacopino et al.[11] showed comparable clinical outcomes between a traditional approach with an ILMC and an ablation strategy solely guided by temperature in the setting of second generation CB ablation. However, although temperature is an extremely important parameter, Time To Isolation (TTI), provided by RTR of PV electrograms, has also demonstrated to be a strong predictor of durable PVI[2,3] . Specifically, the publication by Ciconte et al.[2], focusing on potential predictors of late PV reconnections after CB-A reported that, on a multivariable analysis, longer time to PVI (P=0.03) and failure to achieve –40°C within 60 s (P=0.05), independently predicted late PV reconnection. In addition, a 60-s cutoff for time to PVI guaranteed persistent isolation in the long-term with 96.4% negative predictive value. Most importantly, TTI proved to be the most significant predictor of long lasting PVI. The latter statistically overpowered the temperature parameter of –40°C within 60 s. The above mentioned considerations were confirmed successively by the recent ICE T trial[3]. The ICE T showed that a strategy based on early PVI achieved similar results to the classical freeze-thaw-freeze approach[3]. Baring this in mind, an enhanced visualisation of RTR in conjunction with the analysis of the temperature during the freeze might pave the way to the ideal parameters one should follow in order to guarantee permanency of PV isolation. Therefore, the operator might choose to abort the application and reposition the balloon with another orientation in the PV ostium in case of persistence of LA-PV conduction after 60 s. According to recently published articles the standard 20mm-AC seems to afford visualisation of RTR in roughly 50% of PVs [4,5,6,7]. In the setting of CB ablation occlusion of the targeted PV is paramount in this specific technique and all efforts should be made to obtain a complete seal at the level of the PV ostium[14]. This often forces the operator to position the ILMC deeper in the vessel in order to guarantee support of the CB during its positioning in the PV ostium. A deeper positioning of the ILMC tends to somewhat jeopardize the possibility of visualising potentials because of the short and variable distal extension of muscular sleeves in the PVs [15,16]. In our experience, the novel AC-A proved significantly superior to its predecessor in terms of visualisation of RTR. Although, our standard practice is to deliver 180 seconds duration cryoapplications, a tool permitting a higher rate of RTR visualisation might help paving the way towards the ideal dosing strategy. In this setting the AC-A might prove very useful.

Not surprisingly, in our study, the LSPV was the vein in which RTR could be detected by both ILMC in comparable proportions. This is obviously explained by the fact that only the LSPV' ostium is anatomically coaxial to the CB-A system when crossing the interatrial septum. Therefore, less effort in manoeuvring the latter is required to occlude this particular vein. This leads to favorably positioning the ILMC in a more proximal position without jeopardising the occlusion. The above mentioned consideration is supported by the observations reported in an article by Sorgente et al[17]. In this study, a strong inverse association was found between the PV-ostia angle of orientation in the frontal plane (obtained from Multislice cardiac computed tomographic imaging) and the CB-A degree of occlusion in each vein. The sharper the CB-A angulation, the higher was the probability of loss of the central alignment of the system at the PV ostia. Therefore, the other veins are typically more difficult to occlude with the CB-A, often leading the operator to place the ILMC more distally to ensure balloon stability and this may be the main reason why the AC fails to record RTR frequently.

The novel AC-A has shown to be equally effective in all PV for the detection of RTR, without difference between left or right sided, superior or inferior vessels. This might be due to the larger diameter of the distal loop and the presence of 2 additional electrodes on it's circular tip. These novel characteristics might allow better contact with a wider area of the PVs wall. The approach to the PV ostium might be more straightforward than with the traditional AC in detecting RTR. A recent study by Boveda et al. meticulously described specific manoeuvres designed to maximize RT recordings during second-generation CB-A ablation with the standard 20mm AC [18]. The authors demonstrated that, with specific torqueing and pacing maneuvers, overall RT assessment of PV disconnection was possible in 97.7% of cases, after a mean duration of 48.6 ± 33.0 s. However, the operator had to rely often on exit block verification during CB application. Since entry block implies exit block in the context of PVI[19], exit block verification may be an effective alternative to confirm PV after CB application, even if performig properly these manoeuvres with the ILMC might be difficult. Moreover, direct disappearance or dissociation of PVPs from LA activity might be significantly more simple to interpret. Finally, when pacing to analyse RT documentation of PV exit block in the right-sided veins, an additional external pacing source is needed to pace the phrenic nerve and monitor diaphragmatic contraction. These manoeuvres might therefore render a somewhat originally straightforward

ablation procedure more complex and cumbersome. This is one of the reasons why we didn't perform this complex maneuvers. Then we used the same "standard"/"easy to follow" positioning-technique for both ILMC, in order to make the comparison feasible and more realistic, and also to provide a reproducible result in everyday practice of less experienced centers. We advanced the AC-A inside the PVs to guarantee a complete occlusion, and then we pulled it back closer to the PVs ostium. In this way we observed that the simple approach to the PV ostium might be more straightforward with the AC-A than with the traditional AC in detecting RTR. The AC-A might detect RTR even when it has been placed distally into the vein and the loop is despiralized deep inside the PVs, because it is 1.2 cm longer than its predecessor and the proximal electrodes might be pulled nearer to the PVs ostium to detect electrical activity, without losing CB-A stability. However, performing meticolously the above-mentioned torqueing and pacing maneuvers would have certainly led to a higher incidence of RTR visualization.

Additionally, we did not observe any differences in terms of mean number of freezes or freezing times between both ILMCs. This lack of difference is certainly due to the standardised procedural workflow performed in our laboratory in the setting of CB ablation. To note, this study describes our very first experience with the ACA versus a very established routine with the AC in our team's daily clinical practice. In fact our findings did not show differences in terms of procedural times, fluoroscopy exposure and success rate. However, although it is universally accepted that the success of the cryoballoon technique is tightly related to the achievement of PV occlusion, a greater experience with the ACA might hypothetically lead to shorter procedural and fluoroscopic times in the future. Moreover, the shaft of the novel AC-A is softer if compared to its predecessor's, therefore the supporting action provided by this catheter may seem poorer than the standard AC. In our experience, we could feel this while performing the first cases with the AC-A, however this actually did not prevente either to reach an effective occlusion or to complete successful isolation in all PVs. We did not observe any significant difference in the rate of RTR visualisation between type of veins with the AC-A. This is an important finding. In fact the PV sleeves are typically shorter in the inferior veins with respect to their superior counterparts[15,16] and the occlusion of these veins often requires more handling of the CB system and not seldomly the ILMC has to be positioned more distally[20]. Typically, the rate of visualisation of RTR varies greatly between the different types of PVs when using the traditional AC[4,5]. Observing RTR with similar proportions in the PV ostia is a definite leap forwards in CB-A ablation in conjunction with the novel AC-A.

It is not yet proven if a higher visualization rate of RTR will be clinically significant to improve long-term PVI. However, the growing idea is that a novel tailored approach to each vein based on RTR might be the key to obtain the ideal safety- efficacy balance. For example, if a PV is isolated very early in the freeze, the need to complete a 180 second cycle might not be required. As previuosly discussed, several studies have identified the TTI as a critical procedural variable. TT-PVI emerged as a powerful marker of acute and durable PV isolation[2,3]. Furthermore, it might also be instrumental in reducing the need for the number of cryoapplications as well as the procedural duration and fluoroscopic exposure. Aryana et al.[21] recently described a novel atrial fibrillation cryoablation dosing algorithm guided by time-to-pulmonary vein isolation and compared it with the conventional procedure (Cryo-DOSING Study). In the "Cryo-AF Dosing cohort" a single cryo-application was applied to a given PV if the TTI measured ≤60 seconds and the duration of that application consisted of TTI + 2 minutes. Interestingly, they found that TTI might be effectively used to guide and individualize the ablation dosing strategy during Cryo-AF, yielding an equivalent and high rate of acute PV isolation. Moreover, this approach was associated with improved durability of PV isolation at repeat procedures and a lower incidence of atypical atrial flutters/tachycardias during long-term follow-up. The authors believe that this characteristic was likely a consequence of a more tailored ablation strategy. Third, the TTI–guided dosing algorithm improved the procedural efficiency, allowing for fewer and shorter applications, reduced left atrial dwell, ablation, and procedure times. Adverse event rates and freedom from recurrent AF during long-term follow-up were equivalent between the 2 ablation strategies. The ICE T Trial similarly described that an individualized CB PVI strategy allows faster atrial fibrillation ablation without affecting the favorable clinical outcome and that a short TTI appears to predict freedom from recurrent atrial tachyarrhythmia[3].

This might also hypothetically reduce the incidence of undesired damage to extra cardiac structures such as the oesophagus[22] without jeopardising the permanency of PVI.

Limitations

The study was a non-prospective, non-randomized, single-center case-control trial conducted in a relatively small number of patients. The definition of success was limited to the procedural outcomes and a follow-up period was not considered. Despite the evidence of effective and reproducible manoeuvres to optimize monitoring of RTR, we did not use any of them in order to maintain a simple and straightforward approach. Performing these maneuvers would have certainly led to a higher incidence of RTR visualization. Larger randomized studies with longer follow-up are needed to prove novel Achieve Advance catheter is superior in terms of efficacy and safety during cryoballon ablation of atrial fibrillation and to understand whether the increased capability to detected RTR with AC-A during CB-A PVI means increased number of long-lasting isolated PVs.

Conflict of interest

Carlo de Asmundis receives compensation for teaching purposes and proctoring from AF solutions, Medtronic, member steering committee ETNA-AF-Europe Daiichi Sankyo Europe. Gian Battista Chierchia receives compensation for teaching purposes and proctoring from AF solutions, Medtronic. Pedro Brugada receives research grants on behalf of the centre from Biotronik, Medtronic, St Jude Medical, Sorin, Boston Scientific and speakers' fees from Biosense-Webster, Biotronik, Medtronic and Boston Scientific.

Conclusion

CB-A ablation in conjunction with the novel 25 mm AC-A ILMC is feasible, safe, and affords PVI in all veins. The 25 mm AC-A has proven significantly superior in visualising RTR if compared to the standard 20 mm AC, affording RTR in 74% of PVs without the need

of adjunctive pacing maneuvers.

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Soluble Urokinase Plasminogen Activator Receptor (suPAR) as A Predictor of Incident Atrial Fibrillation

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Abstract

Soluble urokinase plasminogen activator receptor (suPAR) is a biomarker of chronic low-grade inflammation and a potent predictor of cardiovascular events. We hypothesized that plasma suPAR levels would predict new-onset atrial fibrillation (AF) in a large cohort of consecutively admitted acute medical patients during long-term follow-up. In 14,764 acutely ad-mitted patients without prior or current AF, median suPAR measured upon admission was 2.7 ng/ml (interquartile range (IQR) 1.9-4.0). During a median follow-up of 392 days (IQR 218–577), 349 patients (2.4%) were diagnosed with incident AF.

suPAR levels at admission significantly predicted subsequent incident AF (HR per doubling of suPAR: 1.21, 95% CI 1.05-1.41, adjusted for age and sex). After further adjustment for Charlson score, plasma C-reactive protein (CRP), plasma creatinine and blood hemoglobin-levels, the result remained essentially unaltered (HR per doubling of suPAR: 1.20, 95% CI: 1.01-1.42). In multivariate ROC curve analysis, combining age, sex, Charlson score, CRP, creatinine, and hemoglobin (AUC 0.77, 95% CI 0.75-0.79), the addition of suPAR did not improve the prediction of incident AF (AUC 0.77, 95% CI 0.75-0.79, P=0.89).

Plasma suPAR is independently associated with subsequent new-onset AF in a population of recently hospitalized patients, but the addition of suPAR to baseline risk markers appears not to improve the prediction of AF.

Introduction

Atrial fibrillation (AF) is a frequently seen cardiac rhythm disturbance, especially among el-derly patients. In 2010, global estimates of AF prevalence reached 596.2 per 100,000 in men and 373.1 per 100,000 in women[1]. The clinical manifestations of AF span the diorama from asymptomatic affliction, to patients suffering severe hemodynamic consequences and related complications, such as acute progression of congestive heart failure, ischemic stroke, as well as markedly reduced survival[2],[3]. Alterations in the normal physiology of the atria, mediated by metabolic or structural changes, can incite AF [4]. Inflammation and oxidative stress may be linked to the development of AF[5]. Elevation of inflammatory markers, such as plasma C-reactive protein (CRP) and inter-leukin-6, have been shown to predict development of AF[6]. suPAR is the soluble form of the membrane-bound urokinase plasminogen activator receptor (uPAR). Upon activation, urokinase converts plasminogen into plasmin, thus triggering a pro-teolytic cascade participating in thrombosis or degradation of the extracellular matrix, de-pending on the environment. suPAR concentration in blood/plasma/serum correlates to the level of activation of the immune system. As a novel biomarker of chronic low-grade inflam-mation, suPAR is related to a myriad of medical conditions, and it has been shown to surpass CRP and other traditional inflammation markers in predicting cardiovascular disease (CVD)[7]. This may be due to suPAR being more tightly related to subclinical cardiovascular dam-age[7],[8]. Furthermore, unlike other inflammatory markers, suPAR levels remain unchanged during acute cardiac events and suPAR is in this sense not considered an acute phase reactant[7],[9]. In this study, we aimed to investigate whether suPAR was predictive of incident AF in acutely admitted medical patients with no prior history of AF.

Key Words

suPAR, Predictor, Atrial fibrillation, Soluble Urokinase Plasminogen Activator Receptor

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Methods

Setting and study design

The study was a registry-based cohort study of patients admitted to the Acute Medical Unit (AMU), Copenhagen University Hospital Hvidovre, Capital Region, Denmark, between No-vember 18, 2013, and September 30, 2015. Patients were included if they had plasma suPAR levels measured as part of the standard ad-mission blood tests. Patients with a prior or current diagnosis of AF (International Classifica-tion of Diseases-10th Revision (ICD-10) I48) at the time of the index admission were exclud-ed from further analysis. The remaining patients were followed until December 31st 2015. su-PAR data on a subgroup of this cohort has previously been published[10]. The index admission was defined as the first admission where a patient had his or her suPAR level measured. Information on admissions and diagnoses was obtained via the Danish Na-tional Patient Registry (NPR), where all contacts with the secondary health care system are registered. Contacts for hospital admissions less than five hours apart were considered coher-ent and coded as the same admission.

Prevalent co-morbidity at the index admission was defined as diagnoses of interest registered before or during the index admission.

These included ICD-10 codes for diabetes (E10-E14), hypertension (I10–I15), congestive heart failure (I099, I110, I130, I132, I255, I420, I425–I429, I43, I50), stroke (I60-I64, G459), embolism (H341A, I740B, I741A, I742A, I743A, I744A, I744C, I745A, I803A, N280A), and vascular disease (I20-I25, I70, I71, I731, I738, I739, I771, I790, I792, K551, Z958, Z959). Furthermore, the Charlson comorbidity index was calculated for each patient based on the patient's comorbid conditions as previously described[11]. Briefly, the score is calculated based on a weighted scoring system where severe and multiple comorbidities increase the cumulative score[12], using the updated weighting[13].

During follow-up, information on incident AF and vital status was obtained from the NPR and the Danish Civil registration System, respectively.

Measurement of biomarkers

Blood samples were analyzed at the Department of Clinical Biochemistry and results were extracted from the electronic hospital database LABKA. Plasma suPAR levels were deter-mined in singlets using the suPARnostic AUTO Flex ELISA kit on an automated Siemens BEP2000 platform according to the manufacturer's instructions (ViroGates A/S, Birkerød, Denmark). The fresh plasma samples were analyzed in batches once daily during weekdays (within 0–72 hours after blood sampling). The assay had a precision (coefficient of variation) of 5.1% at 2 ng/mL and 1.7% at 7 ng/mL. Plasma CRP and creatinine were analyzed using a COBAS 6000 analyzer (Roche Diagnos-tics, Mannheim, Germany). Hemoglobin was analyzed using a Sysmex XN 9000.

Statistical Analysis

Continuous variables are described by median and interquartile range (IQR), and categorical variables are described by number (n) and percentages (%). Differences between groups were tested with Wilcoxon or chi-square test where appropriate.
Adjusted Cox regression analyses were performed to estimate the effect of suPAR on AF. Ad-justments were made for age and sex, and further adjustments were made for Charlson score, CRP, creatinine, and hemoglobin. In the Cox models, suPAR was used as a continuous varia-ble (log2-transformed) or as a categorical variable stratified in tertiles. Results are presented as hazard ratios (HRs) with 95% confidence intervals (CIs). SAS Enterprise Guide 7.11 (SAS Institute) and R 3.2.3 (The R Foundation for Statistical Computing) were used for statistical analysis. A P value <0.05 was considered to be statistically significant.

Results

During the inclusion period, 20,193 samples were ordered. suPAR was analyzed in 18,009 cases. After exclusions due to invalid civil registration number (n=505), loss to follow-up (n=109), missing NPR data (n=40), suPAR below the assay range (<0.5 ng/ml, n=43), and prevalent AF (n=2,548), the final population comprised 14,764 patients. Baseline characteris-tics of the population are shown in [Table 1].

The ten most frequent index admission diagnoses for the entire population are shown in [Table 2], with the corresponding frequencies for the subpopulation with subsequent AF.

During a median follow-up of 392 days (IQR 218–577), incident AF was diagnosed in 349 patients (2.4%) during follow-up. Patients with subsequently diagnosed AF differed signifi-cantly from the overall population on several baseline parameters, as outlined in [Table 1], in-cluding higher age, more chronic diagnoses, lower blood hemoglobin, and higher plasma lev-els of CRP, creatinine, and suPAR.

Continuous suPAR and risk of incident AF

When adjusted for age and sex, the HR of incident AF per doubling of plasma suPAR was 1.21 (95% CI: 1.05-1.41, P = 0.01), meaning that for every doubling of suPAR, the risk of incident AF increased by 20%. This result remained essentially unaltered after further adjust-ment for Charlson score, CRP, creatinine, and hemoglobin (HR per

Table 1: Baseline characteristics of acutely admitted patients without prior or current atrial fibrillation (AF)

	All patients (n=14,764)	Patients with no subsequent AF (n=14,415)	Patients with subsequent atrial fibrillation (n=349)	P
Male,n(%)	6,801 (46.1)	6,639 (46.1)	162 (46.4)	0.89
Age (years), median (IQR)	57.5 (40.1–73.1)	56.9 (39.7–72.5)	76.6 (68.0–84.7)	<0.0001
Length of index admission (days), median (IQR)	0.76(0.30–2.92)	0.75 (0.30–2.87)	1.3 (0.5–5.5)	<0.0001
Comorbidities*:				
Diabetes, n (%)	2,054 (13.9)	1,989 (13.8)	65 (18.6)	<0.0001
Arterial hypertension, n (%)	4,037 (27.3)	3,852 (26.7)	185 (53.0)	<0.0001
Congestive heart failure, n (%)	1,051 (7.1)	974 (6.8)	77 (22.1)	<0.0001
Previous stroke/TCI/emboli, n (%)	1,713 (11.6)	1,651 (11.5)	62 (17.8)	<0.0001
Vascular disease, n (%)	3,162 (21.4)	3,035 (21.1)	127 (36.4)	<0.0001
Charlson score (median, IQR)	0 (0–1)	0 (0–1)	0 (0–2)	<0.0001
Biomarkers, median (IQR):				
Plasma suPAR (ng/ml)	2.7 (1.9–4.0)	2.6 (1.9–3.9)	3.6 (2.6–5.2)	<0.0001
Plasma CRP (mg/l)	5 (1–29)	5 (1–29)	8 (2–44)	<0.0001
Plasma creatinine (ng/ml)	72 (60–89)	72 (60–89)	82 (64–105)	<0.0001
Blood hemoglobin (mmol/l)	8.3 (7.5–9.0)	8.3 (7.5–9.0)	7.9 (7.2–8.6)	<0.0001

* International Classification of Diseases-10th Revision (ICD-10) diagnoses: Diabetes: E10-E14. Arterial hypertension: I10–I15. Congestive heart failure: I099, I110, I130, I132, I255, I420, I425–I429, I43, and I50. Stroke: I60-I64 and G459. Emboli: H341A, I740B, I741A, I742A, I743A, I744A, I744C, I745A, I803A, N280A. Vascular disease: I20-I25, I70, I71, I731, I738, I739, I771, I790, I792, K551, Z958, and Z959. IQR: Interquartile range. SD: Standard deviation. TCI: Transitory cerebral ischemia.

doubling of suPAR: 1.20, 95% CI: 1.01-1.42, P = 0.037).
In multi variate receiver operating characteristic (ROC) analysis to predict AF, the area under the curve (AUC) for the combination of age, sex, Charlson score, CRP, creatinine, and hemoglobin was 0.77 (95% CI: 0.75-0.79). The addition of suPAR to the model did not change this result (P = 0.66).

suPAR tertiles and risk of incident AF

When dividing suPAR levels in tertiles, we found a significantly increased risk of incident AF in patients with a baseline suPAR in the highest tertile compared to the lowest tertile after controlling for age and sex (HR: 1.42, 95% CI: 1.02–1.97, P = 0.039). After further adjust-ment for Charlson score, CRP, creatinine, and hemoglobin, the result was attenuated (HR: 1.30, 95% CI: 0.92–1.86, P = 0.14).

Discussion

We present data demonstrating a significant, yet modest, correlation between baseline suPAR levels and subsequent incident AF in a large and diverse population of patients seeking emer-gency care, due to medical conditions unrelated to AF. After multivariate adjustment, a dou-bling of suPAR corresponded to a 20% increase in risk of incident AF.

To our knowledge, the relationship between suPAR and incident AF has been investigated in only one prior study. In 2014, Borné and colleagues reported a positive association between suPAR and incident AF among subjects participating in the Malmö Cancer and Diet study during 1991-1996, but after adjustment for conventional risk factors and biomarkers, the cor-relation was not significant[14]. The studies differ on several issues. Primarily, we studied a population of recently admitted patients, whereas Borné and colleagues studied a general population sample from the Malmö Diet and Cancer Study. Furthermore, the observation time in the Swedish study was much longer (mean follow-up 16.3 years) than our median follow-up of 392 days. This large difference in time from baseline to endpoint might explain the different results.

Table 2: 10 most frequent diagnoses during the index admission for acutely admitted patients without prior or current atrial fibrillation (AF)

	All patients (n=14,764)	Patients with subsequent atrial fibrillation (n=349)
1: Z034, n (%)	1097 (7.4)	22 (6.3)
Observation for acute myocardial in-farction		
2: J189, n (%) Pneumonia	619 (4.2)	30 (8.6)
3: Z038, n (%) Observation for unspecified condition	581 (3.9)	7 (2.0)
4: R074, n (%) Chest pain, unspecifiedChest painunspecified	446 (3.0)	6 (1.7)
5: J960, n (%) Acute respiratory failure	368 (2.5)	17 (4.9)
6: Z035, n (%) Observation for other cardiovascular condition	302 (2.0)	5 (1.4)
7: I109, n (%) Arterial hypertension	263 (1.8)	6 (1.7)
8: J459, n (%) Asthma	257 (1.7)	3 (0.9)
9: F100, n (%) Alcohol intoxication	243 (1.6)	1 (0.3)
10: R429, n (%) Vertigo	231 (1.6)	4 (1.1)

Recently, a Japanese study showed an association between prevalent AF, especially non-paroxysmal AF, and increasing suPAR levels, although the association lost significance in multivariate models[15]. The relationship between inflammation and risk of cardiovascular disease is well documented[6,16,17] and it is broadly confirmed that inflammation contributes to the pathophysiology of AF[18-21]. Hence, inflammation seems to play an important role in the development of AF as well as in the pathogenesis of cardiovascular diseases related to incident AF. Especial-ly, CRP has been shown to correlate with increased risk of new onset and recurrent AF[22-24].

Although suPAR and CRP are correlated and both are related to lifestyle risk factors, such as smoking and low physical activity, suPAR and CRP are quite different from each other with respect to their correlation to subclinical organ damage and metabolic relationships and seem to belong to different pathways[7]. Notably, suPAR seems to be more closely related to endothelial dysfunction, which is meticulously associated with AF[25]. Furthermore, in contrast to CRP and other traditional markers of inflammation, suPAR remains unchanged after a major surgical procedure such as coronary artery bypass graft (CABG) and in patients with ST-elevation myocardial infarction undergoing primary percutaneous coronary interven-tion[26,27]. Here, we found a significant correlation between suPAR and incident AF after adjustment for plasma CRP. Although we found a significant association between suPAR and incident AF, the correlation was of modest proportion. Furthermore, when dividing suPAR levels into tertiles, the correla-tion was no longer statistically significant after multivariate adjustment, and in ROC curve analysis, the addition of suPAR (as a continuous variable) to conventional baseline risk mark-ers did not improve the prediction of incident AF during follow-up. Whether suPAR has a po-tential role in future schemes of prediction of AF is uncertain. Our data do not support the clinical use of suPAR for this specific purpose, but further investigation is warranted with re-spect to size and selection of population sample.

Strengths and Weaknesses

We included data from a large sample of acutely admitted patients. The NPR allows near complete follow-up for incident AF. The validity of data from the NPR is generally high in-cluding the diagnosis AF and other cardiovascular diagnoses[28-30].

We cannot exclude the risk of potential underreporting of atrial fibrillation at index admission or during follow up, but we have no reason to believe that this would result in a systematic bias.

Since our study included patients admitted in our Acute Medical Unit, the adjustment for CRP was of particular importance. This was done in order to reduce the risk of indication bias, i.e. that the condition for which the patients were admitted was associated with increased CRP and risk of AF rather than suPAR. To reduce the risk of bias further, we performed separate sensitivity analyses, omitting data from patients with incident AF within 30 days from base-line. The results of these analyses were essentially no different from the main results (data not shown).

The nature of our study does not allow us to imply a causal relationship between suPAR and incident AF. In fact, the specific role of inflammation in AF is yet imprecisely defined and the clinical

relevance of raised inflammatory markers as a correlate to AF is elusive.

Conclusion

We found a significant correlation between suPAR and subsequent risk of AF in a large popu-lation of patients seeking emergency care, due to medical conditions unrelated to AF. After multivariate adjustment, a doubling of suPAR corresponded to a 20% increase in risk of incident AF.

However, the addition of suPAR to conventional baseline risk markers did not improve the prediction of incident AF. Further research is warranted in order to define the role of inflam-mation and inflammatory markers - including suPAR - in AF.

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Biomarkers of Myocardial Injury and Inflammation after Permanent Pacemaker Implantation: The Lead Fixation Type Effect

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Abstract

Background: Permanent pacemaker implantation is accompanied by minor myocardial damage, indicated by elevated serum levels of cardiac biomarkers. Aim of this prospective study was to comparably investigate the lead fixation type effect on the extent of myocardial injury and inflammation following pacemaker implantation, and to assess the possible clinical implications.

Methods: Cardiac troponin I (cTnI) and C-reactive protein (CRP) were measured at baseline, 6 and 24h after implantation in 101 patients, categorized into the active and passive lead fixation group. Patients were followed up for clinical adverse events or abnormal pacing parameters at 24h, 7 and 30 days post-procedure.

Results: cTnI increased at 6h post-procedure ($p<0.05$) in 23.8% of patients, and returned to baseline after 24h. The passive group demonstrated significantly higher cTnI at 6h compared to the active group ($p=0.006$). CRP increased significantly at 6h, and maintained an upward trend after 24h ($p<0.01$) in both groups. The active group demonstrated significantly higher CRP at 6h compared to the passive group. We did not identify an association of positive biomarkers with adverse events.

Conclusions: cTnI and CRP can increase early after permanent pacemaker implantation, indicating mechanical myocardial injury and inflammation. The extent of these biomarkers elevation depends on the lead fixation type, and is not related to worse short-term prognosis.

Introduction

Permanent pacemaker implantation is accomplished by transvenous insertion of endocardial leads, whose stability is secured and maintained using either active or passive fixation. A number of studies have demonstrated that the mechanical effect of both lead fixation types on the myocardium may lead to local injury, as evidenced by raised levels of plasma troponin and inflammatory biomarkers[1-9,12]. However, data are scarce regarding the association of the lead fixation type (active or passive) with the extent of myocardial injury, the subsequent systemic inflammatory response, and the possible clinical significance of cardiac biomarkers elevation, as clinical adverse events or abnormal change in pacing parameters. Aim of this prospective study was to comparably investigate the lead fixation type effect on the extent of myocardial injury and inflammation following permanent pacemaker implantation, by means of alterations in cardiac troponin I (cTnI) and C-reactive protein (CRP) plasma levels, and to assess the possible clinical impact of this phenomenon.

Methods

This was a prospective study, including consecutive adult patients, who underwent permanent pacemaker implantation for symptomatic bradyarrhythmia therapy in our institution. Indications for permanent pacing therapy included sick sinus syndrome, atrioventricular block and slow atrial fibrillation. All patients enrolled in the study were required to have normal baseline cTnI and CRP levels prior to the procedure. Exclusion criteria were unstable coronary artery disease, recent percutaneous coronary intervention, electrophysiological testing or cardioversion within the previous month and patients with temporary pacemaker, signs of any acute infection or chronic inflammatory disease, acute kidney injury or end-stage renal disease. Patients receiving cardiac resynchronization therapy pacing devices were also excluded. The study protocol was approved by the local scientific committee for human research conforming to the ethical guidelines of the 1975 Declaration of Helsinki. All patients gave informed written consent prior to inclusion into the study.

An echocardiographic study was performed to all patients prior to the procedure, for the assessment of left and right ventricular function. All implantation procedures were performed by trained, experienced physicians, ordinarily involved in cardiac pacing therapy, and took place in the relevant operation room of our institution, following our usual protocol for pacemaker implantation. Patients received active (Vitatron Crystalline® Actfix ICQ09B, Vitatron BV, The Netherlands) or passive fixation leads (Vitatron Crystalline® ICM09B/09JB, Vitatron BV, The Netherlands) according to the operators' judgment. Steroid eluting leads were used in all patients. In case of dual-chamber pacemaker implantation, patients received

Key Words

Pacemaker, Lead fixation, Troponin, C-reactive protein

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passive fixation atrial leads in the right atrial appendage, with the only exception of previous cardiac surgery, in consideration of the altered atrial anatomy. In case of use of active fixation atrial leads, the active fixation system was also chosen for the ventricular lead. Patients were categorized into the passive or active group, according to the ventricular lead fixation type. The procedure duration was also recorded and was defined as the time interval between the insertion of the first lead into the cephalic or the subclavian vein and the fixation of the pulse generator.

Blood samples were collected from each patient from a peripheral vein before the beginning of the implantation procedure (baseline values), and at 6 and 24 hours after the end of it. All blood samples were analyzed immediately upon receipt by the biochemical laboratory. Cardiac troponin I and CRP levels were measured by immunoassay technique (cTnI assay troponin I Flex and C-reactive Protein Extended Range Flex) on a Dimension RxL Max analyzer (Siemens Dade Behring, USA). The upper reference limit for cTnI is<0.1 ng/ml and for CRP <5 mg/L.

All patients were monitored for 24 hours after the procedure for clinical signs of myocardial ischemia, hemodynamic instability or any early complication related to the procedure (pneumo- or haemothorax, cardiac tamponade/perforation, haematoma, lead dislodgement, signs of infection, venous thrombosis), and were regularly followed-up at 7 days and at 1 month. Any complication or abnormal change in pacing parameters was also recorded.

Data are expressed as proportions, mean ± standard deviation (SD) and median as appropriate. Student's t-test was applied to continuous variables with normal distribution, whereas non-parametric analyses were applied to variables demonstrating non-normal distribution. Qualitative variables and differences in ratios between the two groups were assessed with the use of chi-square test. The level of statistical significance was set at a=0.05. All statistical analyses were performed using SPSS version 16 (SPSS Inc., Chicago, IL, USA) software.

Table 1: Patients' clinical characteristics and procedural technical variables

	Passive Fixation (n=62)	Active Fixation (n=39)	p-value
Age (years)	79.27 ± 7.56	77.64 ± 7.88	ns
Male sex, n (%)	41 (66.1)	21 (53.9)	ns
Procedure duration (minutes)	32.5 ± 17.14	26.41 ± 9.79	ns
Pacemaker type			
- Dual chamber, n (%)	44 (71)	28 (71.8)	ns
- Single chamber, n (%)	18 (29)	11 (28.2)	ns
Indication for permanent pacing			
- Sick sinus syndrome, n (%)	23 (37.1)	15 (38.5)	ns
- Atrioventricular block, n (%)	21 (33.9)	13 (33.3)	ns
- Bradyarrhythmia - atrial fibrillation, n (%)	16 (25.8)	10 (25.6)	ns
- Other, n (%)	2 (3.2)	1 (2.6)	ns
Approach:			
- Cephalic vein, n (%)	24 (38.7)	16 (41)	ns
Clinical adverse events, n			
- Clinical signs of myocardial ischemia	0	0	ns
- Early complications related to the procedure	1	2	ns
- Abnormal change in pacing parameters	4	3	ns

Data are presented as mean ± standard deviation and percentages. ns = non-significant

Results

A total of 164 patients were enrolled in the study, from which 63 were excluded. The final study population meeting inclusion/exclusion criteria consisted of 101 patients (62 males and 39 females). The average age of the studied population was 78±7 years. Study demographic and clinical characteristics are presented in detail in [Table 1]. Only 4 patients (3.96%) received active fixation atrial (and ventricular) leads. Echocardiographic parameters were similar between the two groups. The use of passive lead fixation was accompanied by a more prolonged procedure duration compared to active, a difference that was found marginally statistically significant (p=0.055).

Biochemical data are presented in [Table 2]. Baseline values of cTnI and CRP were within normal limits without differences between active and passive lead fixation groups. Plasma cTnI increased at 6h post-procedure (p<0.05) in 23.8% of patients, and returned to baseline after 24h in both groups [Figure 1]. Of note, one patient of the passive lead fixation group had a marked increase in serum cTnI level at 6h (1.74 ng/ml), a value that also declined after 24h back to normal [Figure 1]. The passive fixation group demonstrated significantly higher cTnI at 6h compared to the active fixation group (p=0.006, [Table 2]), a discrepancy that was not maintained at 24h (p=0.452). Plasma CRP increased significantly at 6h, and maintained an upward trend after 24h (p<0.01) in both groups. Statistical analysis yielded a significant difference (p<0.05) between the two study groups at 6h, with the active group demonstrating higher CRP levels compared to the passive group [Table 2]. A total of 5 patients (3 in the active and 2 in the passive group) demonstrated marked elevation in CRP levels (above 20 mg/dl), although this was not related to cTnI values.

Table 2: Serial changes of cTnI and CRP plasma levels.

	Passive Fixation	Active Fixation	p-value
cTnI (normal value <0.1 ng/ml)			
- Baseline	0.05±0.02 (0.04)	0.04±0.01 (0.04)	ns
- At 6h	0.21±0.3 (0.11)	0.1±0.11 (0.05)	0.006
- At 24h	0.2±0.68 (0.06)	0.08±0.07 (0.05)	ns
CRP (normal value <5 mg/L)			
- Baseline	2.81±1.49 (2.5)	3.13±1.89 (2.4)	ns
- At 6h	7.21±7.19 (4.55)	14.29±20.41 (7)	0.032
- At 24h	16.29±16.84 (14.3)	15.32±9.55 (13.3)	ns

Data are presented as mean ± standard deviation and percentages. ns = non-significant

There was no correlation between elevated cTnI or CRP levels with demographic, clinical or technical aspects, including age, sex, pacemaker type (single or dual chamber), procedure duration, echocardiographic parameters and implantation approach (p=non-significant).

There was no clinical suspicion of myocardial ischemia, by means of chest pain or anginal equivalent in any patient, and all patients remained hemodynamically stable post-procedure. A total of 3 complications were identified in the post-procedural phase, one

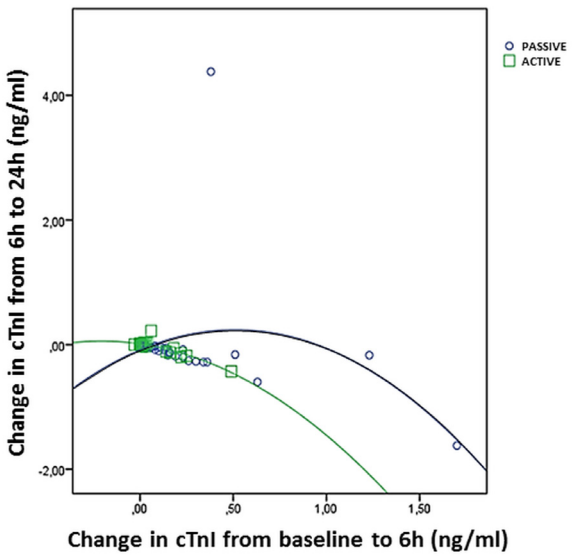

Figure 1: Schematic view of the use of the Needle Free SafeSept wire to cross the atrial septum

patient from the active group with pneumothorax and two patients with lead displacements, recognized at 24h (1 patient from the active and 1 from the passive group). Moreover, there were 7 patients showing significantly increased pacing thresholds during follow-up, from which only 2 patients have had elevated cTnI levels after the implantation. Thus, no correlation could be found between these adverse events and elevated cTnI/CRP levels or study group (active/passive).

Discussion

The important findings of this prospective study are the confirmation that permanent pacemaker implantation can be associated with an early detectable rise of cardiac biomarkers, indicative of reversible mechanical myocardial injury and inflammation, and the demonstration that the pacing lead fixation type seems to be related to the extent of this phenomenon. Our findings are in line with other similar clinical studies which have reported transient increases in cardiac troponin after elective permanent pacemaker implantation[1-4,6,10].

Rapid increase and decrease in cardiac troponin plasma levels are characteristic of reversible myocardial mechanical injury, especially due to the physical contact between lead and endocardium, resulting in direct cardiomyocyte destruction during the implantation procedure[1,2]. A small percentage of troponin is found in the myocyte cytoplasm in a soluble free form, which is released into the circulation under such circumstances[5]. A rapid troponin washout occurs within 24 hours, as there is no obstructive myocardial blood flow[3,4,6]. As we did not identify any association with clinical adverse events, cardiac troponin elevation seems not to be of clinical importance. However, high sensitivity troponin loses its specificity and the early post-procedural period has to be considered diagnostically "blind"[1]. An acute rise of cardiac troponin occurring in this period may raise clinical concern regarding the differential diagnosis of an acute coronary syndrome, tachyarrhythmias, cardiac perforation, pulmonary embolism or direct coronary artery trauma[11].

Concerning the effect of the lead fixation type on the extent of this phenomenon, the type of lead fixation seems to be related to differences in troponin release. Contrary to previous studies[1] and to what one might expect, we have demonstrated that actively fixed leads result in less evident troponin release compared to passive leads, despite the fact that they are screwed into the myocardium[1]. This interesting finding could possibly be attributed to the greater number of lead manipulations and repositioning attempts needed until satisfactory final lead lodgement in passive fixation systems. This hypothesis is further supported by our finding of slight prolongation of the procedure duration using passive, as compared to active fixation leads. Consequently, it is reasonable to assume that the extent of troponin elevation after pacemaker implantation strongly depends on technical procedural issues, as reflected possibly by more prolonged procedure duration.

Furthermore, according to our data, progressively elevating CRP plasma levels illustrate the systemic, non-infectious, inflammatory response following pacemaker implantation. The significantly greater and earlier acute CRP rise of the more traumatic active compared to passive fixation leads corroborates the hypothesis of the primary regional inflammatory response, stimulated by the electrode contact with the endocardium[1,12].

Finally, in this study we attempted to address whether elevations in cardiac biomarkers following pacemaker implantation are linked to worse short-term prognosis. However, we could not identify any relation of increased biomarkers with procedure-related complications, lead displacement or rise in pacing threshold during a 1-month follow-up period. Consequently, this elevation in plasma cardiac biomarkers most likely represents the minimal myocardial damage that occurs during device implantation and seems not to be of clinical importance[13,14].

Limitations

Our study included a relatively small sample size and that allocation of patients into the active or passive lead fixation group was not completely randomized. Moreover, we did not include a control group of patients undergoing pacemaker device replacement, in order to draw safer conclusions with regard to the effect of the surgical preparative manipulations, such as device pocket formation, on CRP elevation. Finally, this study was underpowered to investigate possible clinical implications of elevated biomarkers.

Conclusions

Permanent pacemaker implantation results to mechanical myocardial injury, as indicated by elevated cTnI plasma levels during the early post-procedural phase, a phenomenon that seems to be related to the lead manipulations during pacing lead fixation. The systemic inflammatory response seems to be more pronounced in active lead fixation systems.

Conflict of Interests

None.

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Use of Intraprocedural Ibutilide During Stepwise Ablation of Long-Standing Persistent Atrial Fibrillation

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Abstract

Purpose: Catheter ablation is an effective therapy for symptomatic atrial fibrillation (AF). The aim of this study was to assess the effect of ibutilide administration in patients with long standing persistent AF undergoing catheter ablation.

Methods: We included 25 patients undergoing stepwise catheter ablation with ibutilide 1.0 mg infused prior to mapping and ablation as first step. Procedural and long-term outcomes were compared to a matched cohort of 25 patients in which ibutilide was not used but all other steps remained the same.

Results: Mean age of the cohort was 65.6±8.2 years, and duration of persistent AF 71.7±96.8 months. Termination to sinus rhythm (SR) directly or through an atrial tachycardia (AT) was achieved in 88% of patients administered ibutilide (32% SR/68% AT) vs. 64% in the control group. Ibutilide was associated with increased AF mean cycle-length (mCL) (208.3±31.6 vs. 156.0±23.7 ms; p<0.001) and decreased CFE mean surface area (29.2±20.2% vs. 47.3±13.7%; p=0.002). Procedure and radiofrequency (RF) times were less in the ibutilide group (288.8±49.6 vs. 335.3±47.4 min and 66.0±16.0 vs. 78.0±18.2 min; p=0.002 and 0.029 respectively). The 1-year recurrence was 44% in the ibutilide group and 60% in the control groups (p=0.29). Ibutilide patients had significantly reduced ShEn (6.1±0.14 vs. 7.09±0.14; p<0.001) and ShEn was higher in patients that recurred (6.47±0.24 vs. 5.73±0.15; p<0.001).

Conclusions: In long-standing persistent AF the use of ibutilide in the context of a stepwise ablation results in increased AF mCL, reduction of fractionation and ShEn and higher rates of AF termination, more often through an intermediate AT. Procedure and RF times are also decreased, without compromising long-term outcomes..

Introduction

Catheter ablation is an effective therapy for symptomatic, drug-refractory atrial fibrillation (AF)[1-3]. Pulmonary vein isolation (PVI), the standard ablative strategy for paroxysmal AF is insufficient in patients with persistent AF and long-standing persistent AF. Often, additional atrial substrate modification techniques are employed to improve success[4], however this increases procedure time and the optimal strategy is unknown[6].

Complex fractionated atrial electrograms (CFAE), defined as electrograms of short cycle length or continuous activity, are believed to associate with sources of AF perpetuation and CFAE ablation, as an adjuvant therapy to PVI, has been shown to improve maintenance of sinus rhythm (SR)[5,7-10] in some studies but not in others[6]. Contemporary electroanatomic mapping systems can generate automated maps to localize and quantify complexity of left atrial (LA) electrical activity using a number of signal processing techniques but chiefly the mean cycle length at any single point measured over a period of time[11]. The main limitation of this approach is that the majority of CFAE represent passive collision of wavefronts rather than critical drivers of AF[12] and differentiation of perpetuating from passive sites using current sequential mapping methods is speculative. Thus, currently all CFAE sites are targeted, potentially increasing procedure and ablation time without gain in efficacy.

Class III antiarrhythmic drugs (AAD) prolong the atrial refractory period[13], promote the fusion of fibrillatory wavefronts and decrease atrial fractionation[14]. It has been hypothesized that intraprocedural ibutilide may organize areas of passive atrial activation and help to identify CFAE sites critical for maintaining AF, thus reducing the amount of ablation required for success[15]. We investigated this potential in a cohort of long-standing persistent AF patients described herein.

Key Words

Atrial Fibrillation, Catheter Ablation, Stepwise Approach, Ibutilide

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Methods

Patients

In this descriptive, single-center cohort study we consecutively included adult patients (18 years of age or older) with long-standing persistent AF (sustained for more than 1 year) undergoing catheter ablation between April 2013 and June 2015. All patients had been referred due to symptomatic, drug-refractory AF. Patients with prior ablation procedures, patients who were in SR on the day of the procedure, and patients on amiodarone were excluded. Anti-arrhythmic medications other than amiodarone were discontinued 5 half-lives prior to the study. Therapeutic anticoagulation with warfarin or non-vitamin K oral anticoagulants (NOACs) was

maintained for at least 4 weeks before the ablation procedure and a pre-procedural trans-esophageal echocardiogram was performed in all patients to exclude LA thrombus. The study group consisted of consecutive patients where the drug ibutilide was administered following trans-septal puncture, prior to mapping and ablation. The control group was matched for age, sex, and duration of AF and selected from consecutive patients prior to study commencement. There were no other interventions in that time frame and no change in operators. Only patients with a minimum follow-up of 12 months were considered. The study protocol was approved by the institutional ethics committee of Kingston General Hospital and all patients provided written informed consent.

Electrophysiology Study

The procedure was conducted in the fasting state under conscious sedation with intravenous fentanyl and midazolam. Warfarin was continued through the procedure whereas NOACs were stopped 48 h before the procedure and restarted 8 h after sheath removal. Venous access was gained from the right femoral and left subclavian veins or both femoral veins. A decapolar catheter (St. Jude Medical, St. Paul, MN, USA) was placed via the subclavian or left femoral vein into the coronary sinus, and a quadripolar catheter (St. Jude Medical, St. Paul, MN, USA) was placed at the right ventricular (RV) apex and moved to the right atrial (RA) appendage after trans-septal puncture to monitor RA mean cycle length. After establishing LA access, intravenous heparin was administered with a target activated clotting time of 300-350 s. Following this, a circular mapping catheter with 5 mm electrode diameter and 2-7-2 mm spacing (Reflexion, St. Jude Medical, St. Paul, MN, USA) and an open irrigated ablation catheter (Therapy Coolflex, St. Jude Medical, St. Paul, MN, USA) were advanced into the LA. The EnSite NavX system (St. Jude Medical, St. Paul, MN, USA) was employed to construct a three-dimensional LA geometry and create a subsequent map based on mean local cycle length over 5 seconds (CFE mean). Isoproterenol to disclose non-pulmonary vein (PV) triggers was not used and the administration of adenosine to unmask latent PV connection was left to discretion of the operator.

Ibutilide Administration

The test cohort was composed of patients with long-standing persistent AF deemed unlikely to cardiovert with medication alone. Therefore, an empiric dose of 1.0 mg of ibutilide was chosen to perturb atrial electrophysiology and allow subsequent data collection during continued AF before ablation. Based on our previous experience, this dose rarely results in AF termination in patients with long-standing persistent AF. In addition, some authors have suggested that a therapeutic dose of ibutilide may help discriminate patients in which PVI-alone may be enough from those requiring further substrate modification[16]. Intravenous ibutilide was administered over 10 minutes at the time of trans-septal puncture and before creation of the LA CFE mean map using commercial software (SJM Medical, MN).

CFE Mean Mapping and LA mCL

Before any ablation, a baseline mean cycle length (mCL) CFE mean map was created using the EnSite NavX automated algorithm. Mapping was started 5 minutes after ibutilide bolus completion. Bipolar electrograms were acquired with the 20-pole mapping catheter during a 5-second recording period at each sampled location (30-300 Hz). Color coding of the geometry guided sampling to ensure complete endocardial and pulmonary vein coverage. Areas with CFE mean < 120 ms were identified as CFAE based on previously published data[5,17]. Additional settings included: refractory period of 30 ms, width 5 ms, sensitivity between 0.05-0.08 mV and interior projection of 5 mm. Percentage of fractionation was calculated by summation of all areas with CFE mean <120 ms divided by the total mapped surface area using custom software.

The mCL of AF was measured manually from the mid-coronary sinus bipole after ibutilide administration and before ablation. In the control group measurement was made at the time of CFAE mapping.

Shannon Entropy

Shannon entropy (ShEn) measures the distribution of signal values within the signal histogram and represents a measure of information uncertainty[8]. To investigate the effect of ibutilide we exported all 5-second bipolar electrograms recorded for creation of CFE mean map to the MATLAB environment and calculated a mean ShEn (bits) for each patient.

Ablation Protocol

Radiofrequency (RF) ablation was performed using a 4-mm irrigated-tip ablation catheter (Therapy Coolflex, St. Jude Medical, St. Paul, MN, USA) at a power of 30W on the anterior wall and 25W on the posterior wall to minimize the risk of esophageal injury. A stepwise approach was used, starting with ibutilide (in the test cohort) and followed by circumferential antral ablation and isolation of all pulmonary veins, ablation of CFAE (areas of CFE mean <120 msec remaining after antral isolation) and linear lesions (roof, coronary sinus) [Figure 1] until AF terminated. Mapping and ablation was performed in the RA when the RA mCL exceeded the LA mCL measured periodically in the LAA. Linear lesions were performed at

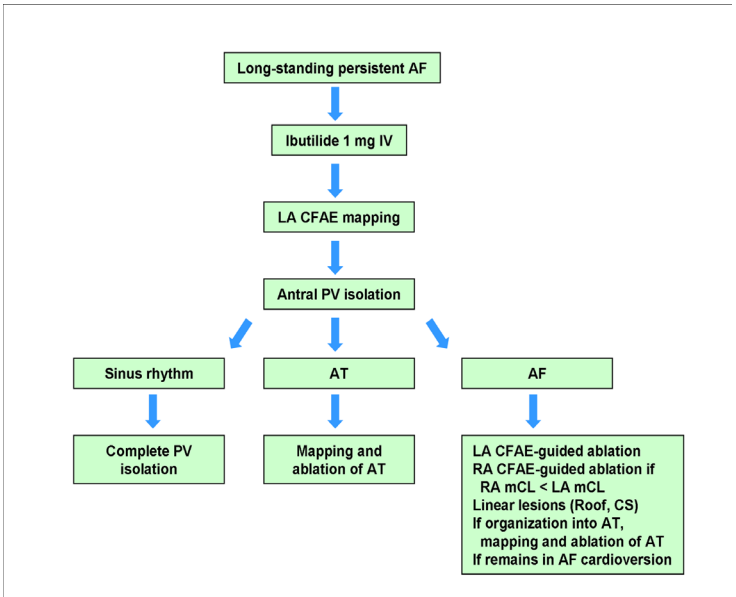

Figure 1: **Stepwise approach for AF ablation in the ibutilide and control groups. AF = atrial fibrillation; AT = atrial tachycardia; CFAE = complex fractionated atrial electrograms; CS = coronary sinus; LA = left atrium; mCL = mean cycle length; PV = pulmonary vein; RA = right atrium.**

the roof and then coronary sinus if AF persisted after CFAE ablation and LA mCL was greater than RA mCL. The endpoint was local electrogram attenuation during AF (loss of fractionated components and reduction of mean amplitude) and bidirectional block at the roof after restoring SR. When AF terminated to an atrial tachycardia (AT) or flutter, subsequent ablation was guided by entrainment and/or activation mapping of the AT. If SR was achieved during ablation, no additional ablation was pursued, with the exception of additional lesions at the PV antrum in case of PV reconnection or additional lesions at the sites of existing linear lesions to obtain bidirectional block. If AF persisted despite extensive CFAE ablation and linear lesions, external cardioversion was performed.

Follow-up

Patients were discharged home on the day after the procedure. Antiarrhythmic medications were restarted post procedure and stopped at 3 months in the absence of symptoms. Patients were followed in the outpatient clinic at 3, 6 and 12 months post-ablation. Follow-ups included clinical assessment, 12-lead ECG and a 24-hour Holter; further monitoring was performed if patients reported symptoms. Recurrence was defined as any documented atrial arrhythmia lasting longer than 30 seconds and classified as AF or AT based upon ECG appearance.

Statistical Analysis

Data were expressed as means and standard deviations for continuous variables and percentages for categorical variables. Independent samples t-tests and Fisher's exact tests were used for comparison between the study and control groups. P values < 0.05 were considered statistically significant

Results

Patients

Twenty-five consecutive patients with long-standing persistent AF were included in the study and compared with a matched cohort of consecutive patients treated prior to study commencement where ibutilide was not used. The clinical characteristics of the patients are summarized in [Table 1]. Both groups were comparable. The mean duration of persistent AF was 71.7±96.8 months and was not significantly different between the 2 groups. Most patients had severe LA dilatation, with a mean LA volume index by echocardiography of 50.7±25.4 ml (normal ≤41 ml). Five patients in the ibutilide group (20.0%) and 4 in the control group (16.0%) had a diagnosis of ischemic heart disease by coronary angiography.

Table 1: Baseline characteristics

Clinical variable	Ibutilide (n = 25)	Control (n = 25)	p-value
Age, years ± SD	66.8±8.9	64.4±7.8	0.32
Male sex, %	76.0 (19/25)	72.0 (18/25)	0.75
Duration of AF, months	63.2±102.5	78.9±93.8	0.63
LA dimension, mm	48.2±6.7	46.4±7.0	0.46
LA volume, ml	95.5±27.7	91.1±19.0	0.68
LA volume index	53.5±22.3	47.9±28.4	0.44
Hypertension, %	60.0 (15/25)	56.0 (14/25)	0.77
Diabetes, %	16.0 (4/25)	16.0 (4/25)	1.0
Ischemic heart disease, %	20.0 (5/25)	16.0 (4/25)	0.71
OSA, %	24.0 (6/25)	28.0 (7/25)	0.75
CHADS VASc	2.16±1.35	1.84±1.51	0.17

AF = atrial fibrillation; LA = left atrium; LVEF = left ventricular ejection fraction; IAB = interatrial block; OSA = obstructive sleep apnea.

Procedural Characteristics

The average procedure time in the ibutilide group was 288.8±49.6 min vs. 335.3±47.4 in the control group (p=0.002). The RF time was also lower in the ibutilide group (66.0±16.0 min vs. 78.0±18.2 min; p=0.029), while the fluoroscopy time did not differ significantly (25.3±9.7 min vs. 27.1±9.1 min; p=0.57). There was one cardiac tamponade requiring pericardiocentesis and one femoral pseudoaneurysm in the ibutilide group. There was also 1 episode of traumatic hematuria in the control group. No other major procedural complications were observed and no ventricular arrhythmias were associated with ibutilide use.

Table 2: Procedure characteristics and follow-up.

Clinical variable	Ibutilide (n = 25)	Control (n = 25)	p-value
Procedure time, min	288.8±49.6	335.3±47.4	0.002
Fluoroscopy, min	25.3±9.7	27.1±9.1	0.57
AF mCL, ms	208.3±31.6	156.0±23.7	< 0.001
CFAE, %	29.2±20.2%	47.3±13.7%;	0.002
AF termination, %	88 (22/25)	64 (16/25)	0.047
Conversion to AT, %	68 (15/22)	50 (8/16)	0.26
Recurrence (AF/AT):			0.24
- 6 m, %	20.7%	30.3%	
- 12 m, %	44%	60%	

AF = atrial fibrillation; mCL = mean cycle-length; AT = atrial tachycardia.

CFAE and LA mCL

When compared with the control group, ibutilide was associated with a significant prolongation in AF mCL (208.3±31.6 ms vs. 156.0±23.7 ms; p<0.001) and decrease in the total CFAE surface area (29.2±20.2% versus 47.3±13.7%; p=0.002). To illustrate the effect of ibutilide, a CFE mean map was performed both before and after ibutilide administration and prior to ablation in one patient shown in [Figure 2].

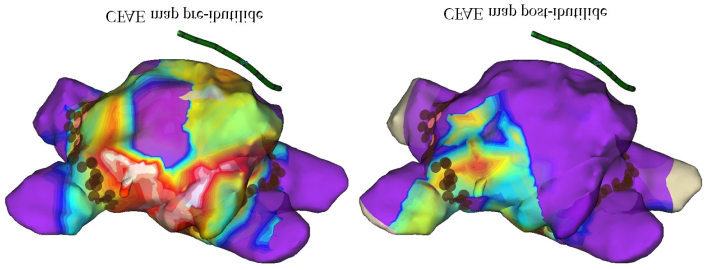

Figure 2: CFAE mean maps of the LA before and after ibutilide administration in one of the study patients. A significant decrease in the CFAE surface area is noted. CFAE = complex fractionated atrial electrograms.

ShEn

Patients administered Ibutilide had significantly reduced ShEn compared with control subjects (6.1±0.14 vs. 7.09±0.14; p<0.001). When we examined the ibutilide group for recurrence, ShEn was

significantly higher in patient that recurred versus those that did not (6.47±0.24 vs 5.73±0.15; p<0.001). This was not observed in the control group (7.02±0.18 for recurrence vs 7.16±0.21 for no recurrence; p=0.14). A weak correlation was observed between CFAE surface area and mean ShEn (0.35; p=0.03).

Acute Success

PVI was achieved in all the patients. In the ibutilide group conversion to SR directly or via organization into an AT was achieved in 88% of patients during ablation (n=22) (32% SR and 68% AT) [Figure 3]. In patients with an intermediate AT (n=15) the mechanism was perimitral in 4 cases, CTI-dependent in 4, roof-dependent in 1, focal in 1 (LA septum), both perimitral and roof-dependent circuits in 1, both perimitral and CTI-dependent in 1, both CTI-dependent and focal (LA anterior wall) in 1 and undetermined in 2 patients. In the control group AF termination during ablation was achieved in 64% of patients (n=16) (p=0.047 compared to the ibutilide group; 50% SR and 50% AT). The remaining patients (3 in the ibutilide group and 9 patients in the control group) remained in AF despite extensive ablation and were electrically cardioverted back to SR. Interestingly, conversion to SR before radiofrequency ablation occurred in 2 of the 25 patients in the ibutilide group (8.0%) and in these patients only PVI was performed. Both patients (age 83 and 69 years; AF duration 48 and 24 months) have remained arrhythmia-free after 12 and 14-month follow-up, respectively.

Follow-up

The mean follow-up in the whole cohort was 15.9±5.5 months (range 12 to 29 months), longer in the controls than in the study group (18.3±6.4 vs. 13.5±2.9 months; p <0.001) and the recurrence rate over this period was 44% (26/50). No significant difference was observed (p=0.24). The 6-month recurrence of atrial arrhythmias was 20.7% in the ibutilide group and 30.3% in the control groups and 1-year recurrence was 44% and 60%, respectively. In the ibutilide group 85% (6/7) of patients recurred with AF and 15% (1/7) with AT, whereas in the control group 66.5% (10/15) recurred with AF and 40% (5/15) with AT (p=0.27).

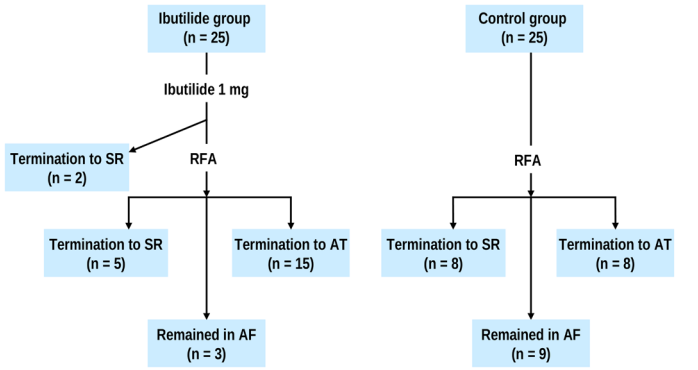

Figure 3: Flowing chart showing the acute procedural outcomes in the ibutilide and control groups. AF = atrial fibrillation; AT = atrial tachycardia; RFA = radiofrequency ablation; SR = sinus rhythm

In the total group ablation failed to restore SR in 12 patients (24%). In these patients the likelihood of AF/AT recurrence was significantly higher than in those where SR was achieved (75.0 vs. 34.2%; p=0.013). Eleven of the 50 patients underwent a repeat ablation procedure.

Discussion

Main Findings

In our study of patients with very long-standing persistent AF the use of ibutilide as initial part of a stepwise ablation approach resulted in higher rates of termination to SR and significantly shorter procedure times. In addition, there was an increase of AF mCL, reduction of LA fractionation and mean ShEn with ibutilide. Despite the less extensive ablation, the long-term outcomes were not impaired, with similar recurrence rates at 6 and 12 months, with a trend toward better outcomes in the ibutilide group.

Effect of Ibutilide

Ibutilide fumarate is a class III intravenous antiarrhythmic agent that acts by induction of a late inward sodium current and blockage of the rapid component of the cardiac delayed rectifier potassium current[19,20]. This ionic mechanism results in prolongation of the action potential duration and the effective refractory period of the cardiac myocytes. The dose of ibutilide used in our study, 1.0 mg, is equivalent to the therapeutic dose recommended for AF cardioversion[21]. In our patients, however, termination to SR by ibutilide before RF delivery was infrequent, occurring only in 2 cases (8%). This can be explained by the characteristics of our study group, with an average AF duration >6 years and severe LA dilatation (mean LA volume index 50.7 ml). In the 2 patients that converted to SR before commencement of RF, PVI alone was performed and both have remained free of AF/AT at 12 and 14-month follow-up. Ibutilide proved to be safe and was not associated with ventricular arrhythmias.

A recent randomized trial, the MAGIC-AF study, assessed the effect of a sub-therapeutic dose of ibutilide during ablation of persistent AF[22]. Consistent with our results, the study showed a reduction in LA surface area with CFAE sites and greater AF termination during ablation with ibutilide compared with placebo, while the 1-year freedom from AF did not differ significantly in both groups. The dose tested in MAGIC-AF, 0.25 mg IV, was selected to minimize the likelihood of AF termination. Other differences with our design can be acknowledged; in MAGIC-AF ibutilide infusion and CFAE mapping was carried out after PVI in patients who remained in AF, in our study the map was acquired prior to antral ablation. This is highly significant as mapping following ablation is compromised by atrial oedema and signal quality is usually poor. Finally, all persistent AF patients were included in MAGIC-AF, of which only 19% were long-standing[22]. As consequence, the duration of AF was much longer in our study (63.2 ± 102.5 months versus 9 ± 21 months).

CFAE mean index maps have important limitations in their ability to accurately identify the rotor pivot zones due to noise, misleading phase and activation times that distort these maps[23]. Other measures of signal complexity might be used instead. There is data in the literature to suggest that ShEn is a more reproducible feature[23], and Ganesan et al. showed the potential for ShEn to locate pivot points[18]. Ibutilide clearly reduced signal complexity as

reflected by mean ShEn and a more marked effect was associated with better outcomes. We might infer this was due to a reduction in pivot points and thus signal complexity not associated with sources of AF. However we did not examine regional ShEn and the observation requires further study.

Optimal Ablation Approach for Long-Standing Persistent AF

Several studies indicate that long-term outcomes after catheter ablation of persistent AF are rather modest. The ablation endpoints in these patients are ill-defined and there is no consensus on the optimal ablation strategy. Current guidelines suggest that substrate modification (linear lesions, CFAE ablation or a combination of these strategies) in addition to PVI is mandatory to improve outcomes[24,25]. A stepwise approach, involving PVI followed by CFAE-guided ablation and lines, may achieve acute termination in up to 87% of patients[26], but long-term results remain relatively poor and repeated ablation procedures are often necessary[27,28]. In addition, this technique involves extensive substrate ablation, with long procedure times, increased complications and potential for arrhythmogenic circuits, with risk of recurrent ATs in the future.

In our study the acute benefits of ibutilide use as part of a stepwise ablation, included termination of AF in a great majority of patients (88%) and significantly less RF ablation, decreasing the need for electrical cardioversion from 36 to 12%. This may have 2 alternative interpretations: either ibutilide terminates AF prematurely and conceals substrate targets that should be otherwise eliminated; or ibutilide is able to eliminate "spurious" CFAEs and thus unmask critical drivers responsible for AF perpetuation. The fact that the outcomes in the ibutilide group were not worse despite the less extensive ablation supports the second hypothesis.

In the ibutilide group the most common mode of termination was via an intermediate AT. Of 18 ATs occurring in 15 patients, 78% were macroreentrant, with the most common mechanisms involving reentry around the tricuspid and mitral valves (6 each). The clinical importance of the ATs induced by ibutilide and the prognostic impact of ablating these circuits is unknown. However, some data suggest that, in general, ATs generated during substrate ablation may have a role in subsequent arrhythmia recurrence and their elimination has a positive impact on arrhythmia-free survival[29].

Long-term Outcomes

Survival free of AF/AT was 58% at 12-months and, despite higher rates of AF termination when ibutilide was used, the long-term outcomes were not significantly different in the 2 groups. However, this study was not powered or designed to detect a difference, merely examine the effect on a cohort with very long-standing AF. Regarding the mode of recurrence, patients in the control group tended to recur more often as macroreentrant rhythms (AT or flutter) than ibutilide patients in proportion. This did not reach statistical significance, but the tendency might reflect less proarrhythmic effect via reduction in ablation burden delivered in the ibutilide group.

Finally, when both groups were considered together, failure to terminate AF was a predictor of arrhythmia recurrence. This is compatible with a study by Scherr et al., which showed that termination of persistent AF by ablation was the strongest predictor of freedom of recurrence during follow-up[28].

Study Limitations

Several limitations can be noted. First, there was no randomization and the comparison group consisted of a similar number of patients ablated without the use of ibutilide as an initial step. However, the primary operators did not change and both groups were consecutive and well balanced in term of clinical characteristics. The sample size was small and the study is underpowered to detect differences in long-term clinical endpoints. Finally, non-PV triggers were not pursued and adenosine not used routinely as the role of these agents in this group of very long lasting AF is unclear, with most studies in paroxysmal patients. The RA was not routinely mapped and guided by the mCL at the appendage. In the absence of more sophisticated tools, ablation of CFAEs in the RA adds little or no benefit versus cardioversion[30]. Finally, several technological advancements have occurred in the time since this study was performed, including improved stability of electroanatomic mapping systems and the availability of force sensing catheters (unavailable at the time of this study). It is possible that the addition of these may have altered the results, however the role of contact force remains debated[31].

Conclusions

In patients with very long-standing persistent AF, stepwise catheter ablation results in good success rates. Ibutilide administration as part of a stepwise approach results in higher rates of termination to SR, more often through an intermediate AT. Procedure and RF times are significantly decreased with a trend toward better long-term outcomes.

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Long Term Risk of Recurrent Atrial Fibrillation and Ischemic Stroke After Post-Operative Atrial Fibrillation Complicating Cardiac and Non-Cardiac Surgeries

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Abstract

Background: New onset post-operative atrial fibrillation (POAF) can complicate both non-cardiac(NCS) and cardiac(CS) surgeries. Long term differences in recurrence of atrial fibrillation (AF) and incidence of ischemic stroke/transient ischemic attack(CVA)between these types of POAFare lacking.

Objective: To compare thelong term recurrence rate of AF and incidence of CVAin patients withnew onset POAF after CS and NCS.

Methods: All patients who developed POAF between May 2010 and April 2014 were included in this single-center, retrospective study Exclusion criteria included a prior history of atrial tachyarrhythmias and pre-operative use of anti-arrhythmic drugs. Recurrence of atrial fibrillation and CVA was identified by review of medical records,electrocardiogram and Holter monitor.

Results: patients identified by the ICD9 code=523, 112 patients (61 cardiac; 51 non-cardiac) met inclusion criteria. Mean follow up was 943 days (range 32-2052 days).AF recurrence rate within 30 days after hospital discharge was higher in CS compared with NCS(10% vs 0%, p =0.03). Kaplan Meier analysis showed a trend towards higher recurrence in NCS compared with CS(HR 2.8; 95% CI 0.78-10.6, log rank p =0.03). In long term follow-up, CVA was numerically more common in patients with POAF after CS compared with NCS(10% vs 2%) though this difference was non-significant(HR 3.1 ; 95% CI 0.72-13.3; log rank p =0.26).

Conclusions: The risk of recurrent AF and ischemic stroke is not different between POAF after CS or NCS. The overall high rate of AF recurrence and risk of ischemic stroke mandate careful long term follow-up.

Introduction

Post-operative atrial fibrillation (POAF) is often precipitated by adrenergic stimulation and local or systemic inflammation affecting a susceptible atrium in the peri-operative period. It affects approximately 30–60% of patients undergoing cardiac surgery(CS) and 5-10% undergoing non-cardiac surgery(NCS)[1,2]. POAF is associated with increased intensive careunit and hospital length of stay, morbidity, mortality, hospital readmission, and long-term risk of stroke[3-6]. Estimates of the average annual cost of treatment of POAF and its sequelae approach $1 billion in the United States alone[7-9]. While POAF after CS has been relatively well studied, the long term implications of POAF after NCS are less well understood. The long term risk of recurrent AF may be as high as 20-48% after CS while the long term risk of recurrence after NCS is unknown[10-14].

Key Words

Post-Operative Atrial Fibrillation, Stroke, Cardiac Surgery, Non Cardiac Surgery, Recurrent Atrial Fibrillation

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Prior studies relied on administrative databases and were limited in the length of follow-up. Since about 50 million NCS are performed each year in the United States alone[13], knowledge of long term implications of POAF after NCS is essential. In addition, differences in long term risk of POAF and cerebro vascular accidents between CS and NCS are unknown.

Methods

A single-center, retrospective study was designed to include all patients (above 18 years of age) with POAF (confirmed by ECG or telemetry) between May 2010 to April 2014. Exclusion criteria included (1) Patients with a prior history of AF or atrial flutter, (2) use of anti-arrhythmic drugs pre-operatively (since the long half life of amiodarone complicates assessment of recurrent AF) (3) lack of confirmed AF post-operatively. Patients were identified using discharge ICD-9 code “427.31” (atrial fibrillation) among all patients who underwent a surgical procedure during this time period. Demographic data, patient characteristics and procedure information were recorded at the time of the indexed surgery/event from review of the electronic medical record. Primary endpoints of the study were recurrence of AF and ischemic stroke or transient ischemic

attack (CVA). Recurrence of AF was identified by chart review and confirmed by ECG, Holter monitor or device interrogation (when available). Ischemic stroke was defined bythe presence of neurological symptoms and supported by radiographic diagnosis (MRI or CT scan) while transient ischemic attack (TIA) was defined by symptoms which resolved spontaneously within 24 hrs with no radiologic evidence of stroke.

Follow-up ended on 1/1/2016 and duration of follow up was defined as the time between 30 days of hospital discharge (to distinguish between early and late recurrence) to either the last recorded clinical encounter or till a study endpoint was met. Local practice pattern for management of POAF during the study period was as follows: patients with a clearly defined onset of POAF received an attempt at rhythm control with a combination of intravenous and oral amiodarone (total loading dose of 2.5gms in 24 hrs) for a day followed by oral amiodarone (400mg a day) for atleast a month. If patients achieved sinus rhythm within 24-48 hrs. of onset, anticoagulation was not started (unless patient had another indication such as prosthetic valve). At discharge, 30 day follow-up was scheduled in the cardiac electrophysiology clinic where the drug was stopped if ECG documented sinus rhythm. A Holter monitor was repeated at 6 months to rule out asymptomatic recurrences. Patients who received rate control strategy were followed up either in the cardiac electrophysiology clinic or primary care physician's office. The study was approved by the institutional review board.

Statistical analysis

Student t tests were used to compare continuous variables while Chi-square test was used for comparing categorical variables. Mann Whitney U test was used to compare medians. Differences in event rates (long term risk of recurrent AF and ischemic stroke) between CS and NCS were estimated using Kaplan-Meier analysis and log rank tests. All statistical analyses were performed with MedCalc (version 14, Ostend, Belgium). Statistical significance was defined by a 2-tailed $p < 0.05$. All authors had full access to the data and assume responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

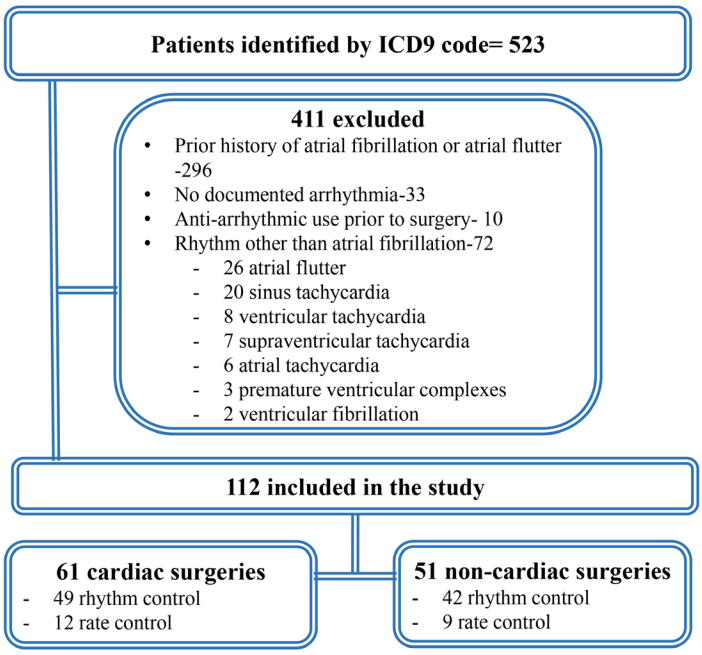

Figure 1: Depicting search strategy to identify patients with post-operative atrial fibrillation

Table 1: Clinical characteristics of patients in the cohort. POAF = post-operative atrial fibrillation; COPD= chronic obstructive pulmonary disease; ACEI- angiotensin converting enzyme inhibitor; CCB= calcium channel blocker.

	Total(n=112)	Cardiac POAF(n=61)	Non-Cardiac POAF(n=51)	P value
Age(years)	65.9± 7.7	65.8± 8.2	66±7.1	0.690
Female, n (%)	24 (21%)	3 (5%)	21 (41%)	0.001
Hypertension, n (%)	83 (74%)	52 (85%)	31 (61%)	0.003
Diabetes Mellitus, n (%)	35 (31%)	25 (41%)	10 (20%)	0.015
Dyslipidemia, n (%)	68 (61%)	50 (82%)	18 (35%)	0.001
COPD, n (%)	23 (21%)	11 (18%)	12 (24%)	0.433
Smoking, n (%)	54 (48%)	29 (48%)	25 (49%)	0.971
Congestive Heart Failure, n (%)	18 (16%)	10 (16%)	8 (16%)	0.955
Coronary Artery Disease, n (%)	65 (58%)	54 (89%)	11 (22 %)	0.001
Vascular disease history, n (%)	21 (19%)	16 (26%)	5 (10%)	0.024
History of Ischemic Stroke, n (%)	9 (8%)	5 (8%)	4 (8%)	0.949
Medications Prior to Surgery				
Statins, n (%)	66 (59%)	50 (82%)	16 (31%)	0.001
Beta-Blockers, n (%)	56 (50%)	40 (66%)	16 (31%)	0.003
ACEI, n (%)	46 (41%)	32 (52%)	14 (27%)	0.031
CCB, n (%)	32 (29%)	20 (33%)	12 (24%)	0.532
Electrical Cardioversion, n (%)	5 (4%)	4 (7%)	1 (2%)	0.374
Ibutilide, n (%)	8 (7%)	6 (9.8%)	2 (3.9%)	0.287
Medications at discharge(n=108)				
Aspirin, n (%)	78 (72%)	56 (92%)	22 (46%)	0.001
Anticoagulants, n (%)	13 (12%)	8 (13%)	5 (10%)	0.643
Beta blockers, n (%)	83 (79%)	54 (90%)	29(59%)	0.001
CCB, n (%)	27 (25%)	13 (23%)	14 (27%)	0.398
ACEI, n (%)	52 (47%)	38 (64%)	14 (27%)	0.001
Digoxin, n (%)	6 (6%)	4 (7%)	2 (4%)	0.691
Amiodarone, n (%)	81 (72%)	45 (74%)	36 (71%)	1.0
Rhythm control strategy, n (%)	91 (81%)	49 (80%)	42 (82%)	0.785
Median CHA2DS2-VASc(interquartile range)	3(2-4)	3(2-4)	2.5(2-4)	0.75
Length of stay(days, mean SD)	11.6±7.9	10.1±5.9	13.6± 9.5	0.007

Results and outcomes

[Figure 1] delineates the search strategy. Patients identified by ICD9 code= 523, 59.6% had a prior history of AF while 13.8% had other arrhythmias that were wrongly coded and had no evidence of AF. The final cohort consisted of 112 patients ; 61 patients with POAF after CS and 51 after NCS. [Table 1] describes characteristics of the cohort. Patients who had POAF after CS had a significantly higher incidence of diabetes, hypertension and coronary artery disease. In the CS group, 27% underwent valve surgery while the rest were coronary artery bypass surgeries. The NCS group was comprised mostly of thoracic (39%) and abdominal surgeries(37%).

POAF occurred aroundthe 2nd to 3rd post-operative day (mean post-operative day of occurrence 2.4 days CS vs. 2.6 days NCS ;p=0.29). Rhythm control (using a combination of intravenous and oral amiodarone) was the treatment strategy in 81% of the entire cohort (80% CS vs. 82% NCS, p= NS). Ibutilide and electrical cardioversion were used to achieve sinus rhythm in 47% and 4% of patients respectively. Length of hospital stay was significantly longer in NCS compared with CS (13.6 ± 9.5 vs. 10.1±5.9 days ; p=0.007). In hospital mortality was 3.5% (5.8% NCS vs 1.6% CS, p =0.32). [Table 2] At hospital discharge, all patients were in sinus rhythm. A majority of patients were discharged on a single antiplatelet agent (43% of the entire cohort-37% aspirin alone, 6% clopidogrel alone), 22% on aspirin and clopidogrel, 2% on warfarin alone, and 9% on combined warfarin and aspirin (all after valve surgery).

At 30 day follow-up, AF recurrence was more common in CS group (10% vs 0%, p=0.03) and was no different in those treated with rate or rhythm control strategy (8.3% vs 10%; p = 0.9). [Table 2] Amongthose treated with rhythm control, mean duration of amiodarone therapy was 2.3 months (1.87 ±1.5 in CS VS 2.88± 2.89 in NCS, p= 0.004).

A Mean follow up duration was 943 days (range 32-2052 days). Median time to AF recurrence was 724 days (IQR 229-1157 days). AF recurred in 11 patients(12.5%; CS 9.4% vs NCS 17.1%). These patients were started on anticoagulation and there was no strokes within the study period. By Kaplan Meier analysis, there was a trend to significantly higher recurrence of AF after NCS compared with CS [Figure 2], HR 2.8; 95% CI 0.78-10.6, p =0.03) though the 95% confidence intervals crossedunity. Nine CVAs (including three TIAs) occurred during the follow-up periodat a median time of 901 days (IQR681-1093). Survival analysis by Kaplan Meier method showed no significant difference between CS and NCS (HR 3.1; 95% CI 0.72-13.3; p =0.26, [Figure 3]).Two patients were in atrial fibrillation

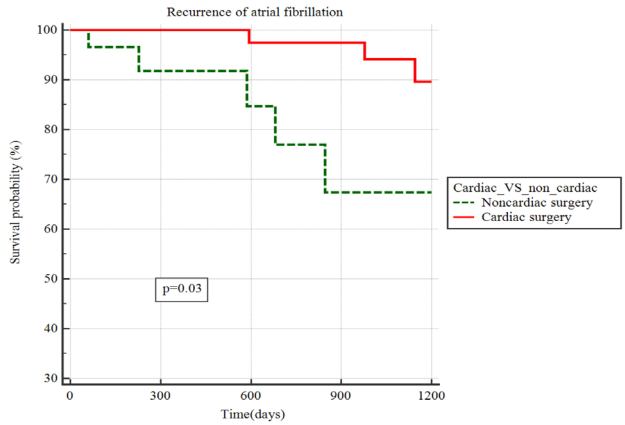

Figure 2: Kaplan Meier analysis of difference in survival probability free of recurrent AF between POAF after cardiac and non-cardiac surgeries.

at the time of the stroke (1 each in CS and NCS). Since paroxysmal AF can remain undetected at the time of the stroke, we reviewed data on all patients with CVA to the last available clinical date (after the end of the study-designated follow-up period) and found that 2 additional patients (both CS) were diagnosed with AF in clinical follow-up.

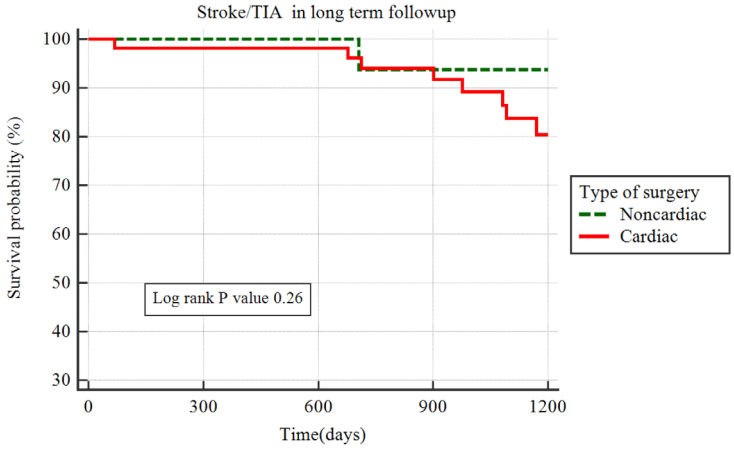

Figure 3: Kaplan Meier analysis of difference in survival probability free of ischemic stroke/TIA between POAF after cardiac and non-cardiac surgeries.TIA= Transient Ischemic Attack.

Table 2: Difference in early outcomes in patients with POAF treated with rate or rhythm control after cardiac and non-cardiac surgeries. POAF= Post-operative Atrial Fibrillation

	Cardiac POAF			Non-Cardiac POAF		
	Total(n=61)	Rhythm(n=49)	Rate(n=12)	Total(n=51)	Rhythm(n=42	Rate(n=9
In hospital mortality	1(1.6%)	1/49(2%)	0/12(0%)	3 /51(5.8%)	3/42(7.1%)	0/9(0%)
Sinus rhythm at discharge	60/60(100%)	48/48	12/12	48/48(100%)	39/39	9/9
30 day mortality	0/60(0%)	0 /48	0/48(0%)	0 /39	16.2±0.3	0/9
Readmission in 30 days	10/60(16.7%)	8/48(16.7%)	2/12(16.7%)	4/48(8.3%)	4/39(10.3%)*	0/9(0%)
Sinus rhythm at 30 days	54/60(90%)	43/48(89.6%)	11/12(91.7%)	48/48(100%)	39/39	9/9

*The only statistically significant different outcome was increased risk of readmission in rhythm control compared with rate control in POAF after non-cardiac surgery (p=0.001)

Discussion

In this study, we found a 15% AF recurrence rate in patients who develop POAF (with no prior history of AF) after both CS and NCS. Early recurrence (within 30 days of hospital discharge) was common after CS. Interestingly, among patients who were in sinus rhythm at 30 day follow-up, AF recurrence was numerically higher in NCS group though the confidence intervals crossed unity. This likely reflects larger arrhythmic substrate as well as local atrial injury in patients undergoing CS which predisposes them to early recurrence. On the other hand, POAF after NCS may reflect systemic factors at the time of surgery(and thus a lower short term recurrence rate between discharge and 30 day follow-up). The risk of CVA was not statistically different. Among patients with stroke, 22% were in atrial fibrillation at the time of the stroke and another 22% were diagnosed with AF in follow-up after the CVA. Overall, three years after POAF, 1 in 6 patients developed recurrent AF and 1 in 10 suffered a CVA. Thus, POAF should not be considered a benign post-operative complication and is an important predictor for recurrent AF and related complications.

Though the effect of POAF on immediate post-operative outcomes has been previously studied, its effect on long term outcomes remains largely unknown. Most POAF converts to sinus rhythm with or without treatment and approximately 80% are in sinus rhythm at discharge[3,8-10]. Long term follow-up of patients with POAF after CS suggests a 20-48% risk of recurrence(depending upon the duration of follow-up)[10-12]. In a single center study of 305 patients after CABG,POAF occurred in 88 (28.9%) patients[10]. Post-discharge symptomatic AF occurred in 25 (8.2%) patients with an annual incidence of 2% during a mean follow-up of 48 + 30 months and recurrence was more common in those with POAF compared with those without POAF (20.4% vs 3.2%, p<0.0003)[10]. Similarly in another single center experience, recurrent AF after POAF was 18.9% after a mean follow-up duration of 41+ 23 months[11]. In a community based study from Olmsted County with the longest available follow-up (8.3+ 2.3 years), the rate of AF was as high as 42.6%[13]. In all these studies, POAF was a significant predictor of future AF. The recurrence rate of AF likely depends on the follow-up strategy employed. Many clinicians follow patients clinically and with periodic electrocardiograms and Holter monitoring as was performed in the current study. An intriguing approach would be the implantation of loop recorders for long term follow-up. In a recent nonrandomized study using this approach, the recurrence rate after CS was as high as 61%[15].

To our knowledge, there are no long term follow-up studies after POAF complicating NCS with the longest available follow-up of 1 year(in an administrative database)[14]. Data on the risk of long term ischemic stroke after POAF is even more limited. In the study by Gialdini et al, 1 year incidence of CVA was 1.47% in patientswith POAF after NCS compared to 0.36% in patients who did not develop POAF[14]. POAF was associated with subsequent stroke both after CS (hazard ratio, 1.3; 95% CI, 1.1-1.6) and NCS (hazard ratio, 2.0; 95% CI, 1.7-2.3) and interestingly, the association was stronger for POAF after NCS (P < .001 for interaction). Despite the large number of patients studied, the lack of detailed medical history and relatively short term duration of follow-up were limiting factors to this analysis.

The current study provides the most comprehensive data (albeit in a small sample) on the risk of recurrent AF and incidence of ischemic stroke in long term follow-up after NCS. In contrast to the study by Gialdini et al. we found no significant difference in risk of stroke after CS and NCS. Mean CHA2DS2-VASc scores were similar in these groups at baseline and in more than half the cases, CVA occurred in the absence of recurrent AF. This suggests that in addition to AF, other vascular risk factors may play a role in causing ischemic stroke in long term follow-up.

Despite the small size of the cohort, this study has several strengths. This is the first study to provide long term follow-up of patients who achieved sinus rhythm after POAF complicating NCS. We systematically eliminated all patients who had a history of AF or were on anti-arrhythmic therapy prior to surgery. The search strategy employed, excluded close to 14% of patients who were miscoded as AF. This emphasizes the limitation of using large administrative databases in studying POAF where individual medical records and ECG recordings are unavailable for review. The current study also provides insight into the optimal management of POAF. Similar to a recent large randomized study in patients after CS[16], there was no significant difference in early recurrence between those treated with rhythm control vs rate control after NCS.

There are several limitations of the study. The management and anticoagulation strategy in thissmall cohort reflects practice patterns in a single center. The small number of patients and the large number of baseline differences between patients undergoing CS and NCS precluded propensity matching. Follow-up was limited to those who survived index hospitalization; was based on chart and ECG review and there was no continuous rhythm monitoring. The event rate may be higher than found in this study since small, clinically silent strokes and a symptomatic paroxysmal AF may have remained undiagnosed during the study period. The absence of a control group without POAF prevents the assessment of the relative risk of developing recurrent AF and CVA.

Conflict of Interests

None.

Conclusions

Despite achieving sinus rhythm, there is a significant risk of long term recurrence of AF and CVA among patients with new onset POAF. The risk of recurrent AF is similar between CS and NCS. These preliminary results should be verified prospectively in a larger, multi-center cohort. In addition, the optimal anticoagulation strategy at hospital discharge and clinical follow-up in this population remain to be determined.

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A Review of the Anatomical and Histological Attributes of the Left Atrial Appendage with Descriptive Pathological Examination of Morphology and Histology

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Abstract

The left atrial appendage (LAA) has a key role in the embolic complications of atrial fibrillation (AF). It has been studied extensively, from recent interest in the thrombotic implications of various LAA morphologies to LAA occlusion and ablation. We collected eleven post-mortem LAA samples for visual analysis, two were not included due to poor sample quality. On examination of the nine remaining samples, several common patterns of pectinate muscle orientation were noted. The LAA samples were noted to have a smooth circumferential neck of muscular tissue giving rise to a dominant singular smooth trunk of papillary muscle in 6 cases and two trunks in 3 cases. These trunks were either shallow (5 samples) or more muscular and raised (4 samples). Shallow trunks tended to be wider than the raised trunks and may even be circumferential (2 samples). The main trunk arborized to give off papillary muscle branches down to third or fourth order branches. The samples were visually assessed for the percentage of smooth papillary muscle versus non-papillary recesses and were found to have ≤50% smooth muscle in 3 samples, 50-75% in 3 samples and >75% in 3 samples. We performed histological analysis of further LAA samples collected during cardiac surgery in a parallel study. We identified a distinct pattern of myocyte orientation from the neck, mid-section and apical section of the LAA demonstrating arborization of myocyte fibers with minimal communication in distal segments of the LAA. We feel that this information may help understanding of the issues surrounding LAA ablation strategies.

Introduction

The left atrial appendage (LAA) has a key role in the formation of thrombus and subsequent embolic complications in atrial fibrillation (AF) and flutter and has been shown to be involved in >90% of transient ischemic attacks (TIA) or strokes related to AF[(1)]. For a small anatomical structure, it has been studied extensively from the recent interest in the various morphologies of the LAA and their relative risk of thrombosis to LAA closure devices and the success of ablation procedures incorporating LAA isolation. In this paper we aim to review atrial anatomy relevant to the electrophysiologist, review the role of the LAA in AF initiation and propagation and we also provide a description of the macro and microscopic properties of the LAA based on post-mortem studies.

Embryology and anatomy of the left atrium

Embryologically the heart begins development by the formation of two tubes into a single tube in an inverted Y structure. Through folding of this structure, the two arms of the Y ultimately form the right and left atria. The left and right atrial appendages form from the respective left and right supero-lateral walls of the primary atrium. The folded structure is then separated into the four chambers along with the pulmonary artery and aorta by the formation of the endocardial cushion, intra-atrial septum, intra-ventricular septum and the aortic-pulmonary septum. When formed, the LAA is smaller and narrower than the extensive right-sided appendage. The LAA forms trabeculae due to cellular protrusion into the lumen. The development of the four pulmonary veins is a late process[(2,3)].

The fully formed left atrium is composed of the postero-superior venous component, the vestibule forming the mitral valve orifice, the LAA and the body of the atrium. The LAA is separated from the left pulmonary veins venous component by the left lateral ridge. This is an infolding of the lateral atrial wall protruding into the LA endocardium[(4)]. The LAA lies anteriorly in the atrioventricular sulcus in close proximity to the left circumflex artery and the left phrenic nerve.

The LAA itself is divided into the os, the neck and the body; all of which can be variable in morphology. The body of the LAA is divided into a number of lobes which is again variable. The internal surface of the LAA is composed of raised pectinate muscles which results in an uneven surface – in direct contrast to the relatively smooth walls of the rest of the left atrium. This irregular surface with deep recesses likely increases its thrombogenicity.

There has been recent interest in the variable morphologies of the LAA. Veinot et al. examined LAA's from 500 normal autopsy hearts

Key Words

Left Atrial Appendage (LAA), Chicken Wing, Windsock, Cauliflower

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and found that 80% of specimens had more than one lobe (54% two lobes, 23% 3 lobes, 3% 4 lobes). They also found that 97% had pectinate muscles ≥1mm in size. Both of these are important considerations when examining the LAA with transesophageal echocardiography to rule out thrombus[5]. Di Biase et al used computed tomography (CT) and magnetic resonance imaging (MRI) to characterize the LAA morphology of 932 patients undergoing catheter ablation for AF and correlate this with a history of prior transient ischemic attack (TIA) or stroke. They identified four discrete morphologies – 'chicken wing' (48%), 'cactus' (30%), 'windsock' (19%) and 'cauliflower' (3%). Chicken wing morphology was found to have the least likelihood of previous TIA/stroke. In a multivariate model, cactus was 4.08 times, windsock 4.5 times and cauliflower 8.0 times more likely to have been associated with TIA/Stroke than a chicken wing morphology[6].

The LAA is composed of both endocardial and epicardial components with variable myocyte orientation. The junction between the LA and LAA has a complex fiber orientation and may support anatomical reentry or anchor functional rotors[7]. LAA myocytes are more similar to ventricular myocytes than atrial myocytes in structure. There is variability in thickness between muscle bundles. Bachmann's bundle runs in a sub-epicardial layer allowing conduction from the right atrial appendage through the inter-atrial septum and encircles the neck of the LAA. Histological changes in those with chronic AF have been noted with expansion of LAA size, loss of pectinate muscle volume and thickening and fibrotic change of the endocardium. Amyloid deposition has also been noted in chronic AF[3].

LAA Ablation

There are several mechanisms proposed for the development and propagation of AF and it is unclear whether it is dependent on automatic focal or reentrant mechanisms. What is clear, however, is that the pulmonary veins are crucial sites of AF triggering and they have become the main target for AF ablation. Pulmonary vein isolation (PVI) has become a mainstream therapy for AF with guidelines supporting its use earlier in the disease process[8]. Current outcomes, however, are not ideal with multiple procedures often required and 5 year freedom from AF being reported as ≈80% in paroxysmal AF and ≈45% in permanent AF[9-12].

Other myocardial sites have also been targeted for additional ablation such as the superior vena cava, ligament of Marshall, posterior left atrial wall, coronary sinus, crista terminalis and the LAA itself. Di Biase et al. have shown that the LAA has been found to be a site of recurrent AF after PVI in 27% of patients with excellent results from subsequent complete isolation of the LAA[13]. Empiric ablation of the LAA along with standard ablation in patients with permanent AF has been investigated in the BELIEF study. Early results have shown improved outcomes with 56% of patients with LAA isolation along with standard ablation being AF free after 12 months as compared to 28% of patients with standard ablation alone.[14]

Materials and Methods

We collected LAA samples from consecutive post-mortems being carried out in a tertiary referral centre with cooperation from the pathology department. Ethical approval was granted in advance of the study by the local ethics committee and written consent was obtained from next-of-kin. All available postmortem subjects were included. LAA's were removed from the heart in a circumferential fashion by the pathologist performing the post-mortem. Once LAA samples were collected, they were subsequently opened up through a longitudinal dissection to reveal the inner surface with particular attention paid to the pectinate muscle orientation. The samples were then examined, photographed and disposed of. Some histological samples were taken for other projects with ethical approval and consent.

Results

Eleven samples were collected for visual analysis, two were not included in this paper due to poor sample quality. On examination of the nine remaining samples, several common patterns of pectinate muscle orientation were noted. The LAA samples were noted to have a smooth circumferential neck of muscular tissue. This gave rise to a dominant singular smooth trunk of papillary muscle in 6 cases and two trunks in 3 cases. These trunks were either shallow (5 samples) or more muscular and raised (4 samples). Shallow trunks tended to be wider than the raised trunks and may even be circumferential (2 samples)(Table 1).

Table 1: Basic Demographics and LAA Morphology

Patient	Sex	Age	History AF	No. muscular trunks	Shallow/raised trunks	% Smooth Muscle
1	Female	83	Yes	1	Shallow	<75%
2	Male	70	Yes	2	Shallow	<75%
3	Male	56	No	2	Raised	≤50%
4	Female	90	Yes	2	Raised	≤50%
5	Male	75	No	1	Shallow	50-75%
6	Female	71	No	1	Raised	≤50%
7	Male	63	No	1	Raised	50-75%
8	Male	66	Yes	1	Shallow	50-75%
9	Male	59	No	1	Shallow	<75%

The main trunk arborized to give off papillary muscle branches down

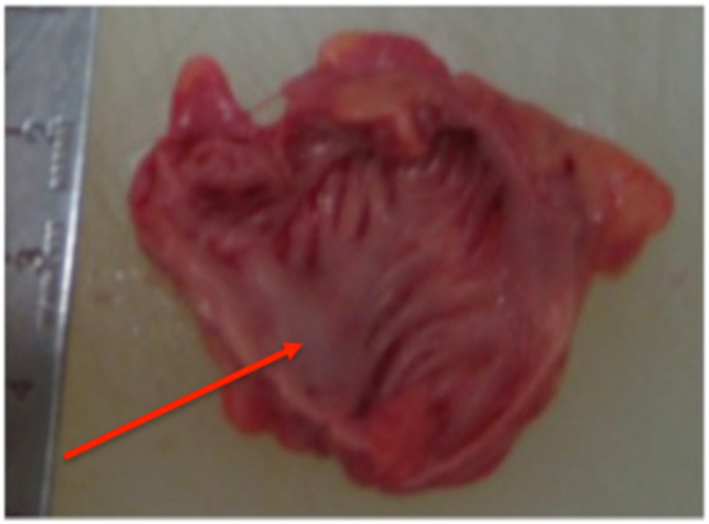


Figure 1: Sample with single shallow trunk (red arrow), ≤50% smooth papillary muscle

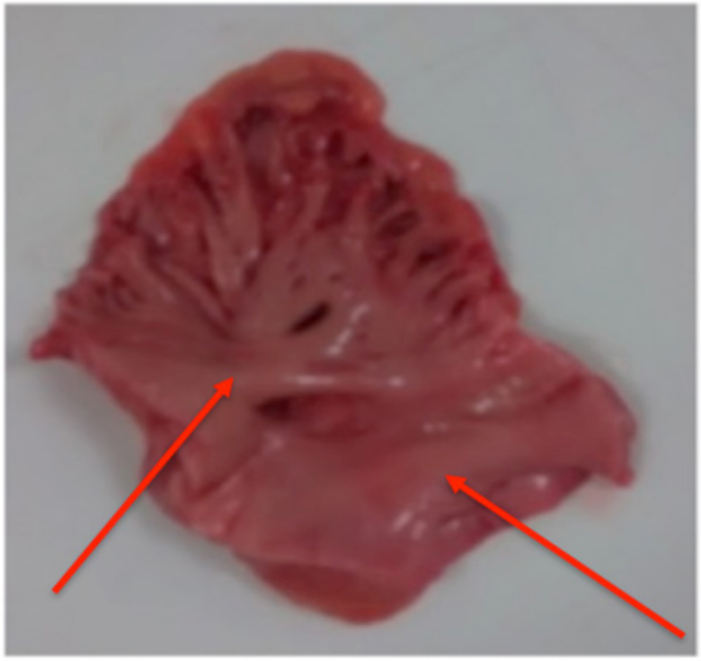


Figure 2: Sample with two raised trunks (red arrows) dividing early into second order branches, ≤50% smooth papillary muscle

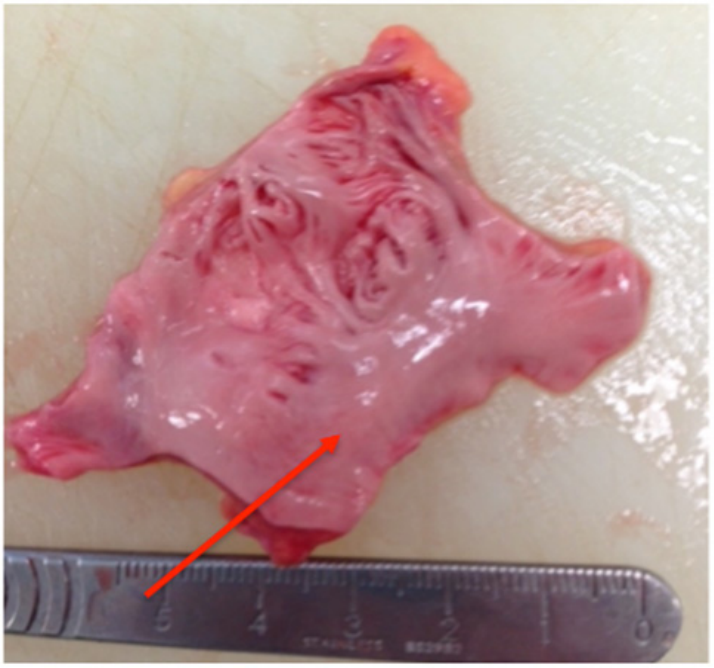


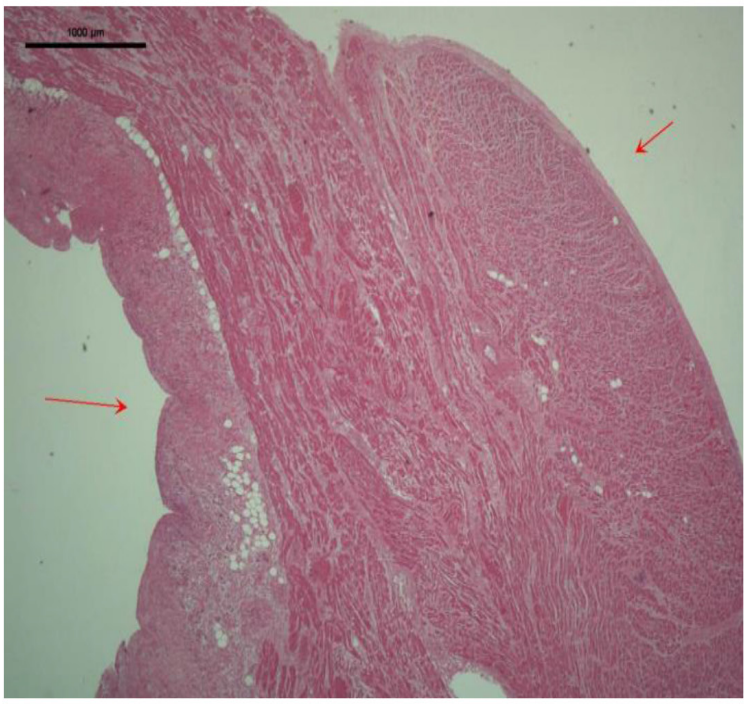
Figure 3: Sample with single smooth trunk (red arrow), >75% smooth papillary muscle

to third order or in some cases to fourth order branches. The samples were visually assessed for the percentage of smooth papillary muscle versus non-papillary recesses and were found to have ≤50% smooth muscle in 3 samples, 50-75% in 3 samples and >75% in 3 samples.

We performed histological analysis of further LAA samples from a parallel study gathered during surgical LAA excision. Using these samples we identified a pattern of myocyte orientation of the neck, mid-section and apical section of the LAA. In the images, the epithelial surface can be identified by the presence of adipose tissue. We found that the neck or proximal portion of the LAA had dense circumferential orientation of the myocytes.

In the mid-section of the LAA, arborization of the papillary muscles can be appreciated with fibrous separation between myocyte bundles.

Finally, in the apical segment of the LAA, myocytes can be seen reaching the epithelial surface in discrete bundles with very little communication between each bundle, often limited to one or two



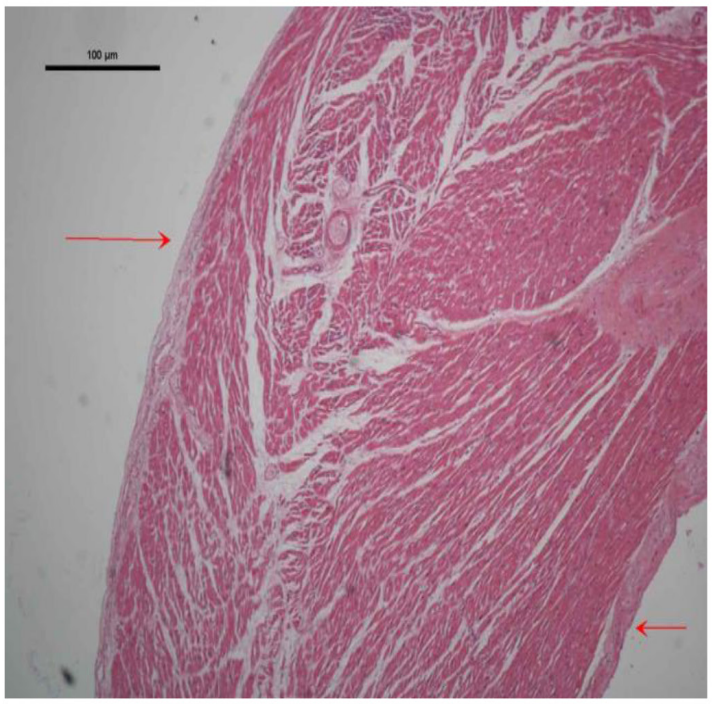


Figure 4/5: Histological samples from the base of the LAA with arrows indicating endothelium and epithelium

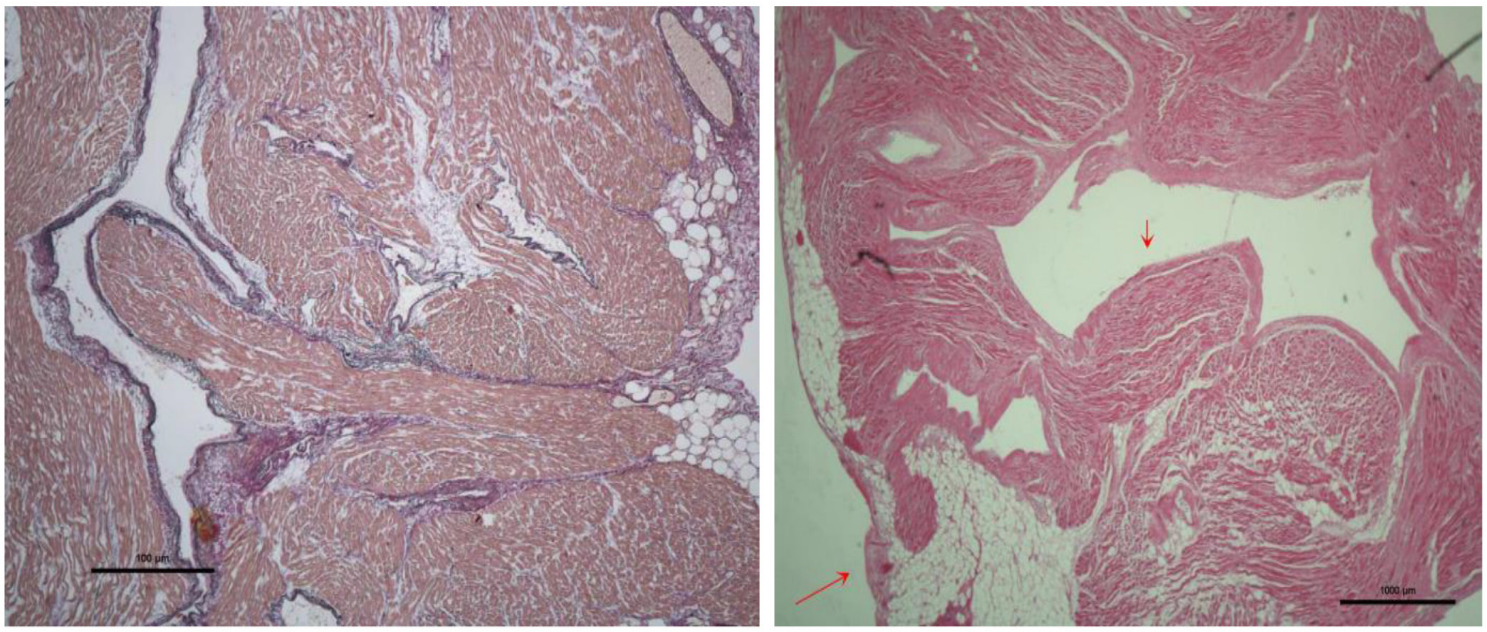


Figure 6/7: Histological samples from the mid-section of the LAA with arrows indicating endothelium and epithelium

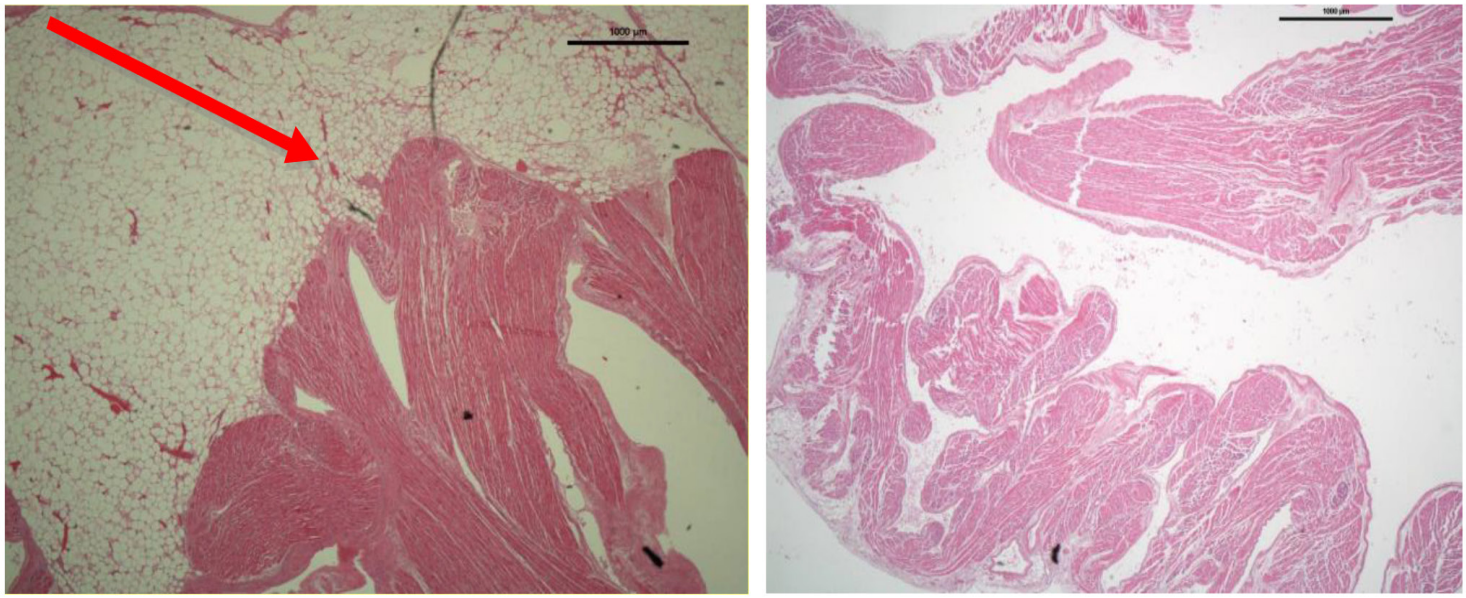


Figure 8/9: Histological sample of LAA apex showing myocyte bundles reaching the epithelial surface with minimal communication between bundles (red arrow)

individual myocytes.

Discussion

We have identified via the examination of a small number of left atrial appendages a common pattern of macroscopic papillary muscle orientation; namely a circumferential smooth ostium with the emergence of one or two papillary muscle trunks. Histological analysis of separate LAA samples have shown arborization of myocyte fibers with minimal communication in distal segments of the LAA. Perhaps the presence of prominent or multiple muscle trunks could result in difficulty in full isolation of the appendage during LAA ablation. These muscular bundles may also serve as a source of triggered arrhythmias. We believe, although our study is limited by small sample size, further study in this area is warranted and that this information could be used to investigate ablation strategies.

It is known that longer p wave durations are associated with increased risk of AF and a reduction post PVI are associated with improved outcomes[16, 17]. Kawamura et al. examined the resultant effects of left atrial ligation on atrial conduction. They found that LAA exclusion in 15 patients with paroxysmal and persistent AF by the LARIAT device, which results in LAA necrosis, results in a significant reduction in p wave duration and amplitude[18]. There were greater reductions in p wave duration and amplitude in those who remained free from AF than those who had recurrence. These p wave changes are consistent with decreased atrial mass and decreased atrial dispersion that may represent reverse electrical atrial remodeling. This may explain in part the positive results seen in LAA isolation.

Concerns regarding empiric ablation of the LAA include the loss of LAA contraction and hence increase thrombogenicity and stroke risk. Indeed LAA ablation has been shown to result in an increase in LAA thrombus formation[15]. Interestingly, although there was no increase in TIA/stroke, in the cohort of patients in the BELIEF trial who underwent LAA isolation, 52% had impaired LAA function[14].

It is note worthy that in some patients who have previously undergone LAA isolation by endocardial catheter ablation, reconduction to the LAA can occur with relative high LAA exit velocities on transesophageal echo. The use of concomitant LAA occlusion devices could be used as a strategy to overcome this issue. Another concern is the risk of perforation due to the thin walls of the structure. There has been found to be a 1.8% risk of cardiac tamponade with LAA ablation[13].

Further investigation as to the macroscopic variations within the LAA and their potential thrombogenicity may reveal pectinate muscular characteristics associated with increased thrombotic risk post ablation.

Conclusions

The left atrial appendage plays a key role in the stroke risk associated with AF, however, its role in the initiation and propagation of AF may be underestimated. We believe that left atrial appendage muscular bundle characteristics are worthy of further investigation as to their potential role in atrial fibrillation with potential implications for ablation strategies.

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High Density Mapping of Pre-Excitation 3D-Illustration of Anatomical Features

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Abstract

While ablation of accessory pathways is usually performed without 3D mapping system, we present a case where high-density mapping helps in illustrating the anatomical features of epicardial and oblique AP connections.

Introduction

Ablation of accessory pathways (AP) is currently performed with conventional mapping based on a well-accepted set of criteria, eliminating the need for 3D mapping systems in most cases, because of the excellent immediate and long-term results using these simple parameters in trained hands[1].

The Rhythmia system ™ (Boston Scientific, Inc.) is a useful mapping tool for achieving very detailed atrial or ventricular activation with high resolution[2]. High-density mapping may be especially helpful in revealing particular features of wave propagation. We report about a mapping case of an epicardial accessory pathway using the Rhythmia system ™, highlighting some specific features of how some accessory pathway may link atrium and ventricle.

Case Report

A 28 years-old man with a left posterior WPW and both antidromic and orthodromic reciprocating tachycardia was referred for ablation. A first procedure had been performed some weeks before, but pre-excitation recurred late after acute success of radio-frequency (RF) ablation into the proximal coronary sinus (CS).

After both retrograde aortic access and trans-septal puncture, electro-anatomical maps of the left atrium, CS and left ventricle were created using the Rhythmia system ™ with the Orion catheter, which is a mini-basket catheter made of eight splines with eight 0.4 mm2 electrodes each (64 electrodes, 2.5 mm spacing). Activation maps at the left atrium, CS and left ventricle were built during pacing at the distal CS. Timings of activation were manually reannotated against the same reference (pacing artifact) in each chamber for allowing vizualisation of complete atrio-ventricular propagation into a single map.

Analysis of propagation showed first a focal activation from the low lateral left atrium facing the distal CS where pacing was delivered, concentrically invading the whole left atrium from bottom to summit. Then, after a 100 ms delay, epicardial ventricular activation emerged as recorded into the external part of the postero-lateral CS, facing the site of earliest atrial activation. Then basal and more superior/medial left ventricular endocardium was depolarized 35 ms later (see Figure 1 to Figure 3). This was considered as a sign of an "epicardial" accessory pathway, connecting both left atrium and ventricle through muscular extensions of the CS coat [3]. There was no CS diverticulum or aneurism.

RF ablation (25 W irrigated) was performed into the CS - near the middle cardiac vein opening - at a site showing QS pattern in unipolar recording and with local depolarization preceding the delta wave by 25 msec, without visible AP potential (Figure 4). Criteria were not better at the endocardial aspect of the mitral annulus. RF application was successful, but multiple RF attempts were needed at this site because of delayed recovery of pre-excitation after 15 to 30 minutes observation in two instances, before anterograde and retrograde conduction over the AP could be finally definitively eliminated. The patient did not present with recurring tachycardia nor pre-excitation over a follow-up of 2 years.

Discussion

AP ablated into the CS are expected to link both left atrium and ventricle through fibers of the CS musculature connecting left atrial myocardium to remote left ventricular epicardium[3]. While direct electro-physiological proofs for this assumption are exceptional[4], this case may serve as an illustration of this hypothesis.

Key Words
Wolff-Parkinson-White, High-Density Mapping, Radio-Frequency Ablation, Accessory Pathway

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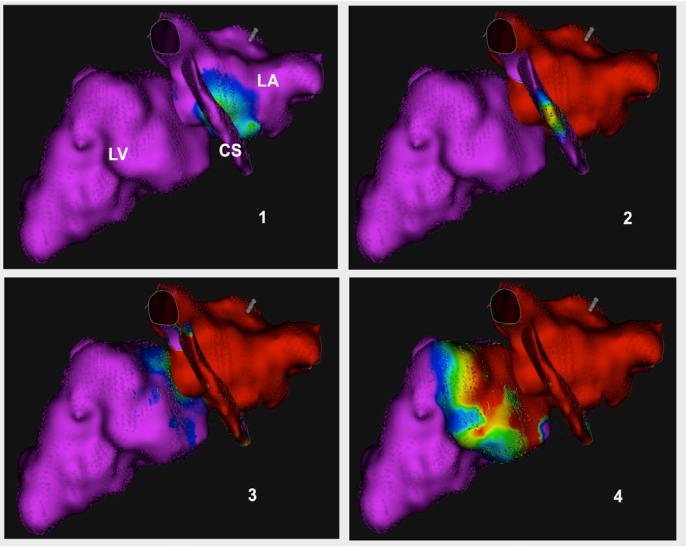

Figure 1: Left atrial, CS and left ventricular activation maps during distal CS pacing. Purple: non depolarized tissues. Green-Blue: onset of activation. Red: depolarized tissues. Activation proceeds from endocardial low lateral left atrium (1) to external CS (2) then to more medial basal endocardial left ventricle (3) before spreading to the whole cavity (4).

around 135 ms between onset of local atrial activation and earliest endocardial ventricular depolarization is more compatible with an AP not directly connecting both atrial and ventricular endocardium, where continuous potentials between A and V are usually seen[1] and where CS is delayed.

Although ablation of AP is better performed without 3D mapping system in most cases, because of easy, rapid, cost-effective and almost always successful procedures with acceptable low fluoroscopic exposure in trained hand[1], high-density mapping in this example helps in illustrating the anatomical features of AP connections.

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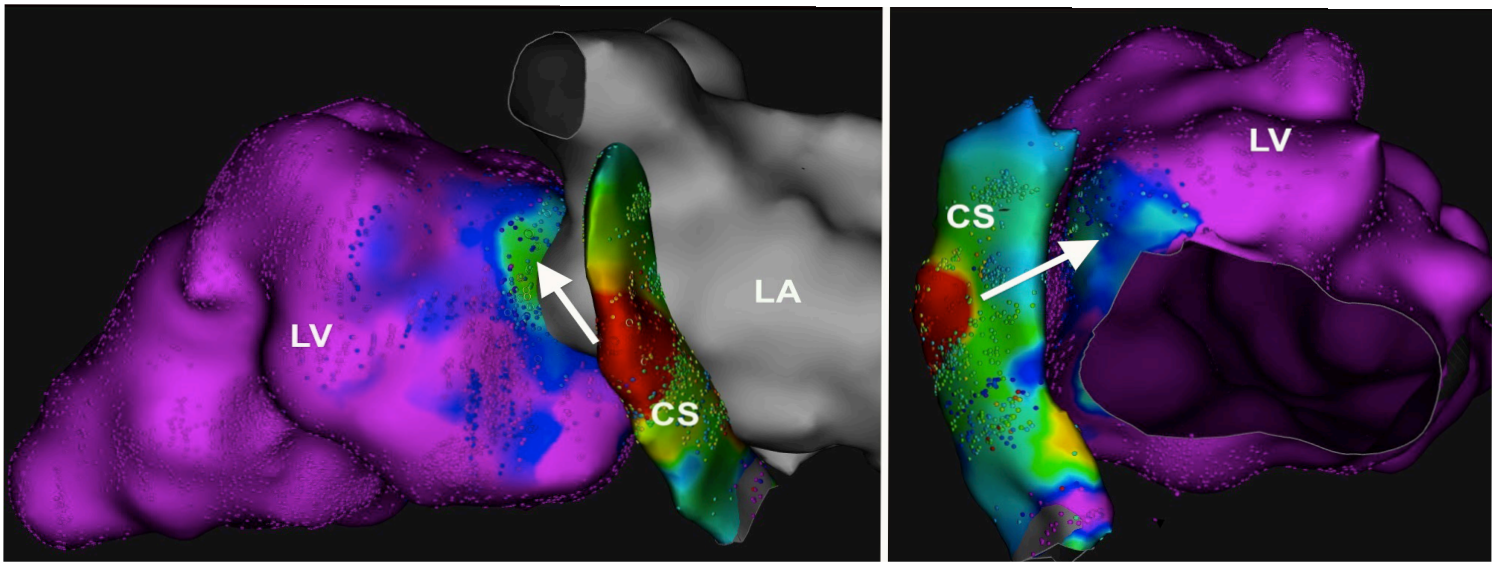

Figure 2: Additional views showing details of ventricular activation, with superior and medial earliest activation occurring after more lateral and inferior CS activation

The oblique direction of most AP have been demonstrated using electro-physiological techniques. Posterior left AP endocardially ablated at the AV groove usually have medial ventricular insertions and lateral atrial insertions[5]. Although location of atrial insertion was not determined here, "epicardial AP" through CS coat may also lead to lateral to medial pattern of activation[3].

The Rhythmia system ™ allows to well illustrate both paradigms in this case. The propagation demonstrated the oblique course of the left AP and its "epicardial" location, since activation of the external part of the CS – i.e. far-fields of the epicardial aspect of the left ventricle - was shown to follow atrial endocardial activation and to precede the ventricular endocardial one, with delays between both endocardial activations compatible with propagation along external structures. Although simple conduction disturbances into a trivial AP can not be ruled out, the lack of any detectable activation during

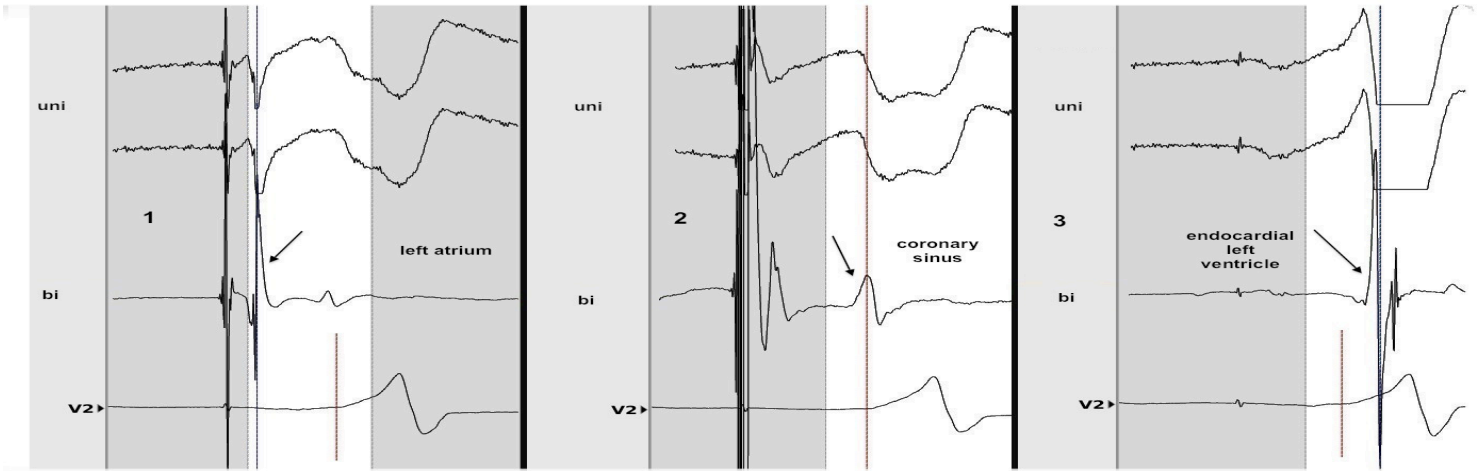

Figure 3: Intracardiac bipolar and unipolar recordings at the same sites as fig 1. Local activation is shown by arrows. Note the precession of ventricular activation at the CS compared to the endocardial ventricular recording, and the QS pattern at the CS in unipolar recording while there was an R wave at the endocardial left ventricle. Ventricular activation at the CS happens 35 ms before the ventricular endocardial one (see text). Vertical dashed line represents the timing of delta wave onset on surface ECG.

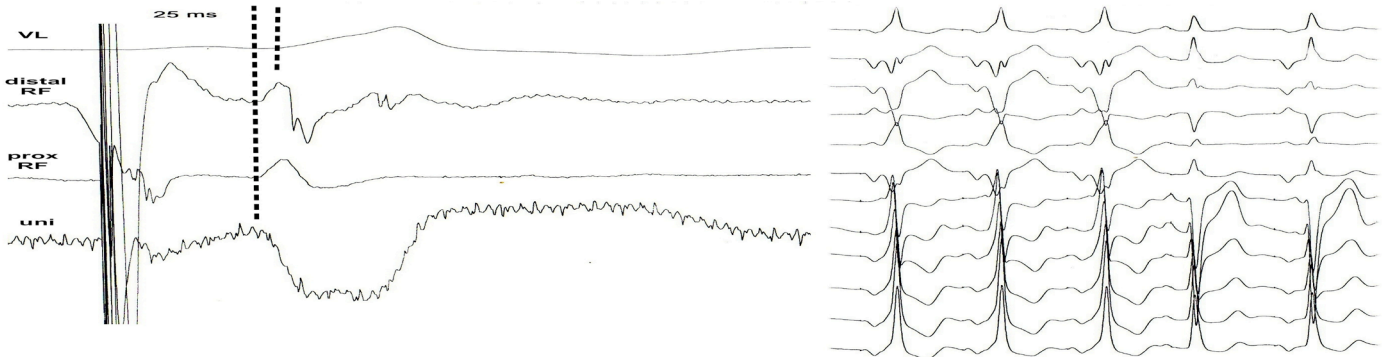

Figure 4: Bipolar and unipolar electrograms at the site of successful ablation (left) and disappearance of pre-excitation during RF (right). Local ventricular depolarization at the CS preceeded the onset of delta wave by 25 ms.

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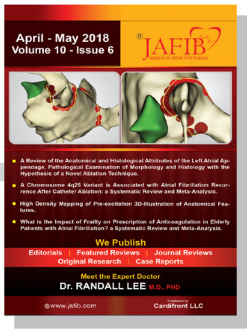

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What is the Impact of Frailty on Prescription of Anticoagulation in Elderly Patients with Atrial Fibrillation? A Systematic Review and Meta-Analysis

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Abstract

Background: Atrial fibrillation (AF) and frailty are both associated with advanced age. Oral anticoagulants (OAC) effectively prevent strokes in AF patients but are underutilized in the elderly, possibly due to misperception of frailty.

Objective: We performed a systematic review to determine the prevalence of frailty in patients with AF, and whether frailty was associated with reduced prescription of OAC.

Methods: We systematically searched Cochrane, MEDLINE, EMBASE, and PubMed databases. Search terms combined relevant words and MeSH headings: 1) atrial fibrillation, 2) frail elderly, and 3) geriatric assessments. Studies that measured frailty using a validated instrument, and involved OAC for AF in frail and non-frail patients were eligible for inclusion. Pooled odds ratios were calculated using random-effects model.

Results: Of 166 reviewed titles, only 3 studies (1204 patients) met the inclusion criteria. Two used the Reported Edmonton Frail Scale (total 509 patients), and one used the Canadian Study of Health and Aging Clinical Frailty Scale (682 patients). All 3 studies involved hospitalized patients with an average age of 85 ± 6 and 45% were male. The weighted mean prevalence of frailty in patients with atrial fibrillation was 39% (95%CI 36-42). The weighted mean rate of OAC use was 57±11%. Frailty was associated with non-prescription of OAC compared to non-frail (OR 0.49, 95% CI 0.32-0.74, I2 =45%).

Conclusions: The prevalence of frailty in hospitalized elderly patients with AF is high, and the use of OAC is low in these patients. Frail elderly are significantly less likely to receive OAC.

Introduction

Atrial fibrillation (AF) is the most common arrhythmia in the elderly and its prevalence increases with age[1]. AF substantially increases the risk of ischemic stroke[2] and is associated with increased mortality.[3] Stroke prevention using oral anticoagulants (OAC) effectively reduces this risk by 64%[4]. Paradoxically, though the prevalence of AF is the highest in the very elderly, the rate of appropriate anticoagulation decreases with age[5-7]. One potential reason for this could frailty.

Frailty is a biologic syndrome of decreased reserve to stressors, resulting from cumulative declines across multiple physiologic systems leading to a decline in homeostatic reserve and resiliency[8]. Frailty is associated with adverse outcomes such as increased falls, hospitalizations, worsening disability, nursing home admissions and mortality[9]. Frailty in community-dwelling adults increases with age, affecting 11% of elderly over the age of 65 years and 25% over the age of 85 years[10]. Although it is also not well known whether frailty affects long term outcomes in elderly patients with AF, it may influence management decisions.

We conducted a systematic review to determine the prevalence of frailty in patients with AF and whether measured frailty is associated with reduced rates of oral anticoagulation in these patients.

Key Words

Atrial fibrillation, Elderly, Frail, Anticoagulation Prescription, Stroke Prevention

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Methods

Details of the protocol for this systematic review were registered on PROSPERO CRD42017056795.

Search Strategy

We systematically searched Cochrane, MEDLINE, EMBASE, and PubMed databases. Our search strategy was designed to provide high sensitivity for finding all relevant studies and was not restricted by language. This was accomplished by using both Medical Subject Headings (MeSH) terminology and key words related to: 1) atrial fibrillation, 2) frail elderly, and 3) geriatric assessments. A search of references and free text search of world wide web was also conducted. Appendix A shows a sample search strategy.

Eligibility Criteria

We included randomized control trials, cohort studies, case control studies and other nonrandomized comparative studies if they compared rates of oral anticoagulation (using warfarin or direct-acting oral anticoagulants) in frail versus non-frail elderly and used any validated frailty instrument to measure frailty. We included studies with either accumulation of deficits (frailty index) model[11] or the phenotype model[12]. Studies without a comparison group of non-frail elderly were excluded. We also excluded articles that were not full length.

Methods of Review

The titles and abstracts of potential papers were independently reviewed by two authors. Full text articles were obtained when there was uncertainty in the studies. Data extraction and assessment of validity were also performed by both reviewers and confirmed by a third reviewer.

Quality assessment

The quality of studies was evaluated independently by two reviewers using the Newcastle-Ottawa Scale (NOS)[13]. Disagreements between reviewers were resolved by discussion. A score above 6 is considered as high quality.

Statistical analysis

Data was analyzed using Comprehensive Meta-Analysis software version 3 (Biostat Inc. Englewood, NJ). Prescription of anticoagulation for each study were expressed as odds ratios and 95% confidence intervals. Weighted mean differences and 95% confidence intervals were calculated for each variable. Pooled odds ratios were calculated using random-effects model. Heterogeneity was estimated using I2 statistic in a fixed effect analysis; a value <25% (low), 25-50% (moderate) and >75% (high)[14].

Results

Search strategy and characteristics of studies

[Figure 1] shows the details of the systematic literature search. We screened 166 relevant titles and abstracts, of which 17 full text articles were assessed for eligibility. Three studies met inclusion criteria and included a total of 1204 patients. The characteristics of each study including co-morbidities and risk factors for stroke and bleeding are described in [Table 1].

Perera et al[15] conducted a single center prospective study of 220 hospitalized adults in Australia with a mean age of 83 ± 6. Frailty was evaluated using Reported Edmonton Frail Scale (REFS)[16] and anticoagulant use was confirmed by medications in the discharge summary. They found that 64% of subjects were frail and 39% received anticoagulation at discharge. Frail patients were less likely to receive warfarin than non-frail on hospital admission (P = 0.002) and discharge (P < 0.001). Nguyen et al[17] conducted a prospective observational study of 302 hospitalized patients in Australia with a mean age of 85 ± 7. Frailty was assessed using REFS and prescription of anticoagulation was confirmed from medications in the discharge summary. They found that 52% of subjects were frail and 56% received anticoagulation at discharge. Frailty decreased the likelihood of anticoagulant prescription (odds ratio (OR) 0.58, 95%CI 0.36–0.93) on univariate analysis but not on multivariable analysis (OR 0.66, 95%CI 0.40–1.11). Lefebvre et al[18] conducted a cross-sectional study of 682 hospitalized patients in Canada with a mean age of 85 ± 4. Frailty was determined using the Canadian Study of Health and Aging Clinical Frailty Scale (CFS)[11] through chart review and the presence of anticoagulation was confirmed from documentation in medical chart. They found that 25% of subjects were frail and 70% received anticoagulation. The absence of severe frailty (CFS < 7; OR, 3.41; 95% CI, 1.84-6.33) was independently associated with anticoagulant use in multivariable analyses.

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

First author, Year	Perera, 2009	Nguyen, 2015	Lefebvre, 2015
Study design	Prospective observational	Prospective observational	Cross-sectional
Frailty instrument	Edmonton Frail Scale	Edmonton Frail Scale	Clinical Frailty Scale
Sample size	207	302	682
Age in Years, Mean ± SD	82.7 ± 6.3	84.7±7.1	85.0 ±4.4
Male %	46	50	40
Frail n (%)	64	53	25*
% anticoagulated	50	55.7	70
# of medications ± SD	8.0 ± 3.4	11.3 ± 4.0	13.5 ± 4.5
Stroke Risks			
CHF	35	43	32
Hypertension	71	69	88
Age≥75	88	90	NR
Diabetes	25	21	31
Previous stroke/ TIA	20	25	33
Vascular disease	NA	37	16
Bleeding Risks %	Applied to all 220 patients	Applied to 161/302 receiving anticoagulation at discharge	Applied to all 682 patients
Hypertension	71	69	88
Hepatic or Chronic Kidney Disease	22	14	16
Bleeding history	NA	48	20
Anemia	17	NR	73
Alcohol use	3	3	4
Malignancy	25	25	NR
Falls	69	NR	49
Other %			
Dementia	NA	9	26
Findings	Frailty was associated with underprescription of OAC	Frailty was not associated with anticoagulation rates	Frailty was associated with underprescription of OAC

*Lefebvre et al dichotomized frailty into non-frail/mildly to moderately frail (<7) and severely frail (>=7). Frailty prevalence reported is based on their cut offs.

Figure 1: **Flow diagram for the systematic literature review**

Quality of studies [Table 2]

The cohort studies included in the final analysis were prone to bias. There is potential selection bias amongst all three studies based on differences in study participant's age of eligibility[15,17,18] and higher bleeding risks[17]. Lefebvre et al also included more females (60%) who are more prone to being frail[10]. These studies also had information bias based on methods of confirmation of anticoagulation. Nevertheless, the quality of the three studies assessed was high based on average NOS score of 6 out of possible maximum of 9.

Table 2: **Quality assessment of studies using Newcastle Ottawa Scale. A cohort study can be awarded maximum of 4 stars for Selection, 2 stars for Comparability and 3 stars for Outcome.**

Study	Selection	Comparability	Outcome
Perera (2009)	***	*	**
Nguyen (2015)	***	**	*
Lefebvre (2015)	***	**	*

Frailty prevalence

The weighted mean prevalence of frailty in patients with atrial fibrillation was 39% (95%CI 36-42). Perera et al reported the highest prevalence of frailty at 64%. The authors used a REFS cut off score of 8 as frail and ≤7 as non-frail. Nguyen et al also used REFS cut of 8 as frail and reported a prevalence of frailty of 53%. Lefebvre et al used the CFS score and a cut of ≥7 as frail and <7 as non-frail by combining non-frail/mildly and moderately frail. Using their cut off, the prevalence of frailty was 25%.

Anticoagulant use and frailty [Figure 2]

The weighted mean prevalence of anticoagulation was 63%. Elderly patients who were classified as frail were significantly less likely to receive oral anticoagulation compared to non-frail elderly (pooled OR 0.49, 95% CI 0.32-0.74). There was a moderate degree of heterogeneity amongst the studies (I^2=45%).

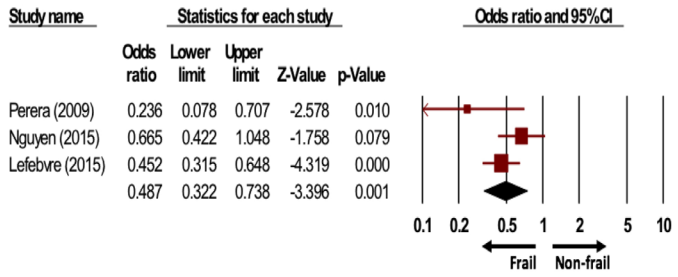

Figure 2: **Random effects model meta-analysis of prescription of anticoagulation in frail versus non-frail elderly. Frail elderly subjects were less likely to receive anticoagulation compared to non-frail elderly subjects.**

Discussion

We performed a systematic review to assess the prevalence of frailty and whether measured frailty affected rates of anticoagulation in hospitalized elderly with atrial fibrillation. Only three qualified reports could be identified and the overall quality of evidence was low.

Frailty prevalence

We found that approximately 40% of adults with AF over the age of 80 who are admitted to an acute care hospital are diagnosed as frail. This is higher than a previous large study of community dwelling adults that found the prevalence of frailty to be 15.7% (aged 80–84) and 26.1% (≥85)[10]. It is also higher than a recent study involving patients admitted to an inpatient ward that found the overall prevalence of frailty to be 13.9%[19]. These studies however did not report on participants' co-morbidities or presence of cardiovascular disease. Therefore, one possible explanation could be that patients with AF are more prone to frailty compared to patients with no AF, a finding supported by a prior study[20].

The differences might also be due to the type frailty instrument used. It has been shown that the prevalence of frailty can range from 3.6-34% in the same patient cohort depending on the frailty instrument that is used[21]. Similar findings were reported in another study involving acute care admissions which found the prevalence of frailty varying between 17.9-66.4% according to frailty instrument used[22]. These variabilities highlight the dynamic and complex nature of the frailty syndrome. It also highlights a potential area of opportunity to identify a "gold standard" which is yet to be defined.

Reporting anticoagulant use in frail patients

This analysis showed that the rate of OAC prescription is lower in frail elderly as compared to non-frail. Geriatric characteristics such as cognitive impairment, malnutrition risk, depression and falls are frequently cited reasons for underprescription of oral anticoagulants[23]. However, evidence supporting these reasons are lacking. Falls are not a strong contraindication to receiving OAC and patients who are prone to falls still receive the benefits of OAC for stroke prevention[24]. Age alone should not be a contraindication to anticoagulation as the absolute risk of intracranial hemorrhage among elderly patients on an anticoagulant is relatively low at 0.2% per year[25]. Furthermore, the use of NOACs in patients aged 75 and older was shown to be safe and effective for stroke reduction[26].

In all three studies the measurement of frailty was not performed by the prescribing physician. Therefore, it remains unclear if the physicians' behavior towards anticoagulation would change if the most responsible physician were to measure frailty. Furthermore, the observed heterogeneity of the studies could be due to different populations of elderly in Canada and Australia, differences in clinical practice in hospitalized patients and stroke prevention management in patients with AF. Accordingly, we can only tentatively conclude that apprehension of frailty was associated with under-prescription of anticoagulants.

Limitations

Our study has several limitations. We eliminated studies in which the methods of measuring frailty were not clearly defined. We also limited studies that did not have a comparison group of non-frail reported. This may have decreased our overall sample size but we think a comparison group of non-frail subjects is essential to ascertain the effect of frailty on anticoagulation prescription. The methods of confirming anticoagulation prescription were done by chart review, a method prone to error. Discharge summaries can contain errors in 12-13% of handwritten and electronic summaries, with errors of omission being particularly common[27]. Medication error rates in hospital and at time of discharge can be as high 50-65%[28]. Therefore, prescription of anticoagulation in elderly patients have inherent limitations, but overall do show an inverse relationship with presence of frailty.

Our results are subject to the limitation of meta-analyses which includes the aggregation of data from different studies with variable methods, definitions of frailty, baseline characteristics and from countries where frailty prevalence maybe different. There is inherent heterogeneity between the frailty instruments used in our studies as such pooling the studies might affect conclusions. However, regardless of the instrument used, all three studies used a cut of severely frail and those who were pre-frail to moderately frail were classified in the non-frail group. Therefore, the conclusions would be more applicable to elderly diagnosed as severely frail. The current studies involved only hospitalized patients and whether the results apply to community dwelling healthy elderly is unknown.

Clinical perspective

These studies were conducted in acute care settings and corresponding community data are unknown. As well whether frailty should be measured in all patients > 65 years or limited to those over the age 80 is unknown. It is also unknown what to do with the severely frail patients in terms of anticoagulation as the majority have a poor prognosis[29]. The current Canadian Cardiovascular Society and international guidelines do not provide advice in this patient population[4,30]. Future studies are needed to determine to what extent are frailty instruments are used in the community by physicians and how do they impact anticoagulation decisions. It would also be important to determine whether measurement of frailty in community dwelling adults prospectively using a validated instrument would increase prescription rates of anticoagulation and study outcomes of stroke prevention and adverse bleeding events.

Conclusions

The prevalence of frailty in hospitalized elderly patients with AF is high, and the use of OAC is low in these patients. Frail elderly are significantly less likely to receive OAC.

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3D Mapping for PVI- Geometry, Image Integration and Incorporation of Contact Force Into Work Flow

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Abstract

Catheter ablation of atrial fibrillation has evolved enormously thanks to rapid improvement of modern mapping technologies, progress in catheter development and current possibilities for reduction of radiation exposure. Pulmonary vein isolation is thereby the cornerstone in this interventional treatment. Increased precision of catheter localization by modern three-dimensional mapping systems, faster and better processing of local electrograms and their immediate color-based visualization make it possible to treat even challenging arrhythmias very effectively. The commonly used three-dimensional mapping systems CARTO 3 (Biosense Webster, Irvine, Ca.) and Ensite Precision (St. Jude Medical, St. Paul, Min) differ in construction and principles of the underlying mapping technology. In this review article, we aim to emphasize the most important aspects of possibilities that make both systems so valuable for interventional treatment of atrial fibrillation. We present a modern workflow, that unites three-dimensional LA mapping with collecting relevant local information, image integration for refining the map and beneficial use of contact force based ablation approach.

Introduction

Catheter ablation of atrial fibrillation has evolved enormously thanks to rapid improvement of modern mapping technologies, progress in catheter development and current possibilities for reduction of radiation exposure. Pulmonary vein isolation is thereby the cornerstone in this interventional treatment. Increased precision of catheter localization by modern three-dimensional mapping systems, faster and better processing of local electrograms and their immediate color-based visualization make it possible to treat even challenging arrhythmias very effectively. The commonly used three-dimensional mapping systems CARTO 3 (Biosense Webster, Irvine, Ca.) and Ensite Precision (St. Jude Medical, St. Paul, Min) differ in construction and principles of the underlying mapping technology. In this review article, we aim to emphasize the most important aspects of possibilities that make both systems so valuable for interventional treatment of atrial fibrillation. We present a modern workflow, that unites three-dimensional LA mapping with collecting relevant local information, image integration for refining the map and beneficial use of contact force based ablation approach.

Fundamentals of mapping technology

CARTO 3

CARTO 3 is the third-generation electroanatomical mapping system from Biosense Webster and is currently available with the latest software version 6. The system consists of a locator pad with three separate low-level magnetic field emitting coils (5x10-6 to 5x10-5 tesla) being arranged as a triangle under the patient, 6 body patches, a mapping catheter with embedded magnetic location sensors in its tip, a data processing unit and a graphic display unit to provide visualization of the electroanatomical model being created. The nonfluoroscopic CARTO system uses hybrid magnetic and current-based measurement to allow precise catheter location inside the heart with an accuracy of less than 1 mm. The CARTO system generates a real-time map by processing the local electrograms and spatial information at the catheter tip, while the catheter is precisely localized by using a triangulation algorithm similar to the principle function of GPS technology. The magnetic field emitter under the catheter table serves this purpose. Three different electromagnets generate three low-intensity magnetic fields. The metal tip of the catheter moves through these fields and generates an electrical current depending on the strength of the magnetic field and orientation of the catheter tip in it. This allows calculation of the distance from catheter tip to each of the three electromagnets (Figure 1A). This calculation adjusts the current-based information generated by the system by sending a small current across a catheter electrode which is then registered via the six body patches and become evaluated. Each electrode emits current at their own unique frequency. For each coordinate, a current ratio is created by measurement of the current strength at each patch and stored by the system for adjustment with the magnetic-based data. In addition to this information, three orientation determinants are detected by the system: yaw, roll and pitch (Figure 1B). The illustrated catheter tip on the display screen presents these 6 degrees of freedom with an additional 4-color-information indicating the current position, rotation and deflection of the catheter and its

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movement in real time. This supports precise catheter navigation in the heart chamber. The accuracy of the catheter position must be maintained despite the artifacts caused by respiration, patient movement, cardiac activity, and system movement. Therefore, three of six body patches (back patches) are used along with the locator pad for the location reference as part of the Body Coordinate System.

Attached to the patients back they constitute a fixed point in space and allows the system to measure the catheters location relative to this reference point for compensation of patient and system movement. Inter-patch-communication via measurement of impedance changes between the back and chest patches are mainly used for compensation of respiratory motion.

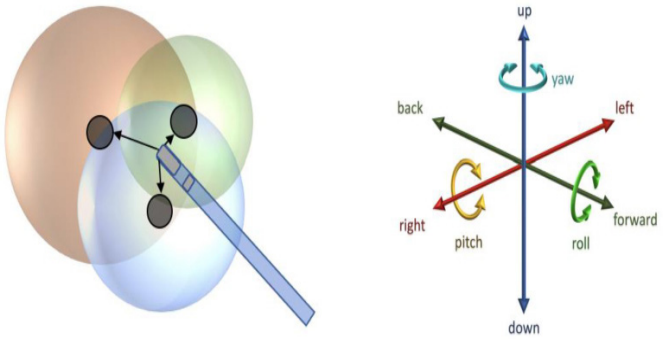

Figure 1: **Illustration of catheter position detection by CARTO 3 system. The three colored spheres represent the emitted ultralow magnetic fields of the 3 coils (black) of the locator pad. The field strength of the three electromagnets is measured by the sensor element of the catheter tip and used for position determination via a triangulation algorithm which allows an exact calculation of the distance from each coil. The system gets total information about 6 freedom degrees for visualization of location and direction of the catheter tip**

The 6 patches also contain magnetic sensors for localization. Additional respiratory information which can be recorded via the ACCURESP module support the calculation. For elimination of artefacts caused by cardiac motion, the system uses the electrical reference to match the coordinates of points with the time in cardiac cycle by point-by-point-mapping. For Fast Anatomical Mapping (FAM) the coordinates are adjusted but averaged leading to stable catheter visualization. The CARTO mapping system is used with deflectable uni- or bidirectional therapeutic catheters of Biosense Webster only which are available in three sizes: 4 mm, 8 mm (solid tips) and 3,5 mm (irrigated tip) and different deflection curves. Therapeutic open irrigated catheters are also available with enhanced surround flow (SF) technology allowing reduction of fluid for cooling process without trade-offs between power and signal resolution. A variety of diagnostic catheters allow the examination of intracardiac signals, adapted to the respective arrhythmia. Diagnostic catheters of other manufacturers can be partially used with CARTO system by using a special connector. Compared to previous models the CARTO 3 system allows visualization of up to 5 catheters at the same time with and without magnetic sensors and provide technology for rapid creation of the three-dimensional map (FAM: Fast Anatomical Mapping) while minimizing the need for radiation exposure. Volume data collection via FAM speeds up the creation of a map compared to point by point mapping. The simultaneous creation of high-density maps with simultaneous acquisition of anatomy, voltage and local activation data (if active) allow rapid mapping while collecting the relevant local data from the endocardium while the arrhythmia is present. Besides activation map, isochronal map, propagation map, entrainment map and voltage map the system has been enhanced with the new option of ripple mapping in the current software version 6. Ripple mapping is independent on mapping annotation and window of interest and allows simultaneous activation and voltage analysis. This additional information is useful for treating challenging arrhythmias, such as atypical atrial flutter caused by local reentry with complex wavefront propagation. For high density mapping and simultaneous acquisition of multiple electrograms and their voltage and activation information, Biosense Webster provide the PentaRay catheter with 20-poles arranged in 5 flexible radiating splines that covers an area with a diameter of 3,5 mm. Thus, the system is prepared for the rapid and accurate three-dimensional mapping of the left atrium including the pulmonary vein ostia. During the mapping process, the voltage can be displayed to obtain a fast overview of the atrial fibrosis. The additional tools mentioned above allow the rapid mapping of the LA geometry and allow colour-based visualization of excitation process and wavefront direction during atrial arrhythmia if necessary.

Ensite Precision

The EnSite Precision Cardiac Mapping System, which is available since 2016, also uses the advantages of hybrid impedance and magnetic field technology for localization of the catheters insight the body. It allows a much higher precision and more accuracy over the entire investigation time compared to the predecessors EnSite NavX and Ensite Velocity. The system consists of the following components: the EnSite Amplifier (which converts the physiological signals from the patients to digital signals for processing by the workstation), the EnSite Precision Field Frame, the display workstation and eight surface electrodes (three transthoracic pairs for three orthogonal axes and two patient reference sensors). It is, compared to the CARTO system, an open platform with compatibility to almost any electrophysiology catheter for mapping cardiac chambers. The basis for impedance-based localization and tracking of the catheters is the proven EnSite NavX Navigation and Visualization technology of previous EnSite systems. The new hardware equipment allows the additional use of the new Sensor EnabledTM (SE) technology. The therefore necessary EnSite Precision field frame is (like the location pad of the CARTO system) attached under the catheter table and generates a weak magnetic field. Sensor Enabled equipped catheters can be additionally located in the magnetic field. This information is used to refine the impact-based location, especially in the peripheral areas. This impedance-based location is based on the following principle: the previous described surface electrodes serve to generate an impedance field. An 8-kHz signal is sent alternately through each of the three pairs of transthoracic patches. Thus, a voltage gradient is generated in the x, y and z axis. The electrodes of the respective catheter, which enters this voltage field, measures the voltage, adjusted to the gradient generated by the 8 kHz signal in the respective axis. The location of each electrode can be calculated in the three-dimensional space. To use the magnetic data, a catheter with Sensor Enabled technology is necessary. The EnSite Precision system uses the magnetic data for real time adjustment of the impedance based catheter localization. Additionally, this information is meaningful for the EnSite stability monitor to preserve the localization accuracy in case of unexpected changes of the impedance field. This leads to an

navigation accuracy of < 1 mm. For creation of left atrial geometry, the Advisor FL can be used as SE capable circular mapping catheter. For ablation, both the FlexAbility catheter (without Contact Force) and the TactiCath Quartz (with Contact Force) are offered. Automation tools like EnSite AutoMap reduce the mapping time and also

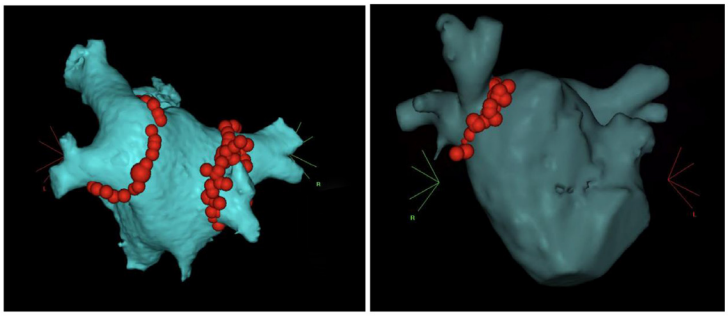

Figure 2: **Electroanatomical reconstruction of the left atrium and fusion with CT data set (left) and MRI data set (right) for pulmonary vein isolation.**

provide the possibility to create an additional map besides recording the anatomy, e.g. a voltage map. The new TurboMap feature allows very fast processing of stored procedure data and works similar to the CARTO Replay module. The EnSite Automark module represents an automated lesion creating tool according to predefined criteria.

This demonstrates that both cardiac mapping systems allow a very precise and stable three-dimensional reconstruction of the left atrium and provide numerous additional tools that allow the user to target even complex atrial arrhythmias.

Image Integration

The use of CT or MRI data sets created prior to study initiation is becoming increasingly common in clinical practice. These data sets are processed so that the atrial anatomy can be represented three-dimensionally with high accuracy. This allows the visualization of anatomical peculiarities that might not have been noticed in a single three-dimensional mapping approach. The virtual 3D model either serves for sole orientation in the left atrium during the electroanatomical mapping process or can be fused with the generated map. The accurate reconstruction of difficult areas of the atrium such as the ridge between the left upper vein and the left atrial appendage improves catheter navigation and visualization of tissue contact during the actual ablation procedure. Efficacy studies currently show no reliable benefit of image integration regarding recurrence rate after ablation of atrial fibrillation [1].

CARTO 3

For the CARTO system, the necessary module is entitled CARTOMERGE. It improves the realistic appearance of the left atrium by providing additional important patient-specific anatomical information. After mapping the atrium, the system can fuse CT/MRI data set with the electroanatomical map after selecting corresponding fiducial points on the CT/MRI map and the created map. The module calculates the ideal fusion of both 3D models. The accuracy of the fusion can be checked by moving the ablation catheter through the atrium and check whether the visualization of the catheter tip projection is adequately displayed while having good local tissue contact. The module helps to guide ablation process with improved procedure safety and efficacy[2]. Another recently released module, the CARTOSeg CT module provides a semi-automatic segmentation function with separating the atria, the ventricles, esophagus and coronary sinus as well as the aorta without additional user-dependent identification. It automates the CT segmentation before it is used as data set for image integration and thus speeds up the workflow[3]. For generating a detailed 3D map it is also possible to combine the electroanatomical map with a map derived from echocardiographic information from real time intracardiac echocardiography (ICE) which in turn is created through combining multiple ECG-gated 2D ultrasound cross sections generated from an ultrasound transducer. This ICE data can be processed via the CARTOSound image integration module[4]. For this purpose, each image is automatically optimized in terms of contrast and frequency, and the endocardial wall side is detected based on different echo intensity between blood and tissue. The special SOUNDSTAR catheter from Biosense Webster provides besides the ultrasonic beam an embedded magnetic location sensor for accurate localization in the left atrium[5]. The CARTOUnivu module is the technology that

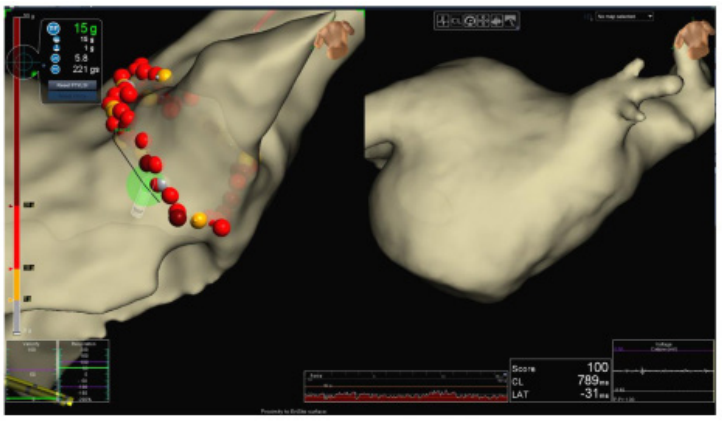

Figure 3: **Illustration of an AF ablation with contact force technology. Ablation with contact force of 15 g at the bottom of RIPV is shown in the left picture. The corresponding MRI image, which is displayed in a synchronized mode, is visualized on the right side.**

allows physicians to interlock a static fluoroscopic image with the current three-dimensional map after prior registration. Similarly, dynamic sequences, such as coronary angiography, can be merged with the map. This provides valuable additional information such as distance from ablation side to coronary vessels and reduce the radiation exposure for the patient and the entire staff. It is also possible to automatically integrate the static or dynamic sequence in a 180-degree rotated map after appropriate calculation by the CARTO system. Using the CARTOUnivu module the fluoroscopy time as well as the fluoroscopy dose can significantly be reduced in an AF ablation procedure without prolongation of procedure time or differences of periprocedural complications or acute ablation success rates[6].

EnSite Precision

The EnSite precision system provide the EnSite Verismo Segmentation Tool to allow segmentation and three-dimensional reconstruction of cardiac models from 2D slice-based CT/MRI data. The fusion of the electroanatomical map and the CT/MRI images is done by EnSite Fusion Registration module. In a split screen the

real-time geometry is visualized on the left side (with field scaling) and the 3D reconstruction from the CT/MRI data set on the right side. In this step, gross deviations in the map can be improved. The fusion of the two 3D reconstructions is initially done by rigid fusion through three fiducial corresponding points. These fiducial points should be placed at positions that are clearly traceable in both maps. In another dynamic fusion step, both maps will be adjusted by further fiducial points to increase the accuracy significantly. In contrast to the CARTOMerge software, the geometry is hereby tugged and compressed locally to align with the CT / MRI surface. So, besides shifting and rotation in three axes, this stretching increases the fusion accuracy through additional fiducial points. The CARTOMerge software only provides shifting and rotation in three axes without relevant resulting differences in registration error. The Fusion module also allows a variety of map types which can be displayed, for instance voltage or activation map.

The non-fluoroscopic catheter tracking system MediGuide is a technology for reduction of radiation exposure during an ablation procedure. With the use of a low-powered electromagnetic field around the patient, catheters with embedded sensors can be located and tracked with an accuracy of 1 mm and 1° on prerecorded 2D x-ray images and loops. The electromagnetic field emitter is integrated in the fluoroscopic detector. The patient receives a reference sensor on the back. Together with the ECG signals it is possible to compensate artifacts caused by movement of the patient and respiration. Using MediGuide for ablation of atrial fibrillation has been proven to be

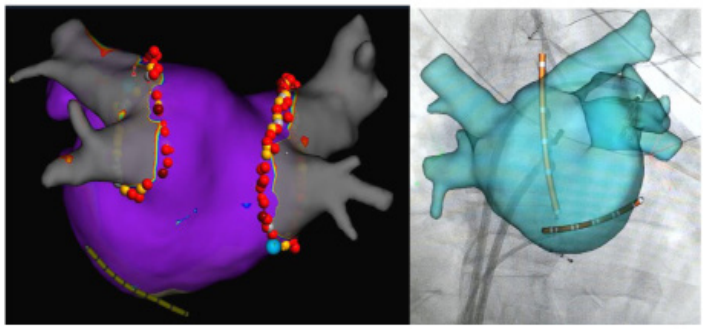

Figure 4: **Left: 3D reconstruction of the left atrium with EnSite Precision. Image integration of MRI data and fusion of both maps with EnSite Fusion. Additional voltage information is seen from an PA view. Right: 3Dreconstruction of the left atrium (MRI data) and integrated fluoroscopic image with CARTOUnivu.**

safe and efficient and accompanied with significant reduction of fluoroscopy time[7].

Influence of Contact Force Measurement

Homogeneous transmural antral lesion formation in treatment of atrial fibrillation without interlesion space is the fundamental requirement for stable pulmonary vein isolation to achieve long-term freedom of AF recurrence by avoiding electrical reconnection of the pulmonary veins. Thus, long-term success rates up to 80% can be achieved with multiple procedures[8]. Sufficient tissue contact ensures adequate energy delivery. Force sensing technologies have been established as valuable part of AF ablation procedure in the last years. The feedback of contact force information also avoids excessive energy transfer to the tissue resulting in risk of overheating, tissue perforation and fistulae[9]. Omitting robotic navigation there are two contact force catheters currently available on the market: the TactiCath Quartz (St. Jude Medical) and the ThermoCool

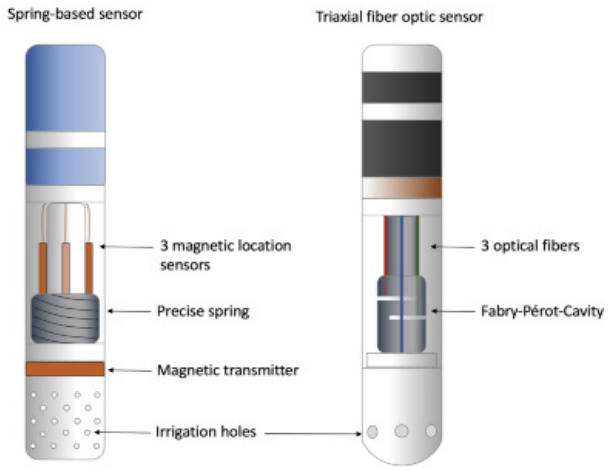

Figure 5: **Illustration of principle construction of both catheters, the Thermocool SmartTouch SF (left) and TactiCath Quartz (right) with fundamental differences in contact force assessment.**

SmartTouch (Biosense Webster) irrigated tip catheter. Both catheters differ in structure and thus in type of contact force measurement (Figure 5).

The 3.5 mm irrigated tip Tacti Cath catheter consists of one thermocouple for temperature measurement at the catheter tip, 6 irrigation holes with 0.4 mm diameter and the contact force sensor. This fiberoptic sensor is made up of 3 optical fibers, which are aligned in parallel and directed towards an elastic polymer layer. By deformation of the membrane upon tissue contact, the wavelength of the reflected infrared laser light is changed, which in turn correlates with the strength and angle of the applied force. The principle of measurement is based on a Fabry-Pérot-Cavity. The axial and lateral CF can be measured and displayed[10].

The Thermo Cool SmartTouch (SF) catheter is also a 3.5 mm irrigated tip catheter. The CF is measured here via a small precise spring being located in the catheter shaft. The CF calculation is based on the measurement of the distance between the magnetic transmitter coil (distal of the spring) and the 3 location sensors (proximal of the spring) with a known spring constant. Contact force and direction is measured in an interval of 50 ms and is displayed as averaged CF every second on screen. With this catheter, the CF should be zeroed in the blood[11].

The accuracy of the force measurement is not influenced by the angle of the acting force in the TactiCath Quartz catheter with triaxial fiber optic sensor technology. Axial and lateral forces deform the gratings of the deformable body and recently published data demonstrate the high accuracy of CF measurement for both axial and lateral forces [12]. In particular, very laterally acting forces, especially on proximal portions of the catheter tip, lead to an underestimation of CF forces in Smarttouch catheters with their spring-based sensor technology[13]. Moreover, the TactiCath Quartz catheter shows significantly higher accuracy of CF measurement in both perpendicular and lateral orientations to the tissue compared to

the Smarttouch catheter (1.2 g vs. 6.0 g mean absolute difference, 5 g vs. 30 g maximum error). This difference in technology has to be kept in mind at ablation sites with a parallel orientation to the tissue.

After Shah et. al. in 2010 had demonstrated in vitro that additional delivery of contact force information during ablation directly correlates with lesion depth and size over time[14], the TOCCATA trial provided the first evident clinical data of safety and efficacy of a novel contact force catheter (TactiCath) based ablation in treatment of atrial fibrillation. With lesions generated with at least 10 g of CF, AF freedom in 80% of patients could be achieved after 12 months[15]. Two years later in 2014, it could be proven for this catheter that stable contact force (CF) during radiofrequency ablation was crucial for the significantly higher success rate (freedom of atrial tachycardia after 1 year) in patients with drug refractory paroxysmal atrial fibrillation[16]. In 2015, evidence was provided that the use of a TactiCath catheter is also noninferior to a catheter without CF technology (Navistar Thermocool, Biosense Webster) and that optimal CF guided ablation (>90% of points with >10 g CF) improve 12 months' outcome (freedom of any atrial arrhythmia recurrence) in patients with paroxysmal atrial fibrillation[17]. The EFFICAS I (2013) and EFFICAS II (2015) trials taught us that at least 10 g of pressure should be applied at each ablation site, but on average 20 g should be the target for achieving rapid transmurality of the lesion[18]. On the other hand, it is important to avoid excessive tip-tissue contact and high energy applications so as not to endanger the safety of the patient. Makimoto et al. could recently show that gradual impedance rise (> 5 / 10 seconds) after 20 seconds of RF ablation with high CF and high applied power may be caused by charring at the catheter tip. This impedance rise can be avoided by using CF below 27 g (negative predictive value of 95 %)[19].

We still have not yet been able to obtain perfect information on the transmurality of a lesion, its homogeneity, size and shape and thus to be sure that this lesion is irreversibly electrically inactive. Nevertheless, in recent years we have succeeded in getting closer to this concern. We know that contact force, catheter stability, RF power, interlesion space and anatomy of the local tissue site are important parameters for getting a good lesion. Several indices were developed and tested for this purpose and currently provide a feedback about lesion quality.

The first of these was the Force Time Integral (FTI) presented by Prof. Shah 2010. The TOCCATA study in 2012 provided the first clinical evidence that the FTI is an independent predictor of outcome after ablation of atrial fibrillation[15]. The EFFICAS I and II trials showed us that at least 400 gs should be achieved at a local tissue site with CF > 20 g on average (range 10-30 g) and lesion index (LSI) > 5 (lesion index also considers applied power) for avoiding PV reconnection after AF ablation with a 95% probability of durable PV isolation after 3 months[20]. The Force Time Integral (FTI) and Lesion Index (LSI) are calculated and displayed using the EnSite Contact Force module in EnSite systems. A recent index that also takes the non-linear relationship between CF and application time[21] into account is the Ablation Index (AI). The CARTO VISITAG module enables the calculation of the Ablation Index based on a logarithmic formula which includes the CF, the applied power and its duration. Recently published data demonstrate the clinical benefit of using AI. Hussein et al. could show, that using the Ablation Index (400 for posterior and inferior wall segments and 550 for anterior and roof segments of LA) leaded to higher rate of first pass PV isolation, lower incidence of acute and long term (12 months) PV reconnection and higher impedance drop suggesting better lesion quality. The control group was treated with standard CF-guided ablation approach[22]. Contrary to the single FTI target value, the AI target value depends on the LA region based on different wall thickness. The latest featured index is the Ablation Line Contiguity Index (ALCI) as a novel automated algorithm combining depth and contiguity (FTI, AI and ILD) into one single criterion and is defined as the ratio of the estimated width of 2 neighboring lesions over their interlesion distance. The interlesion distance (ILD) is the distance between neighboring RF lesions on the circumferential ablation line. The ILD in one segment is predictive of local PV reconnection. The study results suggest an ILD target of < 5 mm[23]. A multicenter study will investigate the clinical benefit of the ALCI.

A good quality of lesion on the entire antral line around the pulmonary veins is of crucial importance for the clinical outcome of our patients. The contact force technology and the use of lesion assessment tools are elementary components of a modern ablation strategy.

Conflict of Interest

OMB, LI, KK and IP have no conflicts to declare. GH and PS received research grants from Abbott Medical and are advisory board members of Abbott Medical and Biosense Webster.

Conclusion

Modern cardiac mapping systems provide a very precise three-dimensional resolution of the left atrium, which is essential for efficient and safe treatment of atrial fibrillation. Image integration tools refine the geometry, do not require relevant effort and should be part of a modern LA reconstruction. They also ensure a significant reduction in radiation exposure for the patient, the investigator and the entire staff. Several mapping tools offers fast and high-resolution visualization of relevant electrical information and therefore enable us to treat even complex arrhythmia. Innovative mapping features like ripple mapping increasingly automate the mapping process and improved catheter development with contact force technology together with lesion assessment tools are an essential part of modern AF ablation approach and therefore should be incorporated into our workflow. The fundamental differences in contact force assessment of the 2 available systems has to be kept in mind.

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A Chromosome 4q25 Variant is Associated with Atrial Fibrillation Recurrence After Catheter Ablation: A Systematic Review and Meta-Analysis

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Abstract

Background: Recent studies suggested that variants on chromosome loci 4q25, 1q21, and 16q22 were associated with atrial fibrillation recurrence after catheter ablation. In this study, we performed a systematic review and meta-analysis to explore the association between variants on chromosome loci 4q25, 1q21, and 16q22 and atrial fibrillation recurrence after catheter ablation.

Methods: We comprehensively searched the databases of MEDLINE and EMBASE from inception to January 2017. Included studies were published prospective or retrospective cohort and case control studies that compared the risk of atrial fibrillation recurrence after catheter ablation in AF patients with chromosome 4q25, 1q21, and 16q22 variants versus no variants. Single-nucleotide polymorphism rs1906617, rs2106261, rs7193343, rs2200733, rs10033464, rs13376333, and rs6843082 were included in this analysis. Data from each study were combined using the random-effects, generic inverse variance method of DerSimonian and Laird to calculate the risk ratios and 95% confidence intervals.

Results: Seven studies from January 2010 to June 2017 involving 3,322 atrial fibrillation patients were included in this meta-analysis. According to the pooled analysis, there was a strong independent association between chromosome 4q25 variant (rs2200733) and the risk of atrial fibrillation recurrence after catheter ablation (risk ratio 1.45 [95% confidence interval 1.15-1.83], P = 0.002). No association was found in other variants.

Conclusion: Our meta-analysis demonstrates a statistically significant increased risk of atrial fibrillation recurrence after catheter ablation in 4q25 variant (only in rs2200733) but not in 1q21 or 16q22 variants.

Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia treated in clinical practice and affects 10% of the population by 80 years of age. It increases risks of stroke, heart failure, and all-cause mortality[1]. The cornerstones of management include stroke prevention, ventricular rate control, and symptomatic relieve. Catheter ablation is another method to restore and maintain sinus rhythm used widely in selected patients with medically refractory AF. Its efficacy and safety have improved during the last decade, and clinical trials have reported fewer episodes and symptoms after the procedure[2]. Unfortunately, recurrence of AF after catheter ablation is common, ranging from 20% to 60%, and results in repeat of the procedure or re-initiation of antiarrhythmic drugs[2,3].

This variable treatment response, among other clinical heterogeneities, has led physicians explore the molecular basis of AF that may optimize the treatment efficacy and safety. Since Gudbjartsson et al. used genome-wide association study (GWAS) to identify 2 risk variants on chromosome 4q25 (rs2200733 and rs10033464) in 2007, multiple single-nucleotide polymorphisms (SNPs) have been shown to be associated with occurrence of AF[4]. Among these discoveries, the SNPs on chromosome loci 4q25, 1q21, and 16q22 have been replicated in many studies[4-8] and recently demonstrated their potential relations to the AF recurrence after catheter ablation[9-13]. We systematically reviewed current evidence on the association, as well as its significance and characteristics, between common variants on 4q25, 1q21, and 16q22 and AF recurrence after catheter ablation.

Key Words

Atrial Fibrillation, Catheter Ablation, Chromosome 4q25

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Methods

Search Strategy

Two investigators (JC and WV) independently searched for published studies indexed in MEDLINE and EMBASE databases from inception to January 2017 using a search strategy that included the terms for "atrial fibrillation", "ablation", "recurrence", "4q25", "1q21" and "16q22". Only English language publications were included. A manual search for additional pertinent studies and review articles using references from retrieved articles was also completed.

Inclusion Criteria

The eligibility criteria included the following: (1) Cohort study (prospective or retrospective) reporting incident of recurrent AF in AF patient after catheter ablation with and without variants on chromosome loci 4q25, 1q21, or 16q22 (2) Relative risk, hazard ratio, odds ratio, incidence ratio, or standardized incidence ratio with 95% confidence intervals or sufficient raw data for the calculation were provided (3) AF participants without 4q25, 1q21, or 16q22 variants were used as controls.

Study eligibility was independently determined by two investigators (PR and PC) and differences were resolved by mutual consensus. Newcastle-Ottawa quality assessment scale was used to evaluate each study in three domains: recruitment and selection of the participants, similarity and comparability between the groups, and ascertainment of the outcome of interest among cohort studies[14].

Data Extraction

A standardized data collection form was used to obtain the following information from each study: title of study, name of first author, year of publication, country of origin, number of participants, demographic data, ablation techniques, outcomes of interest (variants and AF recurrence), and average duration of follow-up. To ascertain the accuracy, all investigators independently performed this data extraction process . Any data discrepancy was resolved by referring back to the original articles.

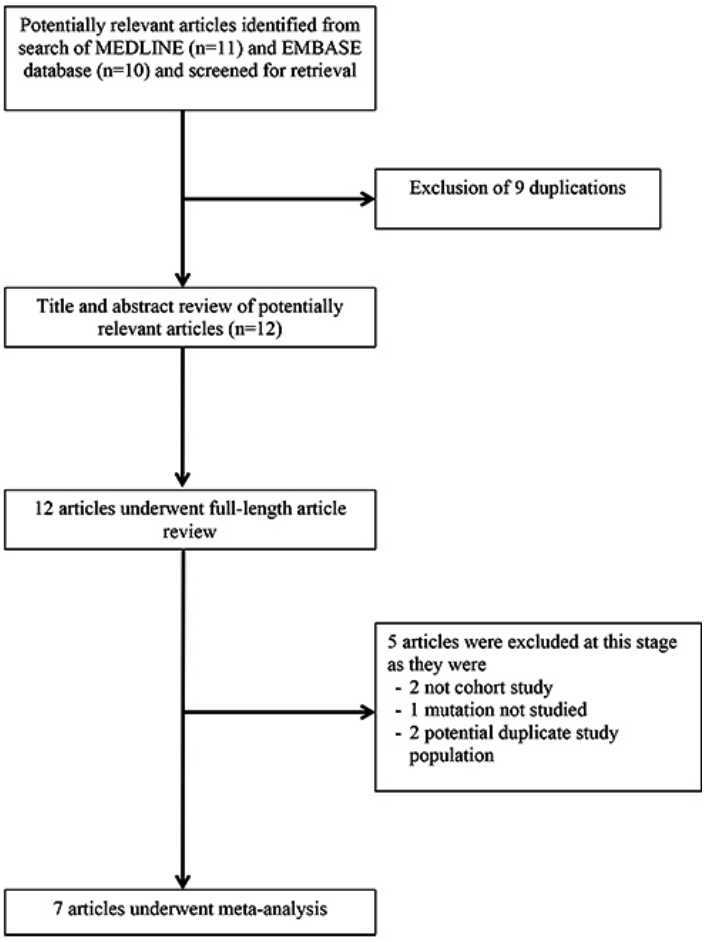

Figure 1: Search methodology and selection process

Statistical Analysis

We performed a meta-analysis of the included cohort studies using a random-effects model. The extracted studies were excluded from the analysis if they did not present an outcome in each intervention group or did not have enough information required for continuous data comparison. We pooled the point estimates from each study using the generic inverse-variance method of Der Simonian and Laird[15]. The heterogeneity of effect size estimates across these studies was quantified using the I2 statistic. The I2 statistic ranges in value from 0 to 100% (I2<25%, low heterogeneity; I2=25%–50%, moderate heterogeneity; and I2>50%, substantial heterogeneity)[16]. A sensitivity analysis was performed to assess the influence of the individual studies on the overall results by omitting one study at a time. Publication bias was assessed using funnel plot and Egger's regression test[17] ($p<0.05$ was considered significant). All data analyses were performed using the Stata SE 14.1 software from StataCorp LP.

Results

Description of Included Studies

Our search strategy yielded 21 potentially relevant articles (11 articles from EMBASE and 10 articles from MEDLINE). After exclusion of 9 duplicated articles, 12 articles underwent title and abstract review. Five articles were excluded at this stage since they were not cohort studies, did not report the outcome of interest (AF recurrence) or were not conducted in patients with AF underwent catheter ablation, leaving 7 articles for full-length article review. Therefore, 6 prospective cohort studies, and 1 case-control studies of 3,322 AF patient underwent catheter ablation were included in this meta-analysis. [Figure 1] outlines the search and literature review process. The clinical characteristics and summary of included studies are described in [Table 1].

Quality Assessment of Included Studies

Newcastle–Ottawa scales of the included studies are described in the supplement [Table 2]. The Newcastle-Ottawa scale uses a star system (0 to 9) to evaluate included studies on 3 domains: selection, comparability, and outcomes. Higher scores represent higher study quality. Intra-study risks of bias of included studies are also described in the supplement [Table 3].

Meta-analysis Results

There were 7 studies from January 2010 to June 2017 involving 3,322 atrial fibrillation patients were included in this meta-analysis. Seven SNPs among 4q25, 1q21, or 16q22 variants were reported in previous AF ablation studies. Four SNPs including rs2200733, rs10033464, rs6843082, and rs1906617 were reported in 4q25 variants. One SNPs, rs13376333, was reported in 1q21 variants. Two SNPs including rs2106261 and rs2106261 were reported in 16q22 variants.

4q25 Variants

For rs2200733, 6 studies from January 2010 to June 2017 were included in meta-analysis [9]-[13],[18]. Five out of six studies reported statistical significant increased risk of AF recurrence in patent with SNP rs2200733[9]-[13]. According to the pooled analysis, there is a strong independent association between chromosome 4q25 variant

Table 1: Characteristics of Included Studies

First author	Husser et al.	Shoemaker et al.	Choi et al.	Kiliszek et al.	Chen et al.	Zhao et al.	Miyazaki et al.
Country	Germany	USA/Germany	South Korean	Poland	China	China	Japan
Study design	Prospective cohort	Prospective cohorts from 3 centers	Prospective cohort	Prospective cohort	Prospective cohort	Case control	Prospective cohort
Year of publication	2010	2015	2015	2016	2016	2017	2017
Study subject	German patients who underwent left atrial catheter ablation for drug-refractory paroxysmal or persistent AF	Patients underwent de novo AF ablation between 2008 and 2012 at Vanderbilt University, the Heart Center Leipzig, and Massachusetts General Hospital	All AF patients underwent radiofrequency catheter ablation from Yonsei AF Ablation Cohort registry	Paroxysmal or persistent AF patients at Medical University of Warsaw	Drug-refractory Chinese Han AF patients at the First Affiliated Hospital	Chinese Han patients admitted to department of cardiology from July 2011 to August 2013 at Shanghai First People's Hospital	Japanese patient whom underwent cryoballoon ablation from July 2014 to January 2016 for paroxysmal atrial fibrillation
Exclusion criteria	Presence of left atrial thrombus	N/A	Permanent AF refractory to electrical cardioversion, valvular disease, structural heart disease other than left ventricular hypertrophy, prior AF ablation.	Hyperthyroidism, significant mitral valve disease, left atrial dimension over 5.5 cm, severe diseases with life expectancy below 1 year	Familial AF, hyperthyroidism, valvular heart disease, cardiomyopathy, left atrial thrombus, other severe diseases with life expectancy below 1 year	Familial AF, lone AF, recent MI (6 months or less), cardiac surgery (30 days or less), NYHA class III or IV, thyroid, renal, or lung dysfunction AF due to trauma surgery, or acute medical illness	N/A
Number of subjects (%M, mean age±SD)	195 (73%, 56±12)	991 from 3 centers: 245 (71%, 61±9.63); 659 (67%, 60±10.4]); 87 (82%, 57±9.63)	1068 (74.6%, 57.5±10.9)	238 (66.80%, 55±10.4	235 (73.7%, 59.41)	438 (52.12%, 63.75 ± 15.93)	157 (72.6%, 64±10.8)
Paroxysmal AF	78%	58.8%	67.9%	N/A	56.7%	N/A	100%
Hypertension	N/A	72.3%	47.8%	58.4%	38.7%	N/A	48.4%
Diabetes	N/A	N/A	13.0%	7.6%	20.0%	N/A	N/A3(4%)
Ablation technique	Radiofrequency pulmonary vein isolation (with linear ablation in persistent AF)	Radiofrequency pulmonary vein isolation (with linear ablation based on operator discretion)	Radiofrequency pulmonary vein isolation (with linear ablation based on operator discretion)	Radiofrequency pulmonary vein isolation	Radiofrequency pulmonary vein isolation (with linear or complex fractionated ablation based on operator discretion)	Radiofrequency pulmonary vein isolation (with linear ablation in unsuccessful pulmonary vein isolation)	Cryoballoon pulmonary vein isolation
Variants : and SNP(s) investigated for the recurrence risk (and its closest gene)	4q25:rs2200733 (*PITX2*), rs10033464 (*PITX2*)	4q25:rs2200733 (*PITX2*), rs10033464 ,1q21:rs13376333 (*KCNN3*), 16q22:rs7193343 (*ZFHX3*)	4q25:rs6843082 (*PITX2*), rs2200733 (*PITX2*), 1q21:rs13376333 N3)16q22:rs2106261 (*ZFHX3*)	4q25:rs2200733 (*PITX2*), rs10033464 (*PITX2*), rs17570669 (*PITX2*), rs3853445 (*PITX2*), rs6838973 (*PITX2*), 1q21:rs13376333 (*KCNN3*), 16q22:rs7193343 (*ZFHX3*)	4q25:rs2200733 (*PITX2*), 16q22:rs2106261 (*ZFHX3*)	4q25:rs2200733 (*PITX2*)	
Endpoints: early recurrence of AF	Within 7 days	N/A	Within the 3-month post-ablation	Within the 6-month post-ablation	N/A	N/A	After the 3-month post-ablation blanking period
Endpoints: late recurrence of AF	Between 3 and 6 months	After the 12 months post-ablation	After the 3-month post-ablation	After the 6-month post-ablation	After the 3-month post-ablation blanking period	After the 3-month post-ablation blanking period	N/A
Mean follow-up	6 months	12 months	18.3±13.9 months	45 months	12 months	N/A [0-48 months]	12 months
Conclusions by authors	rs2200733 and rs10033464, modulate are associated with increased rate of AF recurrence after ablation	rs2200733, but not rs10033464, rs13376333, or rs7193343, is associated with increased rate of AF recurrence after ablation	rs6843082, rs2200733, and rs2106261 were associated with AF	rs2200733 is associated with increased rate of AF recurrence after pulmonary vein isolation in short-term (6 months) follow-up.	rs2200733 is associated with AF recurrence after ablation, potentially by influencing the size of the RA and superior PVs	rs2200733 was associated with AF and was associated with recurrence after ablation	rs1906617 was associated with AF and was associated with recurrence after cryoballoon ablation

* Recurrence is defined as any episode of non-sinus atrial tachyarrhythmia (atrial tachycardia, atrial flutter, or AF) lasting greater than 30 seconds

and AF recurrence after catheter ablation (RR 1.45 [95% CI 1.15-1.83], p = 0.002) with high heterogeneity (I2=59.6%) [Figure 2].

Three studies were included for meta-analysis for rs10033464 [10,12,13]. which reveals no association with AF recurrence (RR 1.11 [95% CI 0.64-1.94], p = 0.703) with high heterogeneity (I2=66.2%) [Figure 3A]. We did not performed meta-analysis in rs6843082 and rs1906617 since only one study of each provided available data. For rs6843082, previous report revealed no association with AF recurrence (RR 0.84 [95% CI 0.61-1.15], p = 0.280)[18]. However, for rs1906617, recent study reported significant association with AF recurrence (RR 2.44 [95% CI 1.06-5.61], p = 0.035)[19].

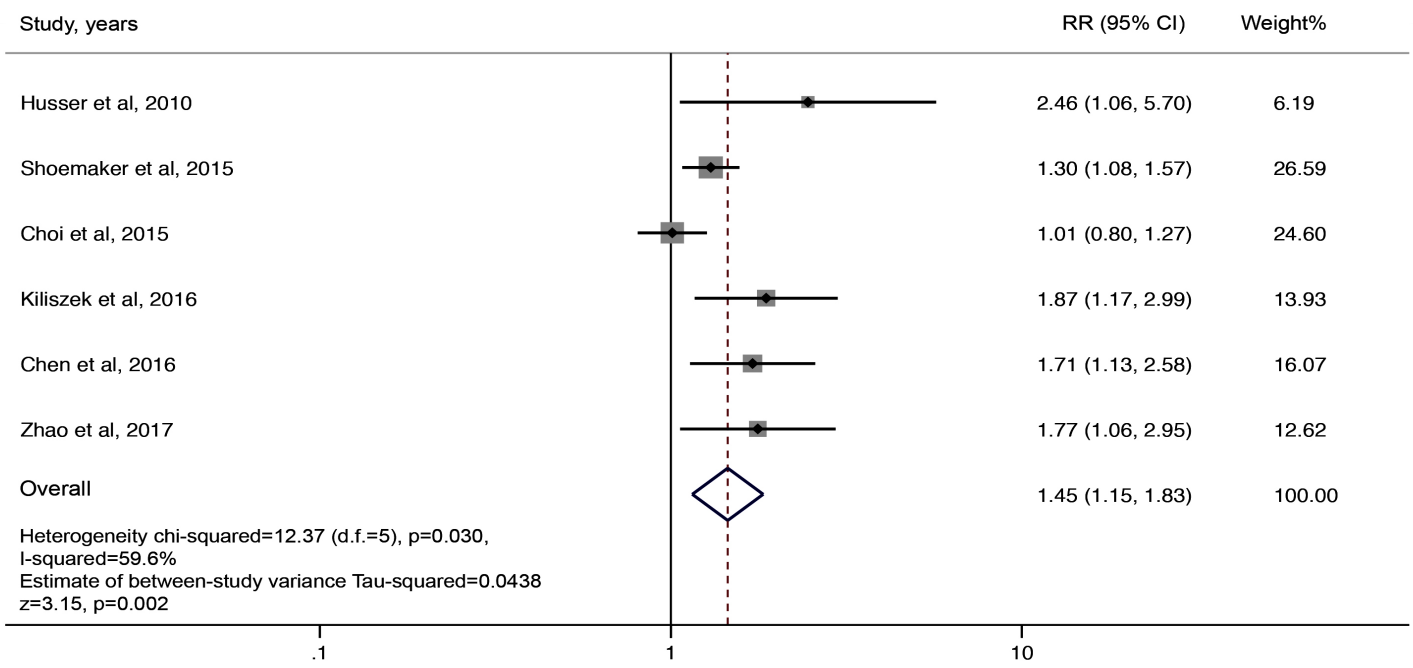

Figure 2: **Forest plot of the included studies assessing the association between recurrence of atrial fibrillation after catheter ablation and variant rs2200733 on 4q25.**

1q21 Variant

For rs13376333, 3 studies from January 2010 to June 2017 were included in meta-analysis[12,13,18]. All of 3 studies reported no association between patients with SNP rs13376333 and risk of AF recurrence. According to the pooled analysis, there is no independent association between rs13376333 in chromosome 1q21 variant and atrial fibrillation recurrence after catheter ablation (RR 0.86 [95% CI 0.71-1.05], p = 0.142) with low heterogeneity (I2=0%) [Figure 3B].

16q22 Variant

For rs2106261, 2 studies from January 2010 to June 2017 were included in meta-analysis[9,18]. All of two studies reported no association between patients with SNP rs2106261 and risk of AF recurrence. According to the pooled analysis, there is no independent association between rs2106261 in chromosome 16q22 variant and atrial fibrillation recurrence after catheter ablation (RR 0.92 [95% CI 0.74-1.14], p = 0.434) with low heterogeneity (I2=21.2%) [Figure 3C]. For rs7193343, two studies from January 2010 to June 2017

Table 2: **Supplementary table 1 Newcastle–Ottawa scales of the included studies**

Study	Selection				Comparability	Outcome			total
	Representativeness	Selection of Thenonexposed Cohort	Ascertainment	End point not present at start	Confounding	Assesment of Outcome	Follow up duration	Adequacy follow-up	
Husser et al.	*	*	*	*	**	*		*	8
Shoemaker et al.	*	*	*	*	**	*	*	*	9
Choi et al.	*	*	*	*	**	*	*	*	9
Kiliszek et al.		*	*	*	*	*	*	*	7
Chen et al.	*	*	*	*	**	*	*	*	9
Zhao et al.		*	*	*	*	*	*	*	8
Miyazaki et al.	*	*	*	*	**		*	*	8

Table 3: **Intra-study risks of bias of included studies**

Study	Clear definition of study population	Clear definition of outcomes and assessment	Independent assessment of outcomes? (e.g. by third party)	Sufficient Follow-up duration?	Selective loss during Follow-up?	Limitations identified?
Husser et al.	yes	yes	no	no	no	yes
Shoemaker et al.	yes	yes	no	yes	no	yes
Choi et al.	yes	yes	no	yes	no	yes
Kiliszek et al.	no	yes	no	yes	no	yes
Chen et al.	yes	yes	no	yes	no	yes
Zhao et al.	no	yes	no	yes	no	yes
Miyazaki et al.	yes	**no**	**no**	**yes**	**no**	**yes**

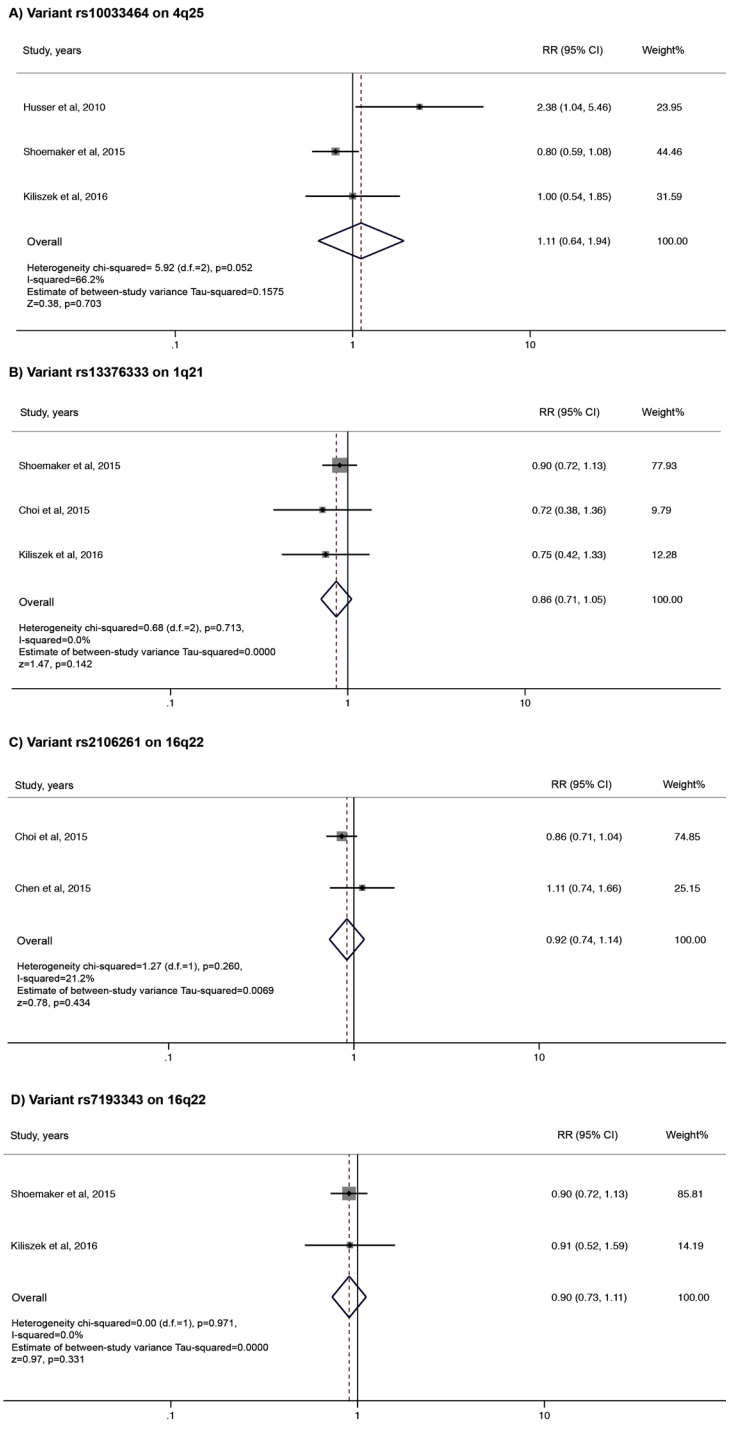

Figure 3: **Forest plot of the included studies assessing the association between recurrence of atrial fibrillation after catheter ablation and variant rs10033464 on 4q25, B) rs13376333 on 1q21, C) rs2106261 on 16q22, and D) rs7193343 on 16q22.**

were included in meta-analysis[12,13]. All of two studies reported no significant association between patients with SNP rs7193343 and risk of AF recurrence. According to the pooled analysis, there is no independent association between rs7193343 in chromosome 16q22 variant and atrial fibrillation recurrence after catheter ablation (RR 0.90 [95% CI 0.73-1.11], p = 0.331) with low heterogeneity (I2=0%) [Figure 3D].

Sensitivity Analysis

To assess the stability of the results of the meta-analysis, we conducted a sensitivity analysis by excluding one study at a time. We used a sequential exclusion strategy, as described by Patsopoulos and colleagues, to examine whether overall estimates were influenced by the substantial heterogeneity observed[20]. None of the results was significantly altered, indicating that our results were robust

Publication Bias

To investigate potential publication bias in rs2200733, we examined the contour-enhanced funnel plot of the included studies in assessing change in log OR of AF recurrence [Figure 4]. The vertical axis represents study size (standard error) while the horizontal axis represents effect size (log odds ratio). From this plot, distribution of studies on both sides of the mean is asymmetrical. The Egger's test was not significant in rs2200733 (p = 0.060), and rs10033464 (p = 0.279) which confirmed no small study bias. However, small study bias was observed in rs13376333 (p = 0.007).

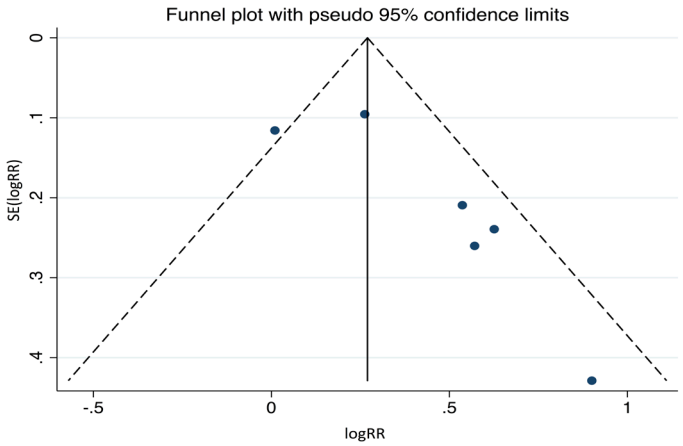

Figure 4: **Funnel plot of recurrence of atrial fibrillation after catheter ablation and variant rs2200733 on 4q25. Circles represent observed published studies.**

Discussion

Our analysis found that the variant rs2200733 on 4q25 significantly associated with AF recurrence after catheter ablation (RR 1.45 [95% CI 1.15-1.83], p = 0.002), whereas no association was found among variants rs10033464 from 4q25, rs13376333 from 1q21, and rs7193343 and rs2106261 from 16q22. We did not analyze SNPs that presented only in single publication; among these non-analyzed SNPs, only rs1906617 from 4q25 increased a risk of AF recurrence, with a relative risk of 2.44, in the report by Miyazaki et al[19].

Genetics of AF has been emerging in recent years. Researchers from Framingham Heart Study initially found that parental history could double the risk of AF in offspring[21]. Variants in genes encoding cardiac potassium and sodium channel complexes and gap junction proteins were found to cause a familial form of AF[22]. In contrast to these high-penetrant rare variants, the low-penetrant polymorphisms found via GWAS tend to interact with environment and result in the more common non-familial phenotype. The variant rs2200733, not surprisingly, has been studied the most and strongly associated with AF occurrence, with an odd ratio of 1.89, according to the recent meta-analysis of 10,546 subjects with AF[23]. Presence of rs2200733

also implicated in cardioembolic stroke[24] and postoperative AF after coronary artery bypass graft surgery[25,26]. Our study is the first meta-analysis to evaluate this variant, along with others, and its risk of AF recurrence after catheter ablation. We believe that only a variant with strong molecular signals (e.g. rs2200733) will affect AF recurrence after catheter ablation, whereas the others (e.g. those in 1q21 and 16q22 loci) will not[13]. Nonetheless, the precise mechanism how they affect AF recurrence is yet to be determined.

The paired-like homeodomain transcription factor 2 (*PITX2*) gene is located closest to variant rs2200733, and the hypotheses underlying the AF susceptibility of 4q25 loci lies, probably, in this gene[4]. *PITX2* expressed in left atrium of mice and humans, and both over- and underexpression of the gene are associated with AF[27]. In mice, its haploinsufficiency resulted in ectopic automaticity in the left atrium and thus predisposed to atrial arrhythmia[28]. Moreover, *PITX2* promotes cardiac left-right asymmetry and development of pulmonary vein sleeves, which are isolated during AF ablation procedure–referred to pulmonary vein isolation[13,27,29]. No known gene was identified in the linkage disequilibrium block containing variant rs2200733[4]; thus, the variants at this location may indirectly be a marker of unidentified mechanisms independent of *PITX2*, or, on the other hand, may have an unknown direct relation with the gene[10].

Chen et al. have additionally demonstrated that, when compared to AF patients with wild-type allele, carriers of rs2200733 had larger superior pulmonary veins, which are more common AF-driving ectopic loci than the inferior pulmonary veins[9]. This might explain the propensity of AF recurrence, and shows how genetic data promisingly suggests a different ablation method in this patient population.

Among the early researchers who showed how the variant potentially implicated clinical practice on AF recurrence, Shoemaker et al. found that the presence of rs2200733 risk allele in patients having left atrial diameter larger than 5cm–which usually used as a cutoff for AF ablation eligibility–increased the risk of AF recurrence from 40% to 87.5% [30]. In the multivariate analysis, the risk allele predicted a 24% shorter recurrence-free time with a survival time ratio of 0.76 (CI 0.6-0.95)[30], this is crucial since patients with earlier recurrences tend to have less sporadic episodes and respond poorer to anti-arrhythmic drugs and repeat ablation[31]. We know that established risk factors of AF recurrence after catheter ablation include hypertension, obesity, sleep-disordered breathing, metabolic syndrome, left atrial dilatation, and longstanding persistent AF[3,32], and the decision to pursue ablation procedure depends on type of AF, left atrial size, symptom severity, systolic dysfunction, estimated risk of complications, and patient preference[2]. Thus, adding rs2200733 to the list may help physicians predict outcomes and risk stratify patients before performing the procedure–reducing patients and physicians' frustration and creating the most efficacious strategy for this invasive, high-cost, success-limited procedure. Accordingly, a large-scale study exploring its accuracy and cost-effectiveness, especially with the rapidly decreasing cost of genomic sequencing, are required.

Limitations

Our study is not without limitations. Different study populations and designs were included and thus might introduce potential sources of heterogeneity. We also did not demonstrate independent predictors of recurrence in AF such as age, sex, diabetes, and hypertension because of insufficient data from included studies to perform meta-analysis in these subgroups. Theses factors might introduce potential sources of heterogeneity as well. Some heterogeneity exists among studies. Nonetheless, we used sensitivity analysis methods in the random-effects model and found no difference of the imputed risk ratio and its 95% confidence interval.

Conclusion

We systematically reviewed variants from chromosome loci 4q25, 1q21, and 16q22, and demonstrated that only rs2200733 from 4q25 confers an increased risk of AF recurrence after catheter ablation. The most plausible mechanism is related to the closest gene, *PITX2*; however, its molecular pathophysiology is yet elusive and more studies are warranted to explore how these variants impact the clinical course and prognosis of AF. Incorporation of this variant as a pre-procedural risk factor to predict an outcome of catheter ablation is an attractive paradigm in personalized AF management in the near future.

Disclosures

None.

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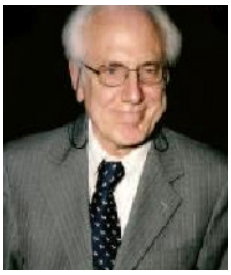

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