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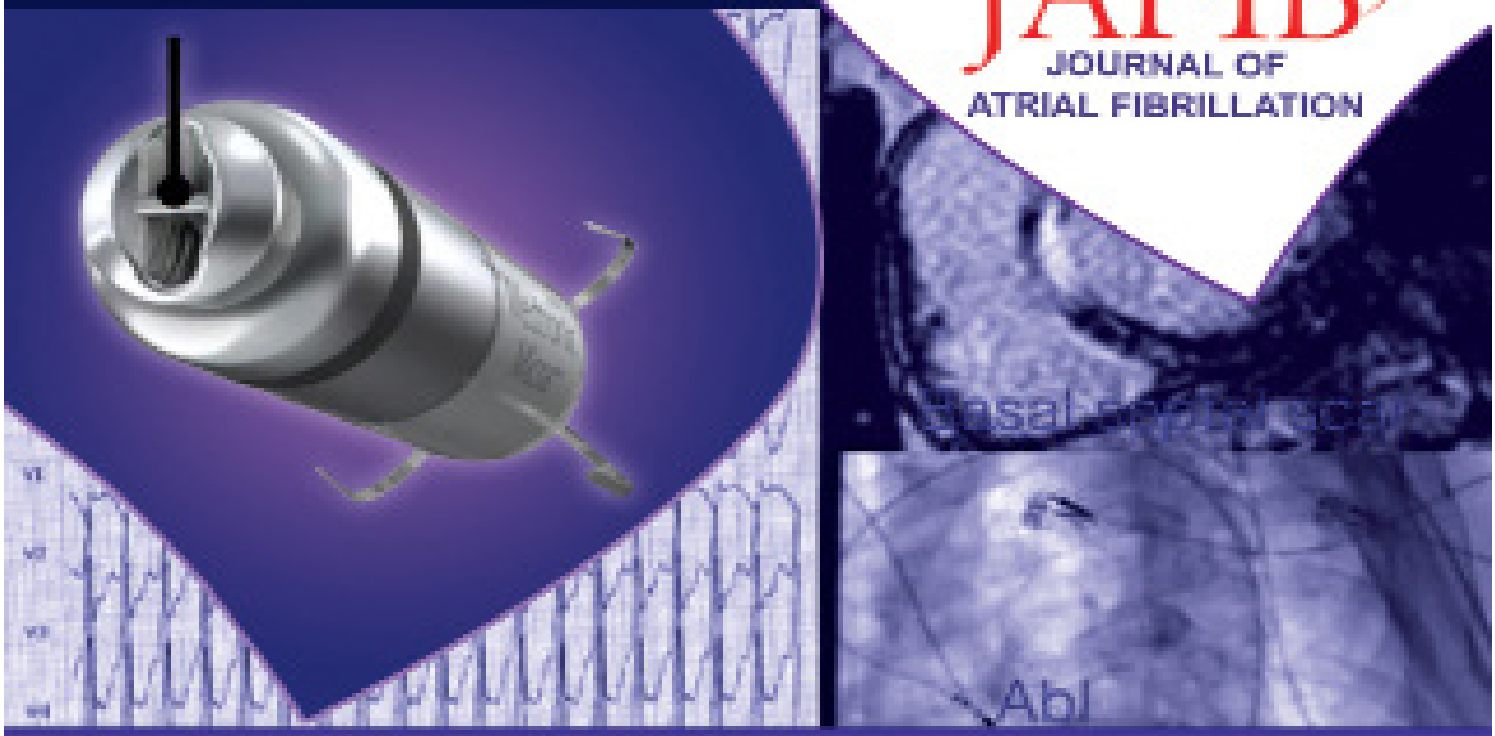

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Advances in Electrophysiology

Dear Friends and Colleagues from Around the World

Hope this edition of JAFIB finds you in good health and better spirits. Congratulations to Jeremy Ruskin and team on yet another successfully organized Atrial Fibrillation Symposium in Orlando. The focus this year seems to be on stroke prevention, left atrial appendage and therapies for non-paroxysmal AF. The interim results of REAFFIRM trial have been presented. It was not surprising to see that there was no difference between the FIRM ablation group compared to the control which did very well compared to any other historical groups in similar persistent AF studies. The lesion set used in these patients is not properly controlled and is mostly left to the operator discretion. Results from the long-term will be interesting to watch even though it will come at significant costs.

In this issue of the journal we have excellent work presented by authors from all over the world. Agner etal's manuscript on the impact of rhythm on the global left ventricular systolic function using strain analysis is very interesting and perhaps could play a very important role in understanding the maladies of AF. Yarlagadda etal show the differences in the QT interval prolongation and side effect profiles of Dofetilide and Sotalol in their retrospective analysis. Connection between reduced p-wave amplitude in coronary artery disease patients and AF. There are several educational case reports that are great teaching material.

We would like to invite you to the 2018 version of the International Symposium on Left Atrial Appendage (ISLAA) in Long Beach on February 9th and 10th. For those of you who are actively involved in the LAA space and or those who are thinking of starting a program this will be a fantastic opportunity worth attending. A great mixture of didactic sessions, live cases and robust discussions with the experts will be worth your while.

We once again thank you for your unwavering support of the journal and your eternal belief in the humanity and kindness of the world. May the New Year help promote sanity, humanity and kindness succeed in combating insanity, poverty and disease?

Best warm regards

Dhanunjaya (DJ)Lakkireddy
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Safety and Efficacy of Inpatient Initiation of Dofetilide Versus Sotalol for Atrial Fibrillation

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Abstract

Background: We sought to investigate and compare the safety and efficacy of two commonly used antiarrhythmic drugs, Dofetilide (DF) and Sotalol (SL), during inpatient drug initiation in patients with symptomatic atrial fibrillation (AF).

Methods: We performed a single center retrospective study of consecutive patients, admitted for initiation of either DF or SL, for AF between 2012 and 2015. Rates of successful cardioversion, QT interval prolongation, adverse events and drug discontinuations were calculated and compared. A two-tailed p value less than 0.05 was considered statistically significant.

Results: Of 378 patients, 298 (78.8%) received DF and 80 (21.2%) SL, mean age was 64 ± 11 years, 90% were Caucasians and 66% were males. Among the patients who remained in AF upon admission (DF: 215/298 (72%) vs. SL: 48/80 (60%)), no significant differences were noted in pharmacological cardioversion rates (DF: 125/215(58%) vs. SL: 30/48 (62.5%); p = 0.58). Baseline QTc was similar between the groups, with higher dose dependent QTc prolongation with DF (472.25± 31.3 vs. 458± 27.03; p = 0.008). There were no significant differences in the rates of adverse events such as bradycardia (7.4% vs. 11.3%; p = 0.26), Torsades de pointes (1.3% vs. 1.2%; p = 1.00), and drug discontinuation (9.0% vs. 5.0%; p = 0.47) between the two groups.

Conclusions: In our large, single center experience, we found that the use of Dofetilide resulted in significantly higher QTc without differences in the rates of successful cardioversion, adverse events, and drug intolerance when compared to Sotalol in AF patients.

Introduction

Advances in catheter ablation have revolutionized the management of symptomatic atrial fibrillation (AF). Despite current progress in ablation strategies, its invasive nature and risk of rare but life-threatening complications limits its use to patients with drug refractory symptomatic AF. Antiarrhythmic drugs (AAD) are proven to be more effective than placebo in conversion and maintenance of normal sinus rhythm (NSR) in AF[1]. They also alleviate symptoms, facilitate electrical cardioversion and decrease the risk of recurrence of AF [2][4]. Class I AADs though effective, have high proarrhythmic potential in patients with structural heart disease [5],[6]. Amiodarone is the most effective AAD, but its use is limited by a myriad of non-cardiac side effects [7],[10]. Dofetilide (DF) and Sotalol (SL) on contrary have minimal non-cardiac side effects. DF, a class III antiarrhythmic agent, acts by blocking rapid component of delayed rectifier potassium current (IKr). It increases action potential duration due to delayed repolarization and prolongs QT interval because of prolongation of effective and functional refractory period of the His-Purkinje system and the ventricles. Sotalol on the other hand exhibits both class II and class III antiarrhythmic effects by non-selective beta blockade and blocking rapid component of delayed rectifier potassium channels respectively. It shows class II properties at relatively low doses (as low as 25mg/day) and class III effects at higher doses (>160mg/day).

In view of QT prolongation and proarrhythmogenic potential of Dofetilide 2014 ACC/AHA guidelines recommend inpatient drug initiation with close electrocardiographic monitoring [11]. Earlier recommendations for Sotalol loading favored inpatient initiation if risk factors for arrhythmias were present[2]. Newer guidelines however are not quite clear on this [11]. As a result of lack of data supporting the safety of outpatient initiation of Sotalol some experts prefer inpatient initiation with electrocardiographic monitoring.

Currently there is limited data directly comparing these two agents in AF populations. We sought to investigate the safety and efficacy of inpatient initiation of Dofetilide compared to Sotalol for symptomatic AF.

Key Words

Atrial fibrillation, Antiarrhythmic Drug, Normal Sinus Rhythm, QT interval Corrected for Heart Rate, Dofetilide, Sotalol.

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Methods

Study Population

We retrospectively screened consecutive patients with symptomatic AF who were admitted to our institution for initiation of Dofetilide or Sotalol for rhythm control from 01/2012 to 12/2015. Patients were included if they underwent initiation of oral formulation of either Dofetilide or Sotalol, had an electrocardiogram at baseline and 2-3 hours after each dose of AAD. Patients with cardiac implantable electronic device (CIED), prior bradyarrhythmias, prior ventricular arrhythmias requiring AAD, and atrial arrhythmias who failed either prior AAD or catheter ablation were excluded from the final analysis.

Dosing

Patients were dosed according to University of Kansas Medical Center protocol for inpatient initiation of Dofetilide and Sotalol. Patients CrCl and QTc (or QT interval if heart rate is <60 beats/minute) were checked ≤24 hours prior to first dose. If baseline QTc is >480 msec (>500 msec in patients with ventricular conduction abnormalities) drugs were contraindicated. If baseline QTc is between 440- 480 msec, physician was notified and medication was dispensed based on his/her discretion.

Dofetilide (Tikosyn®)

Patients with QTc <440 msec, CrCl > 60 mL/min were started on Dofetilide 500mcg BID. For patients with CrCl between 40 mL/min - 60 mL/min and 20 mL/min - 39 mL/min, initial Dofetilide dose was reduced to 250 mcg BID and 125 mcg BID respectively. If CrCl < 20 ml/min, Dofetilide was contraindicated. A 12 lead EKG was repeated 2-3 hrs after each dose. If QTc increases to more than 15% above baseline QTc or if the QTc is >500 msec (>550 msec in patients with ventricular conduction abnormalities), Dofetilide dose was reduced by 50%. If QTc is still excessively prolonged after one dose reduction, Dofetilide therapy was discontinued. Telemetry monitoring was continued for a minimum of three days (at least 5 doses) or 12 hours after conversion to normal sinus rhythm, whichever is longer.

Sotalol (Betapace®)

Patients with QTc <450, CrCl > 60 were started on Sotalol 80 mg twice daily. If the initial dose does not reduce frequency or relapse of AF and excessive QTc prolongation did not occur after 3 days, the dose was increased to 120 mg twice daily; may further increase to a maximum dose of 160 mg twice daily if response is inadequate and QTc prolongation is not excessive. If CrCl 40-59 ml/min dosing is changed to every 24hrs. If CrCl<40 ml/min, Sotalol is contraindicated. A 12 lead EKG was repeated 2-3 hrs after each dose. If the QTc increases to more than 15% above baseline or if the QTc is >500 msec (>550 msec in patients with ventricular conduction abnormalities), Sotalol dose was reduced to the next dosage down. Telemetry was continued for a minimum of three days (at least 5 doses).

Study Outcomes

The primary safety endpoints of the study include QTc Interval prolongation with each dose, rates of adverse events (Bradycardia, Sinus node arrest (SNA), High grade AV block (AVB), New onset premature ventricular contractions (PVCs), Nonsustained ventricular tachycardia (NSVT), Torsades de pointes (TdP), Ventricular fibrillation (VF)) and drug discontinuation during hospitalization.

Bradycardia was defined as ventricular rate less than 60 beats per minute (bpm) while awake, SNA was defined as sinus pauses of 2 seconds or more while awake, High grade AVB was defined as either Mobitz type 2 second degree AVB or third degree AVB (complete heart block). Indication for drug discontinuation was left to discretion of the treating physician and is usually due to QTc interval exceeding 500 milliseconds despite dosage adjustments, significant bradyarrhythmias either resulting in symptoms or requiring pacemaker, or new onset ventricular arrhythmias as detailed above.

The primary efficacy end point of the study was rate of chemical cardioversion, defined as conversion of underlying AF to NSR after at least two doses of AAD.

Data measurements

Baseline demographics; medical history; medication use, renal function, baseline potassium, magnesium levels, left ventricle ejection fraction (LVEF) and left atrial size on 2D transthoracic echocardiography were obtained from the electronic medical records. Data on QT interval prolongation, adverse events as detailed above, and successful chemical cardioversion were obtained from the serial electrocardiograms performed during hospitalization.

Statistical Analysis

Continuous variables are expressed as mean ±standard deviation (SD) if variables are normally distributed, and median (interquartile range) when deviations from normality were present. Categorical variables are expressed as counts and percentages. Categorical variables were compared between the groups using chi-squared test or fisher's exact test. Continuous variables were compared using independent sample t test. A two tailed p value less than 0.05 was considered statistically significant. Statistical analysis was performed using IBM SPSS Statistics version 23.0 (IBM, Armonk, New York).

Results

Out of 378 patients, 298 (78.8%) received Dofetilide, and 80 (21.2%) received Sotalol. The cohort had mean age of 64 ± 11 years; 90% were Caucasians; 66% were males; 61.6% had paroxysmal AF and 41.1% were on AV nodal blockers for rate control. Patients who received Sotalol had higher proportion of patients with coronary artery disease (DF vs. SL: 31.2% vs. 51.2%; p = 0.001), ACE inhibitor/ARB use (DF vs. SL: 55.5% vs. 70%; p = 0.01) and NSR up on admission (DF vs. SL: 27.8% vs. 40%; p = 0.03). No other significant differences were observed in the baseline characteristics between the two groups [Table 1].

Dosing

Of the 298 patients who received DF, 200 were on a stable dose during admission. Of these, 158 patients received 500mcg BID, 40 received 250mcg BID and 2 received 125mcg BID. Of the 80 patients on Sotalol, 49 were on a stable dose. Of these 30 patients received 120mg BID, 15 received 80mg BID and 4 received 160mg BID.

Safety

Mean baseline QTc intervals were similar between the groups (DF vs. SL: 448.9 ±33.2 vs. 444± 42.6 msec; p = 0.35). Dose dependent QTc prolongation was noted in both the groups but was significantly higher in Dofetilide compared to Sotalol with each dose and at discharge (DF vs. SL: 472.25± 31.3 vs. 458± 27.03 msec; p = 0.008) ([Table 2], [Figure 1]).

Despite higher QTc prolongation with Dofetilide, there were no statistically significant differences, in the rates of adverse events between the groups during the hospitalization (DF vs. SL: bradycardia – 7.4% vs. 11.3%; p = 0.26, NSVT - 2.3% vs. 1.25%; p =

1.0, TdP - 1.3% vs. 1.2%; p = 1.00) [Table 3].

Overall 28/378 (7.4%) patients had drug discontinuation prior to discharge because of various side effects with most common reason being QT interval exceeding 500 msec. There was no statistically significant difference in the drug discontinuation rates between the groups, (DF vs. SL: 24/298 (9.0%) vs. 4/80 (5.0%); p = 0.47).

Table 1: Baseline Characteristics between Dofetilide and Sotalol groups (n = 378)

Characteristics Demographics	Dofetilide (n = 298)	Sotalol (n = 80)	p value
Demographics			
Age (years)	64 ± 10.3	64 ± 11.6	0.46
Gender: Male (%)	205 (68.8%)	46 (57.5%)	0.06
Race: Caucasian (%)	270 (90.6%)	71 (88.7%)	0.14
Body Mass Index (BMI)	33 ± 7.4	33 ± 7.8	0.90
Co morbidities			
Paroxysmal AF	183 (61.4%)	50 (62.5%)	0.22
Hypertension	252 (84.5%)	67 (83.7%)	1.00
Diabetes mellitus	63 (21.1%)	20 (25%)	0.45
Hyperlipidemia	218 (73.1%)	66 (82.5%)	0.08
Coronary artery disease	93 (31.2%)	41 (51.2%)	0.001
Stroke/Transientischemic attack	25 (8.4%)	10 (12.5%)	0.10
Medication			
Beta Blockers	89 (29.0%)	28 (35.0%)	0.57
Calcium Channel Blocker	165 (55.5%)	56 (70.0%)	0.01
ACE Inhibitor/ARB	89 (29.0%)	28 (35.0%)	0.57
Labs			
Creatinine Clearance (ml/min)	105.2 ± 41.2	102.3 ± 37.4	0.58
Baseline Potassium level (mEq/L)	4.12 ± 0.41	4.17 ± 0.36	0.90
Baseline Magnesium level (mEq/L	2.11 ± 1.1	2.0 ± 0.18	0.38
EKG/Echo			
Sinus rhythm on arrival	83 (27.8%)	32 (40%)	0.03
Baseline QTc (msec)	448.9 ± 33.2	444 ± 42.6	0.35
Left Atrial Size (cm)	4.53 ± 0.8	5.45 ± 0.60	5.45 ± 0.60
Left ventricle Ejection Fraction (%)	51.7 ± 12	52.5 ± 12.6	0.65

Data were represented as mean ± standard deviation or counts (percentage)

Table 2: Safety outcomes between Dofetilide and Sotalol groups - QTc Intervals (n = 378)

QTc Measurement (msec)	Dofetilide (n = 298)	Sotalol (n=80)	p value
Baseline QTc	448.9 ± 33.2	444 ± 42.6	0.35
QTc Post 1st dose	464.5 ± 43.1	453 ± 32.6	0.03
QTc Post 2nd dose	**476.7 ± 37.2**	**476.7 ± 37.2**	**0.02**
QTc Post 3rd dose	474.2 ± 34.8	463.5 ± 34	0.02
QTc Post 4th dose	473.5 ± 32.5	450 ± 64.8	0.01
QTc Post 5th dose	472.25 ± 31.3	458 ± 27.03	0.008

Data were represented as mean ± standard deviation

Efficacy

In terms of efficacy, among patients who remained in AF upon admission (215/298 (72%) - Dofetilide group; 48/80 (60%) - Sotalol group), no significant differences were noted in pharmacological cardioversion rates between the groups (Dofetilide - 125/215(58%) vs. Sotalol - 30/48 (62.5%); p = 0.58, [Table 4]). Patients who failed pharmacological cardioversion underwent electrical cardioversion subsequently.

Table 3: Safety outcomes between Dofetilide and Sotalol groups - Adverse events (n = 378)

Adverse events	Dofetilide (n = 298)	Sotalol (n = 80)	p value
Bradyarrhythmias			
Bradycardia (HR < 60)	22 (7.4%)	9 (11.3%)	0.26
Sinus pause > 2 secs	0 (0%)	0 (0%)	-
High grade AVB	6 (2.0%)	2 (2.5%)	0.67
Ventricular arrhythmias			
New onset PVCs	0 (0%))	0 (0%)	-
Non Sustained VT	7 (2.3%)	1 (1.3%)	1.00
Torsades de pointes (TdP)	4 (1.3%)	1 (1.2%)	1.00
Ventricular fibrillation (VF)	0 (0%)	0 (0%)	-
Drug Discontinuation	24 (8.8%)	4 (5%)	0.47

Data were represented as counts (percentage)

Table 4: Efficacy outcomes between Dofetilide and Sotalol groups (n = 263)

Successful Cardioversion	Dofetilide (n = 215)	Sotalol (n = 48)	p value
Pharmacological cardioversion (%)	125 (58%)	30 (62.5%)	0.589
Requiring DC cardioversion (%)	90 (42%)	18 (37.5%)	0.578

Data were represented as counts (percentage)

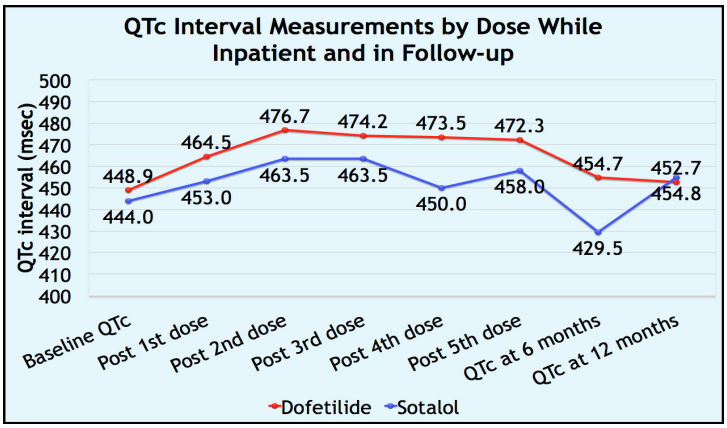

Figure 1: Dose dependent QTc prolongation associated with Dofetilide and Sotalol (n = 378).

Discussions

Main findings

We studied the safety and efficacy of inpatient initiation of Dofetilide (DF) compared to Sotalol (SL) in patients with symptomatic AF. Among the patients who remained in AF upon admission, no significant differences were noted in pharmacological cardioversion rates between the two drugs. Baseline QTc was similar between the groups, with higher dose dependent QTc prolongation with DF. There were no significant differences in the rates of adverse events such as bradycardia, Torsades de pointes, and drug discontinuation between the groups.

All AADs are proarrhythmogenic. The most severe pro-arrhythmia comes from drugs that prolong action potential duration. Both

Dofetilide and Sotalol by the virtue of their potassium current (IKr) blockade, cause prolongation of action potential duration and effective refractory period, resulting in concentration dependent QT interval prolongation in order to be effective. This is suspected to be high with Sotalol compared to Dofetilide because of its inherent beta blockade properties resulting in simultaneous bradycardia while QT prolongation. In the presence of appropriate substrate (hypokalemia, hypomagnesaemia, bradycardia or genetic predisposition) this QT prolongation may predispose to torsades de pointes. The risk of life threatening ventricular arrhythmias warrants inpatient initiation of both Dofetilide and Sotalol with electrocardiographic monitoring.

At the outset, current practice patterns at our institution reflected a predominant use of Dofetilide (78.8%) over Sotalol (21.2%). In part, this is because of safety data supporting the use of DF in chronic heart failure (CHF). Moreover, In DIAMOND sub study, Dofetilide was found to improve survival in patients with AF and LV dysfunction when sinus rhythm was restored and maintained [12]. Safety and efficacy of Sotalol has not been systematically evaluated in CHF patients, but its use has been associated with a reduction in the risk of death and shocks in patients with implantable cardioverter defibrillators (ICDs), many of whom have LV systolic dysfunction [13].

In our study, 70 %(215) of patients in the Dofetilide group and 60 %(48) in the Sotalol group had AF on admission. Of these patients, there was no statistically significant difference in the pharmacological conversion rates between the two groups (Dofetilide- 125/215(58%) vs. Sotalol - 30/48 (62.5%)). Our study contradicts earlier reports which suggest Sotalol is not effective for chemical cardioversion and thus not indicated for this purpose[14]. This discrepancy may be because of the large proportion (approximately 60%) of our study population with paroxysmal AF. There is a possibility that these patients might have spontaneously converted to sinus rhythm.

Our primary safety endpoint was occurrence of adverse events like QT prolongation, bradyarrhythmias and tachyarrhythmias. We did not observe significant differences in the rates of overall adverse events or bradyarrhythmias/tachyarrhythmias individually between the groups. Dosage specific outcome stratification was not relevant as dosages were selected based on calculated creatinine clearance. Serum drug levels would have been the same between groups if adjusted for renal function. In a similar study by Agusala et al, there was no difference in overall adverse events between Sotalol and Dofetilide groups however, DF group had more QT prolongation and ventricular arrhythmias. They also reported higher baseline QTc as an independent predictor of adverse events in patients treated with Dofetilide[15].

We reported dose dependent QTc prolongation in both groups but was significantly higher in Dofetilide compared to Sotalol. Despite Dofetilide being associated with higher QTc prolongation it did not translate into an increase in risk of ventricular arrhythmias including TdP. This observation could have been because of the way both medications are dosed. Dofetilide is usually started at a higher dose and titrated down if patient develops adverse effects. In case of Sotalol, patients are started at a lower dose and then titrated up if tolerating the dose well. Moreover, Sotalol's class III effects which causes the QT prolongation is only seen with doses ≥160mg.

Future directions

As these two drugs clearly cause dose dependent QTc prolongation, in-hospital monitoring is required to avoid rare but life-threatening arrhythmias. This incurs a high cost burden of nearly 3,400 $ per patient and the major brunt of this cost is due to hospital room and overhead costs, while the pharmacy costs account for only $200-$230 per patient[16]. Attempts to identify low risk population that can safely undergo outpatient initiation of AAD were unsuccessful so far [15]. Unlike Dofetilide, Sotalol is available in both oral and intravenous formulation and the overall risk of torsades in patients treated with a single infusion of IV Sotalol is low compared with that of patients given chronic oral Sotalol therapy [17]. A consideration would be to use IV Sotalol loading followed by transition to PO medication thereby considerably reducing the length of hospitalization. The center for translational medicine at the University of Maryland, Baltimore, USA developed a dosing strategy for patients with postoperative AF based on body weight with 40 mg IV Sotalol infusion for 2 hours followed by 80 mg PO bid immediately after the infusion. With this strategy, the target dose was achieved in less than 6 hours vs. ~36 hours in standard oral dose (80 mg bid) [Figure 2]. Development of a standard intravenous to oral switch regimen for inpatient initiation of Sotalol for symptomatic AF, to reach target maintenance dose faster may cut down the cost associated with the Sotalol initiation and expedite discharge on a stable oral regimen.

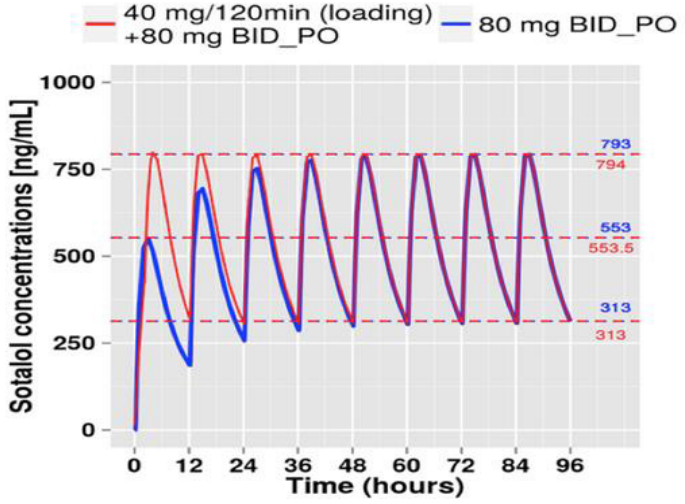

Figure 2: **Intravenous versus oral Sotalol loading for postoperative atrial fibrillation. Notice that the target dose was achieved in less than 6 hours with intravenous regimen compared with ~36 hours in standard oral regimen (80 mg po bid) (Courtesy: Center for translational medicine - University of Maryland Baltimore, USA.)**

Limitations

Our study presents the obvious limitations of a retrospective observational study. Predetermined selection criteria were not used prior to initiation of either Dofetilide or Sotalol thus leading to the possibility of selection bias. Specific drug titration and discontinuation parameters could not be enforced due to the retrospective nature of the study. Despite higher proportion of patients receiving Dofetilide at our institution, we did not notice any statistically significant differences in the safety and efficacy profiles of Dofetilide and Sotalol.

Conclusion:

In our large, single center experience, we did not observe significant differences in the safety or efficacy between inpatient initiations of Dofetilide and Sotalol in AF patients. The use of Dofetilide resulted in significantly higher QTc when compared to that of Sotalol however, it did not translate to a difference in pharmacological cardioversion rates, tolerance, or adverse events.

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Reduced P-wave Voltage in Lead I is Associated with Development of Atrial Fibrillation in Patients with Coronary Artery Disease

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Abstract

Background: Reduced P-wave voltage in lead 1 (PVL1) has been associated with atrial fibrillation (AF) recurrence.This study sought to determine the association between reduced PVL1 and AF in the NSTEMI population and the correlation between reduced PVL1 and interatrial block (IAB)/coronary artery disease (CAD).

Methods: Data were recorded for clinical, echocardiographic, angiographic, electrocardiographic and outcome variables. Patients were followed for a minimum of one year. Chi-square tests, independent samples t-tests and one-way ANOVA were used for the analysis, which was done using IBM SPSS.

Results: A total of 322 consecutive patients were included in the analysis. Patients with new-onset AF had a significantly lower PVL1 (0.085 ± 0.030mV vs. 0.103 ± 0.037mV; p=0.007). There was a significant difference in mean PVL1 between those with no IAB, partial IAB and advanced IAB (p = <0.001). Those with any type of IAB had a significantly lower mean PVL1 than those without (0.094 ± 0.032 mV vs. 0.106 ± 0.038 mV; p=0.005). Patients who developed AF had a significantly longer P-wave duration (126 ± 20ms vs. 119 ± 17ms; p=0.022). Patients with IAB were more likely to develop new-onset AF (15.4% versus 7.5%, p=0.025). There were significant co-linear associations between reduced PVL1 and IAB (p=0.005); reduced PVL1 and diffuse CAD (p=0.031) and IAB and diffuse CAD (p=0.022).

Conclusions: Reduced PVL1 and IAB are associated with new-onset AF in patients with NSTEMI. Reduced PVL1 and IAB are correlated with each other indicating a possible common underlying mechanism. Both parameters are associated with CAD.

Introduction

Reduced P-wave amplitude in lead I (PVL1) has recently been shown to be associated with recurrence of atrial fibrillation (AF) [1]. In this study, conduction was shown to be displaced in the Bachmann region in patients with lower P-wave voltages using left atrial voltage and activation maps. A possible mechanism for the higher rates of AF recurrence in patients with reduced PVL1 was proposed to be abnormal interatrial conduction along the Bachmann region, the same mechanism as believed to underlie interatrial block (IAB).[1] Interatrial block has previously been shown to be associated with atrial fibrillation in multiple cardiac populations. [2-13] The P-wave represents atrial depolarization and as such is an indirect measure of atrial conduction.[14] With normal anatomy, in sinus rhythm, the P-wave initiates at the sino-atrial node and travels inferiorly through the right atrium via the intra-atrial conduction pathways and most commonly crosses the interatrial septum superiorly via the Bachmann region, a broad muscular set of fibers.[15-18] Partial interatrial block (IAB) results from a delay of conduction on this interatrial pathway at the Bachmann region. When this pathway is completely blocked, the right atrium is activated cranio-caudally; however, the left atrium is depolarized from the level of the coronary sinus to the posterior and superior region (retrograde activation) producing the classic biphasic P-wave of advanced IAB.[19] IAB is clinically important due to its correlation with the development or recurrence of AF in various cardiac populations.[2-13] While the exact pathology underlying the conduction abnormalities seen in IAB have not yet fully been determined it has been hypothesized that electrical remodeling and fibrotic atrial remodeling due to reduction of the blood supply to the Bachmann region may play a key role.[20-23] In support of this, IAB has been shown to be associated with diffuse coronary artery disease (CAD).[11] This study sought to determine the association of reduced PVL1 with development of AF in a population of patients with NSTEMI and its correlation with IAB and diffuse CAD.

Key Words

Interatrial Block, Atrial Fibrillation, P-Wave Voltage, NSTEMI..

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Material and Methods

Patient Selection

Electronic records of a consecutive cohort of patients at Kingston

General Hospital who had presented with a NSTEMI between November 2013 and August 2015 and had an ECG completed in-hospital as part of their work-up were retrospectively reviewed. Exclusion criteria were (i) prior history of AF (ii) lack of at least one significant coronary artery lesion (>70% occlusion) (iii) any STEMI within 90 days prior to the NSTEMI, (iv) significant valvular disease or cardiomyopathy and (v) any device pacing the atrium (vi) active hyperthyroidism.

Electrocardiogram, echocardiogram and angiogram parameters

ECGs were scanned at 300 dpi and blindly analyzed using ICONICO semi-automatic calipers. PVL1 was measured from the peak of the P-wave to the isoelectric line of the TP interval (Figure 1a). This method has been previously described and validated with high levels of agreement in both interobserver and intraobserver

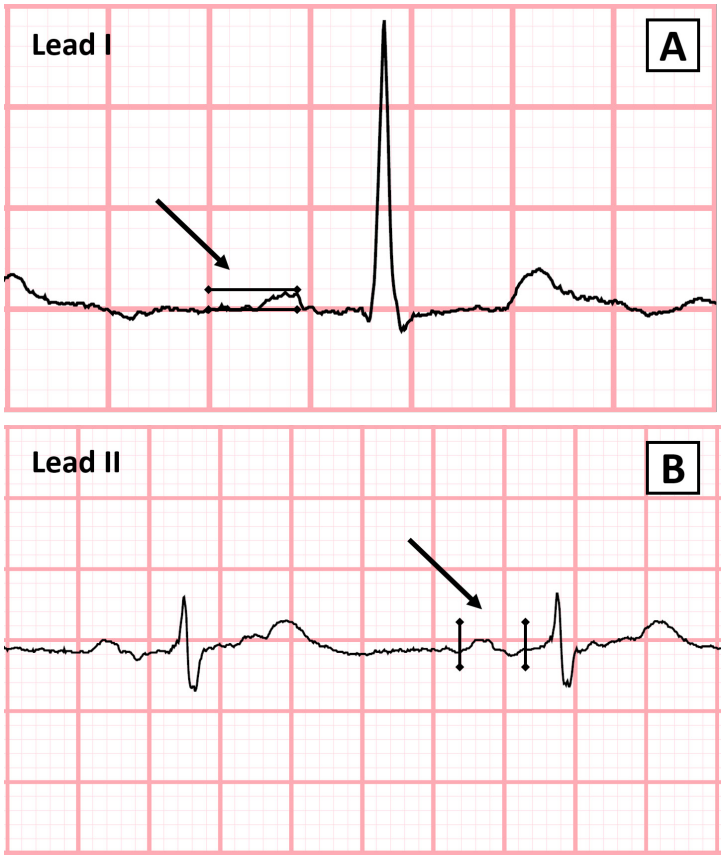

Figure 1: Method for the Measurement of P-Wave Duration and Amplitude

variability.[1],[24] P-wave onset was defined as the first upward or downward deflection from the isoelectric baseline and the P-wave offset as the return of the waveform to the baseline (Figure 1b). P-wave duration measurement has been previously described and validated.[25] Partial IAB was defined as a P-wave ≥120ms while advanced IAB was defined as a P-wave ≥120ms with biphasic (±) morphology in the inferior leads (II, III and aVF) according to the most recent consensus definition.[19] Reduced PVL1 was defined as a P-wave voltage in lead I less than 0.10 mV. Echocardiographic and angiographic data were taken from clinical reports. Atrial fibrillation was evaluated through review of medical records, EGG's and holter monitors. AF ≥ 6 minutes' duration was considered as outcome[26].

Statistical Methods

Data were collected in Excel and imported into IBM SPSS (version 24.0 for Windows) for statistical analysis. Data were initially described using means and standard deviations for continuous data, and frequencies and percentages for categorical data. This was followed by a univariate analysis to assess the association of the collected data with the outcome, using one-way ANOVA and independent sample t-tests for the continuous data and chi-square tests (Pearson or Fisher's Exact as appropriate) for the categorical data.

Results

Population Demographics

A total of 322 consecutive patients were included in the analysis. The population was 72.3% male, the mean age was 65.4 ± 11.9 years, the mean ejection fraction was 55.2 ± 12.7% and the mean left atrial diameter was 38.7 ± 6.0mm. Population characteristics are presented in [Table 1]. The prevalence of PVL1 less than 0.10 mV (reduced PVL1) was 50.3%, PVL1 between 0.10 and 0.20 mV was 48.8% and PVL1 > 0.20 mV was 0.9%. The prevalence of partial IAB was 31.7% and the prevalence of advanced IAB was 6.5%. The incidence of new onset AF within one year was 10.6%. The population was normally distributed in terms of P-wave voltage and duration.

Associations with Atrial Fibrillation

Participants who developed new-onset AF within one year had a significantly lower PVL1 (0.085 ± 0.030mV vs. 0.103 ± 0.037mV;

Table 1: Population characteristics.

Clinical Variable	Value (n = 322)
Age (years) ± SD	65.4 ± 11.9
Male sex	233 (72.3%)
BMI (kg/m2)	29.8 ± 6.6
Partial interatrial block	102 (31.9%)
Advanced interatrial block	21 (6.5%)
Prior smoker	204 (63.4%)
Hypertension	232 (72.0%)
Dyslipidemia	182 (56.5%)
Diabetes	104 (32.3%)
Prior transient ischemia attack or stroke	35 (10.9%)
Obstructive sleep apnea	37 (11.4%)
Pulmonary disease	49 (15.2%)
Prior known coronary artery disease	118 (36.6%)
Congestive heart failure	15 (4.7%)
Previous cardiac surgery	43 (13.4%)
Prior atrial flutter	3 (1.0%)
Left ventricular ejection fraction (%)	55.2 ± 12.7
Body surface area (m2)	1.97 ± 0.22
Left atrial diameter (mm)	38.7 ± 6.0
Left atrial volume indexed to BSA (ml/m2)	31.6 ± 21.1
Right atrial volume indexed to BSA (ml/m2)	22.6 ± 15.6

p=0.007) and significantly longer P-wave duration (126 ± 20ms vs. 119 ± 17ms, p=0.022) than those who did not develop AF ([Table 2]). Multivariate logistic regression analysis was not completed due to substantial co-linearity between the three variables in the model (IAB, reduced PVL1 and diffuse CAD defined as the presence of two or more significant coronary artery lesions in the same patient). There were significant co-linear associations between reduced PVL1 and IAB (p=0.005); reduced PVL1 and diffuse CAD (p=0.031) and IAB and diffuse CAD (p=0.022).

Correlation of P-Wave Voltage with P-Wave Duration

There was a significant difference of mean P-wave duration between PVL1 categories (<0.10mV, 0.10-0.20mV and >0.20mV) (p = 0.009) ([Table 3]). This difference favored increased P-wave duration with decreased PVL1 category. There was also a significant difference in the presence of advanced IAB between the PVL1 categories (p = 0.014) and in the prevalence of any IAB (p = 0.035) ([Table 4]).

Table 2: Difference in IAB Categories between P-Wave Voltage Categories

	Any IAB (either partial or advanced)		
	Absent (n = 199)	Present (n = 123)	P-Value
P-Wave Voltage (mV)	0.106 ± 0.038	0.094 ± 0.032	0.005
	Advanced IAB		
	Absent (n =301)	Present (n = 21)	
P-Wave Voltage (mV)	0.103 ± 0.362	0.074 ± 0.029	<0.001
	New Onset Atrial Fibrillation		
	Absent (n =288)	Present (n = 34)	
Mean P-Wave Voltage (mV)	**0.103 ± 0.037**	**0.085 ± 0.030**	**0.007**
Mean P-Wave duration (ms)	**119 ± 17**	**126 ± 20**	**0.022**

Correlation of IAB Category with P-Wave Voltage

There was a significant difference of mean PVL1 between those with no IAB, partial IAB and advanced IAB (p = <0.001) ([Table 3]). This difference favored decreased PVL1 with increased severity of IAB category. Patients who had advanced IAB had a significantly lower mean PVL1 than those without advanced IAB (0.074 ± 0.029 mV vs. 0.103 ± 0.362 mV; p=<0.001). Patients who had any type of IAB had a significantly lower mean PVL1 than those without IAB (0.094 ± 0.032 mV vs. 0.106 ± 0.038 mV; p=0.005) ([Table 2]).

Table 3: Difference in P-Wave Voltage and Duration by IAB and Voltages Categories

Inter Atrial Block Category	Mean P-wave Voltage (mV)	P-Value
No interatrial block	0.106 ± 0.038	
Partial interatrial block	0.098 ± 0.031	<0.001
Advanced interatrial block	0.074 ± 0.029	
Voltage Category	Mean P-wave Duration (ms)	**P-Value**
< 0.10 mV	122.1 ± 18.1	
0.10 - 0.20 mV	117.0 ± 16.0	0.009
> 0.20 mV	105.0 ± 2.6	

Table 4: Method for the Measurement of P-Wave Duration and Amplitude

	Any IAB (either partial or dvanced)		
P-Wave Voltage	Absent (n = 199)	Present (n = 123)	P-Value
<0.10 mV	90 (45.2%)	72 (58.5%)	
0.10 - 0.20 mV	106 (53.3%)	51 (41.5%)	**0.035**
>0.20 mV	**3 (1.5%)**	0 (0.0%)	
	Advanced IAB		
	Absent (n = 301)	Present (n = 21)	
<0.10 mV	145 (48.2%)	17 (81.0%)	
0.10 - 0.20 mV	**153 (50.8%)**	**4 (19.0%)**	**0.014**
>0.20 mV	**3 (1.0%)**	**0 (0.0%)**	

Discussion

Reduced PVL1 was found to be significantly associated with the development of new-onset AF in this population. In addition, reduced PVL1and IAB were found to be significantly correlated with each other. It is plausible that reduced PVL1 and IAB may be associated with the same pathological process leading to increased P-wave duration and reduced voltage, namely atrial fibrosis. Park et al. have recently demonstrated a significant correlation between reduced PVL1 and displaced conduction in the Bachmann region using left atrial voltage and activation maps.[1] Atrial fibrosis delays cardiac electrical conduction and reduces voltage, phenomena which have been well described previously.[27-31] Since the P-wave voltage depends on the direction of electrical propagation relative to the axis of the lead being measured and the myocardial mass and intervening substrates; it has been proposed that reduced P-wave voltage may be a result of an altered atrial conduction pattern and decreased myocardial mass due to atrial fibrotic scarring and increased degree of electro-anatomical remodeling.[1] It has recently been shown that diffuse CAD is associated with IAB and development of AF in the NSTEMI population.[11] In this current study, both reduced PVL1 and IAB are also significantly correlated with diffuse CAD. Therefore it is possible that the mechanism underlying both decreased PVL1 and IAB is fibrosis of the atria, particularly in the Bachmann region. [32],[33].

Limitations

This study was retrospective in nature and as such may present inherent bias. AF was determined by clinical examination, ECG and Holter monitor reports; thus silent AF episodes may not have been recorded.

Conclusions

Reduced PVL1 is associated with new-onset AF in the NSTEMI population. In addition, PVL1 and IAB are significantly correlated with each other and with diffuse CAD. While the exact mechanism responsible for each have yet to be worked out, it is possible that the underlying cause could stem from fibrosis of the atria

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Surgical Epicardial left Atrial Appendage closure:A True Alternative

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Abstract

Background: Left atrial appendage closure was originally described by Madden in 1949 who was the first to perform appendix amputation.

Background

Left atrial appendage closure was originally described by Madden in 1949 who was the first to perform appendix amputation [1]. This was a very invasive procedure with poor outcome, but preformed for stroke prevention. Much later, it was James Cox whom described the Cox-Maze procedure, which included multiple incisions to create a maze like pathway for the electrical impulse to go undisturbed from the sinus node down to the atrio-ventricular node[2]. Since then cardiac surgeons stopped focusing on the left atrial appendage and went on about seemingly more important things. Only with the advent of catheter based options for stand alone left atrial appendage closure did the interest in the field light up again. It is the very impressive clinical outcomes from the protect AF trial which has declared left atrial appendage closure as mainstream therapy in modern cardiovascular care[3]. Not only does the current data suggest that left atrial appendage closure with a Watchman when compared to oral anticoagulation is non inferior, but moreover a long term survival benefit has been demonstrated. Not only clinical adoption has led large-scale enthusiasm about left atrial appendage closure options but also pressure from the financial markets driving Industry into this direction has created a huge interest[4]. As predicted by certain financial institutions market growth for left atrial appendage closure is exponential and it's going to have a huge financial impact in the coming years, with great opportunities not only in the field of medicine. It appears that the main focus of development is on the endocardial space. The epicardial approach are seen by the financial visionaries, and also clinicians, remains a limited. It is this part of the vision which we herein see as a problem. In many fields of medicine the interdisciplinary care has become the basis of any therapeutic decision. No cancer patient undergoes any form of therapy before being assessed by a interdisciplinary tumor board. And as such it is crucial that interdisciplinarity becomes the standard in the setting of left atrial appendage therapies. And more importantly an honest exchange excuded from financial and power interest must take place in favor of obtaining the best clinical outcoems possible.

Key Words

left atrial appendage, Stroke, Atrial fibrillation..

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The left atrial appendage – the surgeon's perspective

To mention the left atrial appendage is to acknowledge a highly variable anatomical structure. The left atrial appendage comes in many shapes and forms which can be described in many words[5]. Every different size and shape creates a true therapeutic challenge when addressing closure modalities especially when coming from the endocardial space but also epicardially. As basic consideration the fact that the ostium of the left atrial appendage is endo-atrial creates a problem in itself. Furthermore the ostium is an oval structure, a circle pulled in the length of the so-called Coumadin ridge. Therefore it becomes clear that catheter based device being round may present a certain challenge to accommodate this characteristic[6]. This will lead to the necessity of device over sizing with consequences on the surrounding structures.. In addition it appears that even though this area is supposed to be free of muscular trabeculations, which are hypothesized to be the source of the underlying trombo-embolic problem. It is the neck which presents itself to the cardiac surgeons as the target for left atrial appendage therapies. The neck is not difficult to address – for surgeons.

It is very important to understand the difference of concomitant left atrial appendage closure and stand-alone. As part of any open-heart surgery the necessity to address the left atrial appendage must be taken into account in all patients. It is crucial to asses every patient in this regard and to choose the means by which the left atrial appendage will be addressed. As for stand-alone left atrial appendage closure, this is an invasive procedure which must be applied to a very select patient population. This is not a mainstream procedure as it involves thoracic surgery skills and interdisciplinary patient selection[7]. Two last issues remain to be investigated, one is the role of electrical isolation of the left atrial appendage. It appears that with the epicardial approach complete electrical isolation can be achieved[8] in addition we believe that this might even be an explanation for the excellent results seen in the FAST[9] trial when comparing catheter ablation to thoracoscopic ablation with appendage amputation, i.e. silencing [7]. The precise neurhormonal implication of left atrial appendage clipping remain to be investigated.

1) Open surgical left atrial appendage therapies

Open surgical left atrial appendage treatment can become necessary in several settings. It appears that all patients undergoing open heart surgery could benefit if a certain risk profile is necessary of a left atrial appendage therapy. As such it is included in the most recent guidelines[10]. The available surgical strategies are few, as a perfect results are necessary to obtain durable surgical closure. Suture or staple ligation should be abandoned as these lead to reperfusion over time with very poor clinical outcome[11]. In the open chest setting resection of the left atrial appendage can still be performed easily, but provide a technical challenge as the stump left behind may lead to some oozing and bleeding problems, adding a certain degree of complexity to any surgical case. Therefore we use the newly available open chest Atriclip as this provides safe, effective and very durable left atrial appendage closure[12], [13].

2) Minimally invasive stand alone left atrial appendage therapies

As for minimally invasive options for LAA closure, the bulk of data comes from the thoracoscopic ablation literature. Up to very recently these patients were undergoing a video assisted thoacoscopic procedure with epicardial pulmonary vein isolation and left atrial appendage amputation by stapler. Only recently has the new Atriclip Pro2 become available. With this new epicardial clip it is possible to occlude the left atrial appendage at its base under trans esophageal echocardiographic guidance and obtain perfect closure. The procedure – which can be part of a thoracoscopic ablation procedure or done in a stand alone setting is done through three ports. A 12mm is used for the Atriclip. As such a 10mm port is inserted in the 4 or 5th Intercostal space on the midaxillary line in the left chest with CO2 insufflation with a 10mm straight camera. Two additional ports for two instruments are inserted in the 3rd and 5th intercostal space more anteriorly. The phrenic nerve is identified and an incision 1 cm below exposes the left atrial appendage. A sizing device 35 to 50mm is used to assess the dimensions of the base of the left atrial appendage. Then the Atriclip is applied to the base of the left atrial appendage. In meantime on trans oesagphageal echocardiography the closure is documented before final release. Only wen perfect closure is obtained is the clip deployed for good. It must however be noted that due to the epicardiac nature of the clip and the endocardial portion of the ostium a certain part of endocardial pouch can be observed. This varies in all patients and between 0.5cm to 1.5 cm.

"Surgical" patient selection

As the surgical procedure is more invasive than a catheter based intervention. The pro and con needs to be weighed in a very precise manner. For this a functioning heart team setting is necessary. We suggest following criteria for patients to undergo a thoracoscopic stand-alone left atrial appendage closure:

- Failure to treat by endovascular devices due to size or morphological considerations..
- Necessity to discontinue all anticoagulants or antiplatelet agents in the setting of fresh stroke, other bleeding problems

Contraindications:

- Presence of smoke and or chronic thrombi in the left atrial appendage
- previous heart or lung surgery .

Summary

Left atrial appendage closure should be done in a dedicated manner. Open heart surgery is a great opportunity to use foresight in dealing with this important issue. Only device enabled left atrial appendage closure or surgical resection should be done to achieve perfect results. As for stand-alone epicardial left atrial appendage clip closure, in limited series to date only, offers safe, durable and effective results over time. Interdisciplinary heart team offering a tailored approach based on patient and procedure selection for all approaches (endovascular vs. epicardial) offers a great opportunity to achieve perfect outcomes in this patient population.

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Left Atrial Strain Predicts Pro-Thrombotic State in Patients with non-valvular Atrial Fibrillation

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Abstract

Background and Purpose: Atrial fibrillation (AF) has a high prevalence in the population and it is responsible for up to the 25% of the strokes in elderly people. The aim of our study was to assess the correlations of left atrial (LA) functional parameter, global peak atrial longitudinal strain (PALS), derived from speckle tracking echocardiography (STE), with transesophageal echocardiography (TEE) findings in patients with persistent AF undergoing TEE before electrical cardioversion or ablation procedures.

Methods: 79 patients (58 males, 21 females) with persistent AF waiting for cardioversion were included in the study. The patients underwent conventional two-dimensional (2D) and 2D speckle tracking echocardiogram. PALS were measured in all subjects. Patients were divided into two groups according to the presence of reduced LA appendage (LAA) emptying velocity (<25 cm/s) and/or thrombus in the LAA at TEE examination.

Results: Patients with reduced LAA emptying velocity and/or thrombus at TEE examination showed a significantly higher LA volume and increased E/E' ratio. 4-chamber, 2-chamber and global PALS were significantly lower in patients with reduced LAA emptying velocity and/or thrombus (6.8 ± 2.0% vs. 27.5 ± 5.4%, P < 0.0001; 8.6 ± 3.5% vs. 29.4 ± 7.1%, P < 0.0001; 7.9 ± 3.2% vs. 28.5 ± 6.1%, P <0.0001, respectively). Among all variables analyzed, global PALS demonstrated the highest diagnostic accuracy (AUC of 0.92) and, with a cut-off value less than 8.1%, good sensitivity and specificity of 87% and 94%, respectively, to predict LAA thrombus and/or reduced LAA emptying velocity.

Conclusion: Among all parameters derived from transthoracic echocardiography, global PALS was the best predictor of LAA thrombus and/or reduced LAA emptying in patients with persistent non-valvular AF undergoing TEE before electrical cardioversion or ablation procedures..

Introduction

Atrial fibrillation (AF) is a major risk factor for systemic embolic events (SEE), accounting for up to 25% of all strokes in the elderly [1]. Ischemic strokes in AF are often more severe portending a higher risk of death and long-term disability. The risk of stroke and SEE is not homogeneous among AF patients as it is influenced by the presence of various clinical individual risk factors. The stroke risk in AF patients is graded as a continuum rather than as a categorization as assessed through the use of several risk scores[2],[3]. Recently, the CHADS2 scoring system has been expanded into the CHA2DS2-VASc score including additional clinical risk factors [4]. Left ventricular (LV) dysfunction, as assessed through imaging modalities, is the only non-clinical risk factor acknowledged in these scores, although many other findings provided by cardiac imaging may be potentially useful in further refining the individual thromboembolic risk [2]. Despite this emerging evidence, the role of transthoracic echocardiography (TTE) is currently restricted to the assessment of LV systolic function (as a component of CHADS2 and CHA2DS2-VASc scores) while transesophageal echocardiography (TEE) is still the gold standard for the evaluation of left atrial appendage (LAA) thrombus in candidates to cardioversion or ablation procedures [5].

There is a growing body of evidence suggestive of the association between CHA2DS2VASc score and TEE findings of high embolic risk, such as LA thrombus and spontaneous echo contrast (SEC) [6],[7]. The presence of LA or LAA thrombus is a powerful predictor of increased risk and stands as the only absolute contraindication to cardioversion or ablation; conversely SEC is associated with a high incidence of thrombus formation and thromboembolic events, but there is no consensus that such procedures are contraindicated in patients without coexistent LA or LAA thrombus identified [8],[9]. TEE, however, is semi-invasive and not so widely available, hence, given the central role of LA and LAA size, morphology and function, a non-invasive imaging modality capable of providing complete information also on these variables, beyond LV dimensions and function and heart valves, would be of great clinical interest and utility.

Key Words

Atrial Fibrillation, Transesophageal Echocardiography, Left Atrial Strain, Speckle Tracking Echocardiography..

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deformation, born for the analysis of LV function [10],[11] has extended its application to the study of LA [12],[13]. Considering the limitations of classical indices of LA function, assessment of LA strain by STE may represent a relatively rapid and easy-to-perform technique to explore LA function, due to its semi-automated and angle-independent nature and to its off-line processing [12]. Accordingly, the parameter of LA longitudinal strain (PALS) has been consistently reported as the first parameter useful for functional analysis of LA [12],[14],[15],[16],[17].

The aim of this study was to assess the correlations of LA deformation using STE with TEE findings in patients with persistent AF undergoing TEE before electrical cardioversion or ablation procedures.

Study population

All patients with persistent AF referred to our Echo Laboratory for a pre-procedural (electrical cardioversion or ablation) TEE from September 2015 to March 2016 were screened as potential candidate to the study. Common indications for TEE were: TEE-guided strategy of electrical cardioversion for AF ≥48 h of duration or with duration unknown, suboptimal anticoagulation in the previous 3 weeks in subjects scheduled for elective cardioversion, routine evaluation as per local protocol before AF ablation procedures. Eligible patients underwent both a TEE and conventional complete two-dimensional (2D) TTE and 2D speckle tracking analysis of LA.

The main exclusion criteria were AF duration <48 h, heart transplantation, valve repair or presence of prosthetic heart valve, more than mild mitral valve stenosis, previous closure of the LAA, presence of relevant valvular disease, technical inability to perform either TEE or STE analysis (i.e. inappropriate endocardial border definition of the LA).

All the patients provided their written informed consent for the participation to the study that complied with the declaration of Helsinki. The study was approved by our local ethic committee.

Echocardiographic evaluation

Echocardiographic studies were performed using a high-quality echocardiograph (Vivid 7, GE, USA), equipped with a 2.5 MHz transducer. Subjects were studied in the left lateral recumbent position. Measurements of LV and LA dimensions, LV ejection fraction, and diastolic LV filling velocities were made in accordance with current recommendations of ASE [18]. LV ejection fraction (EF), measured using Simpson's method, was used as a standard index of global LV systolic function. M-mode measurements of mitral annular plane systolic excursion (MAPSE) was performed by placing the cursor perpendicular to the lateral site of the annulus [19] and was used as an index of LV longitudinal function.

Regarding LA dimension and size, the following measurements were obtained: LA AP diameter, measured by M-mode from the parasternal long- axis view, LA area, measured using planimetry in TTE apical four-chamber and two chamber views, and LA volumes using the area-length method, from the apical four and two chamber views. LA volumes were subsequently indexed by body surface area (BSA). Care was taken to exclude the pulmonary veins and LA appendage from the LA tracing.

For speckle tracking analysis, apical four- and two- chamber views images were obtained using conventional two dimensional gray scale echocardiography, during breath hold and with a stable ECG recording. Care was taken to obtain true apical images using standard anatomic landmarks in each view and not foreshorten the left atrium, allowing a more reliable delineation of the atrial endocardial border. Three consecutive heart cycles were recorded and averaged. The frame rate was set between 60 and 80 frames per second. The analysis of files recorded was performed off-line by a single experienced and independent echocardiographer, who was not directly involved in the image acquisition and had no knowledge of other echocardiographic parameters representing LV, LA and valvular structure and function, using a commercially available semi-automated two-dimensional strain software (EchoPac, GE, Milwaukee, USA). As previously described [12], and as stated in the current ASE/EAE Consensus [20], LA endocardial border is manually traced in both four- and two-chamber views, thus delineating a region of interest (ROI), composed by 6 segments. Then, after the segmental tracking quality analysis and the eventual manual adjustment of the ROI, the longitudinal strain curves are generated by the software for each atrial segment. Peak atrial longitudinal strain (PALS), measured at the end of the reservoir phase, was calculated by averaging values observed in all LA segments (global PALS), and by separately averaging values observed in 4- and 2-chamber views (4- and 2-chamber average PALS). In patients in whom some segments were excluded because of the impossibility of achieving adequate tracking, PALS was calculated by averaging values measured in the remaining segments. The reproducibility and the feasibility of the speckle tracking measurement of LA longitudinal strain has been previously reported by studies conducted in our echocardiographic laboratory [12],[13].

Regarding the TEE, images were acquired with a multiplane transoesophageal probe (2.9–7.0 MHz). LA thrombus was diagnosed by the presence of an echo-dense mass in the left atrium or the LAA. SEC was diagnosed by the presence of characteristic dynamic smoke-like swirling echoes in the LA or the LAA, distinct from background white noise caused by excessive gain [22], and was classified according to the classification (1 to 4+) proposed by Fatkin et al. [23]. Dense SEC was defined as grade 3+ or 4+. LAA flow velocities were assessed with a pulsed Doppler sample placed 1 cm from the entry of the LAA into the body of the LA. Maximum emptying and filling velocities were estimated from an average of five well-defined emptying and filling waves. Patients with maximum emptying and filling velocity ≤ 25 cm/s were classified as having low flow velocities.

Statistical analysis

Continuous variables are expressed as mean ± SD. A P value <0.05 was considered statistically significant. Pearson's correlation coefficients were calculated to assess the relationships between continuous variables. Sensitivity and specificity were calculated using standard definitions, receiver operating characteristic curves were constructed and the area under the curve was calculated for the prediction of LAA thrombus and/or reduced LAA emptying velocity.

Analyses were performed using the SPSS (Statistical Package for the Social Sciences, Chicago, Illinois) software Release 12.0.

Results

Among 86 patients screened, 79 (58 males) met eligibility criteria for the study. Five patients were excluded because of valvular AF (more than mild mitral stenosis and mitral valve replacement), and two because of impossibility to perform TEE (difficulties in intubation). Included patients were categorized in 2 groups according to the presence or absence of reduced LAA emptying velocity (<25 cm/s)

and/or thrombus in the LAA at TEE examination. [Table 1] [Table 2]show the main clinical and echocardiographic characteristics of the two study groups.

Table1: Main clinical data

	LAA velocity < 25 (cm/s) and/or thrombus (n = 28)	LAA velocity >25 (cm/s), no thrombus (n = 51)	p Value
Clinical data			
Age	71.5 ± 9.2	70.1 ± 8.3	**0.22**
Gender (%female)	38	35	0.23
Body Mass Index (Kg/m2)	23.6 ± 4	22.3 ± 5.2)	0.53
Hypertension (%)	75	77	0.41
Diabetes mellitus (%)	29	27	0.33
Hypercholesterolemia (%)	64	68	0.25
Current smoker (%)	29	31	0.38
Previous TIA/stroke (%	29	6	0.001
CHA2DS2-VASc score	3.5 ± 2.2	2.9 ± 2.1	0.01
CHADS2 score	3.1 ± 0.9	2.3 ± 1.1	0.02
Medical therapy			
VKA o NOAc (%)	82	80	0.40
Antiplatelet therapy (%)	18	20	0.35

TIA: transient ischemic attack; VKA: vitamin-K antagonist therapy; NOAc: new oral anticoagulant therapy.

Table2: Echocardiographic data

	LAA velocity < 25 (cm/s) and/or thrombus (n = 28)	LAA velocity >25 (cm/s), no thrombus (n = 51)	p Value
Echocardiographic data			
LA diameter (mm)	45.2 ± 9.2	46.2 ± 8.6	**0.55**
LA area (cm2)	26.2 ± 7.2	**24.6 ± 6.4**	0.45
LA volume (ml)	47.2 ± 15.2	**39.8 ± 13.5**	0.01
LV End-diastolic diameter (mm)	52.6 ± 6.1	53.1 ± 6.4	0.69
LV End-systolic diameter (mm)	37.2 ± 3.2	37.2 ± 3.2	0.82
LV End-diastolic volume (ml)	92.3 ± 18.1	96.5 ± 17.6	0.84
LV Ejection Fraction (%)	53.1 ± 7.3	53.2 ± 8.3	0.59
LV relative wall thickness (cm)	0.39 ± 0.19	0.35 ± 0.11	0.42
LV† mass/BSA (g/m2)	100.3±10.2	96.5 ± 7.7	0.61
CHADS2 score	3.1 ± 0.9	2.3 ± 1.1	0.02
E/E'ratio (cm/s)	14.3 ± 7.1	11.6 ± 7.3	0.01
MAPSE (mm)	13.5 ± 4.6	13.8 ± 4.8	0.74
2-chamber PALS (%)	8.6 ± 6.3	29.4 ± 8.1	< 0.001
4-chamber PALS (%)	7.9 ± 6.0	27.5 ± 7.6	< 0.001
Global PALS (%)	7.9 ± 6.0	27.5 ± 7.6	< 0.001

LA: left atrium; LV: left ventricle; E: early transmitral flow velocity; E': early diastolic mitral annular velocity; MAPSE: tricuspid annular plane systolic excursion; PALS: peak atrial longitudinal strain.

No significant differences were observed between groups regarding age, sex, body mass index and cardiovascular risk factors. The incidence of previous episodes of stoke and/or TIA was higher in patients with reduced LAA emptying velocity and/or thrombus, accounting for a significantly higher CHA2DS2VASc score.

There were no significant differences in anti-thrombotic therapy before TEE examination between the two groups.

As for echocardiographic data, there were no significant differences in any of LV function parameters between the two groups.

The patients with evidence at TEE examination of reduced LAA emptying velocity and/or thrombus showed a significantly higher LA volume and increased E/E' ratio. Moreover, 4-chamber, 2-chamber and Global PALS were significantly lower in patients with reduced LAA emptying velocity and/or thrombus (6.8 ± 2.0% vs. 27.5 ± 5.4%, P < 0.0001; 8.6 ± 3.5% vs. 29.4 ± 7.1%, P < 0.0001; 7.9 ± 3.2% vs. 28.5 ± 6.1%, P < 0.0001, respectively). [Figure 1]

Moreover, close positive correlation between global PALS and the value of LAA emptying velocity was found (r=0.82, p<0.0001;[Figure 2].The correlation analysis was then performed after adjustment for age, severity of mitral regurgitation, LV EF and severity of diastolic dysfunction (different conditions that could determine a reduction of PALS), obtaining again a good grade of correlation between LA strain and LAA emptying velocity (r=0.77, p<0.0001).

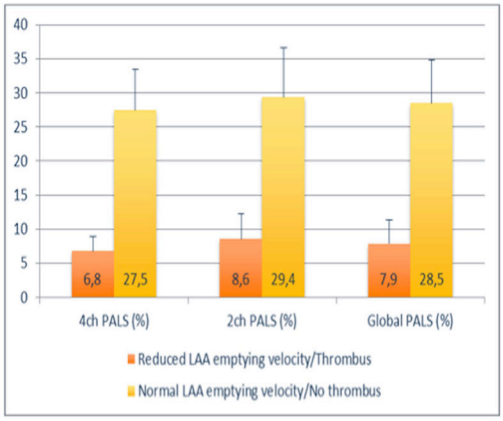

Figure1: Differences of the values of 4-ch PALS, 2-ch PALS and Global PALS in patients with reduced LAA emptying velocity/thrombus or normal LAA emptying velocity/No thrombus.

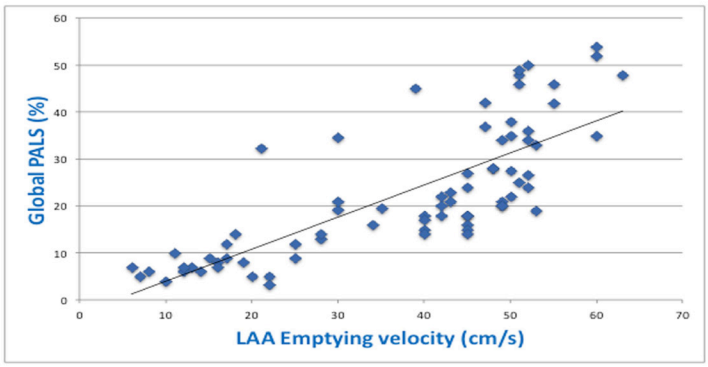

Figure2: Correlation between global peak atrial longitudinal strain (global PALS) and LAA emptying velocity.

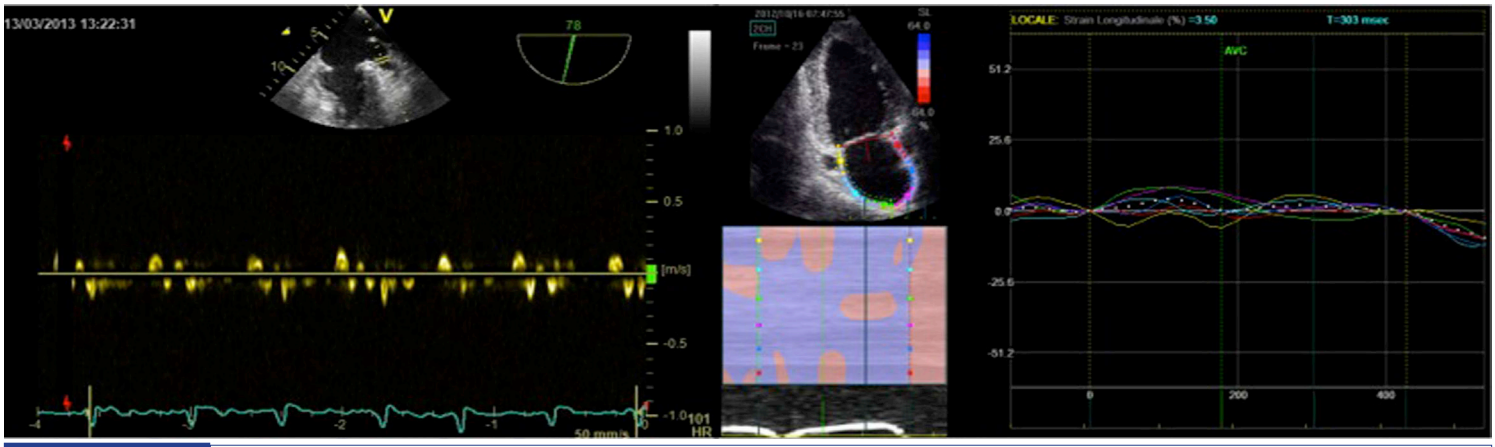

Figure 3: **Left panel: pulsed Doppler measurement of LAA emptying velocity (<25 cm/s) at TEE; right panel: measurement of PALS by STE in the same patient.**

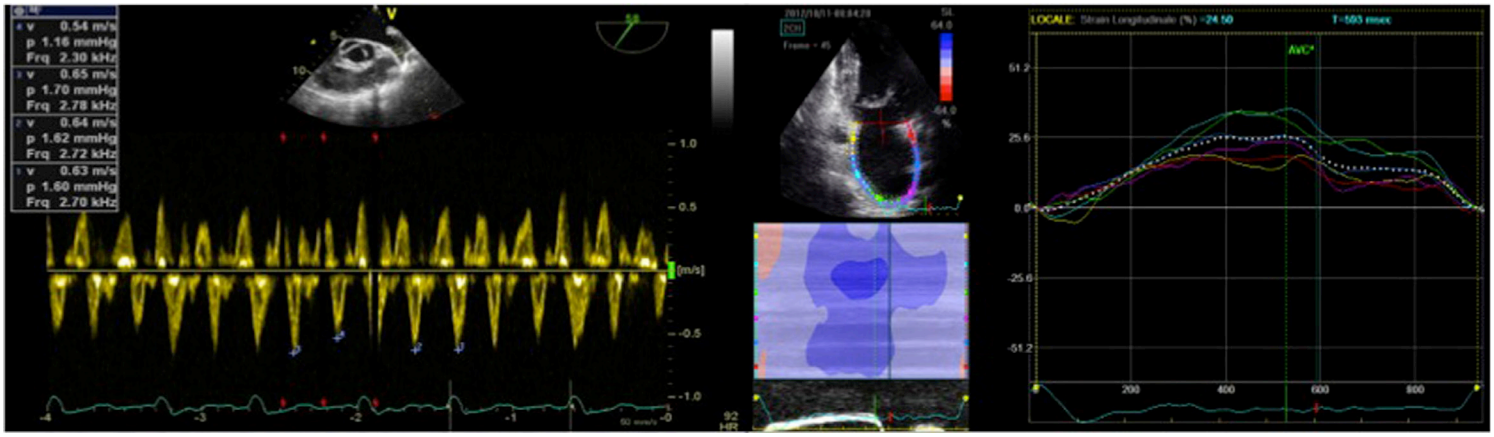

Figure 4: **Left panel: pulsed Doppler measurement of LAA emptying velocity (> 25 cm/s) at TEE; right panel: measurement of PALS by STE in the same patient.**

[Figure 3] and [Figure 4]display a representative case of each study group: the patient with evidence of reduced LAA emptying velocity at TEE examination shows a low value of PALS at STE analysis while the patient with normal LAA emptying velocity has higher PALS. Among all transthoracic echocardiographic variables analyzed, global PALS demonstrated the highest diagnostic accuracy (AUC of 0.92) and, with a cut-off value less than 8.1%, good sensitivity and specificity of 87% and 94%, respectively, to predict LAA thrombus and/or reduced LAA emptying velocity.

Discussion

Our results showed the correlation between reduced LA longitudinal strain, assessed by STE, with the presence of LAA reduced emptying velocity and/or thrombus on TEE examination in patient with persistent AF candidate to cardioversion or ablation. We were able to demonstrate a close positive correlation between reduced LA deformation in AF and echocardiographic findings linked to thromboembolism and stroke. Moreover, among all transthoracic echocardiographic variables analyzed, global PALS demonstrated the highest diagnostic accuracy (AUC of 0.92) to predict LAA thrombus and/or reduced LAA emptying velocity.

Two-dimensional TEE provides excellent characterization of the LA appendage and LA morphology because of the anatomic proximity of these structures to the esophagus. However, TEE findings are part of a dynamic process: LAA thrombus disappears either because of embolization or adequate anticoagulation; SEC appears or increases over time alongside with dilatation, fibrosis, and progressive atrial dysfunction or stunning; and LA appendage flow decreases with time as AF episode duration progresses or increases some weeks after an effective cardioversion. Therefore, a single TEE examination is like a single photograph of the LA milieu and may not be fully representative of past and future changes at this level. TTE with STE study given its noninvasiveness offers the advantage of being potentially used for serial assessments and evaluation of the patient devoid of the limitations, mainly tolerability, of TEE. Traditional TTE-derived parameters (LA diameter, LA area and LA volume), play a minor, if any, role in current risk scores since only LV ejection fraction <40% is included as a surrogate for congestive heart failure consistent also with the observation that a normal LV ejection fraction has been associated with the absence of LAA thrombus at TEE [24]. STE as an adjunct to standard TTE may allow for a more complete analysis of the LA thus providing valuable information on the pro-thrombotic state of LA and LAA deemed critical in some clinical settings of the decision-making in AF patients.

It has been widely demonstrated that AF is associated with tissue as well as overall atrial chamber structural remodeling in both animal models and humans [25]. This remodeling process is intrinsic to the pathophysiology of the arrhythmia and constitutes the substrate required for its maintenance [26]. Replacement of healthy atrial tissue with fibrotic tissue in AF can lead to reduced atrial contractile

function and blood stasis and can potentially be mechanistically linked to the process of thrombus formation [5]. Moreover, atrial fibrosis may constitute tissue injury that can also contribute to the thrombogenesis cascade and this is supported by the finding that some AF patients have thrombi outside the LAA [27]. In addition, in a recent study, Akoum et al. [27] demonstrated that atrial fibrosis quantified using magnetic resonance imaging (MRI) appears to be an independent predictor of thrombus formation.

For these reasons, the measurement of functional echocardiographic parameters might provide more insights to the major site of thromboembolism in patients with AF. Kuppahally et al. [28] demonstrated that LA wall fibrosis, as assessed by delayed enhancement-MRI, is inversely related to the strain and strain rate in patients with persistent AF and that patients with persistent AF had significantly greater delayed enhancement (as a marker for fibrosis) and decreased strain and strain rates, compared with patients with paroxysmal AF, supporting the concept that progressive remodeling occurs once AF develops[29].

In one of our investigations [30], we showed a strong relationship between the extent of LA fibrosis, assessed by and the value of LA strain, showing the higher sensibility of this new index respect to other echocardiographic parameters of LA size and function. Moreover, a recent prospective study demonstrated also the strong and independent power of global PALS to predict cardiovascular events [31]. Nonetheless, patients with permanent AF and history of stroke seem to have lower peak systolic LA strain rates assessed using STE during the reservoir phase compared with matched controls with no history of stroke [32].

Providência et al. [33] hypothesized that speckle tracking derived strain and strain rate could be of interest to evaluate the risk of LA stasis among patients with AF, reporting lower values of peak positive strain in patients with LAA thrombus or sludge.

Limitations

Some main limitations of this study need to be acknowledged. Sample size was small and the findings need to be confirmed in larger cohorts, until then the results are hypothesis generating only. Exclusion criteria, mainly those regarding concomitant valvular disease, were rather restrictive but, in our opinion, necessary to avoid introduction of numerous selection biases. No data may be inferred with respect to the potential impact of anticoagulation therapy since patients were included regardless of the anticoagulation regimen (ranging from non-anticoagulated to effectively anticoagulated). Finally, the measurement of global PALS requires more capability and is contingent on the presence of adequate apical views; optimal 4 and 2-chamber apical view is required, permitting an easy delineation of endocardium border and, at the same time, avoiding LA foreshortening and auricular visualization. However, in this study, the feasibility was excellent at 95%. An additional limitation is that we used the current software for LV analysis to study the LA pattern strain because a dedicated software for LA analysis has not yet been released.

Conclusions

IIn conclusion, even if TEE remains the gold standard for the exclusion of LAA thrombus, global PALS, this new promising parameter derived from TTE, might have a role in thromboembolic risk assessment of patients with non-valvular AF. Further prospective studies are necessary to define its additive role in clinical practice.

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Left Ventricular Systolic Function Assessed by Global Longitudinal Strain is Impaired in Atrial Fibrillation Compared to Sinus Rhythm

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Abstract

Background: Atrial fibrillation (AF) is the most common aberrant cardiac arrhythmia. Many AF patients present with symptoms of dyspnea and fatigue, but have normal left ventricular ejection fraction (LVEF).

Purpose: To determine the reproducibility of measurements of global longitudinal strain (GLS) and strain rate in patients with AF and examine if the arrhythmia is associated with abnormal LV strain and strain rate independent of age, sex, heart rate, LVEF and LV mass. We hypothesized that AF independently reduces ventricular systolic performance.

Methods: The study was conducted as a retrospective analysis of images from 150 randomly selected patients with AF compared to an equal number of subjects with sinus rhythm (SR) matched for age, sex, heart rate, LVEF and LV mass. Half of the patients had normal LVEF (LVEF > 50%) and half had reduced LVEF (LVEF < 50%). GLS and strain rate were measured in each group, as were quantitative LV volumes and standard systolic and diastolic parameters. Results: GLS was significantly impaired in patients with AF compared to subjects with SR, both in the overall population (-12.25 ± 4.1% vs. −16.13 ± 4.7%, p<0.0001), in patients with normal LVEF (-14.41 ± 3.9% vs. −19.42 ± 3.1%, p<0.0001) and in patients with reduced LVEF (-10.10 ± 3.1% vs. −12.85 ± 3.5%, p<0.0001). Linear regression and Bland Altman analyses demonstrated good intraobserver and interobserver agreement for measurements of GLS and strain rate parameters even in patients with AF.

Conclusions: Measurements of GLS and strain rate parameters are reproducible in patients with AF. Patients with AF have significantly impaired values of GLS when compared to similar patients with SR independent of age, sex, heart rate, LVEF and LV mass.

Introduction

Atrial fibrillation (AF) is the most common arrhythmia in the adult population and the prevalence of the arrhythmia is increasing [1]-[3]. AF is often associated with marked elevation in heart rate (HR), which over time may result in a tachycardia mediated cardiomyopathy characterized by reduced left ventricular ejection fraction (LVEF) and congestive heart failure [4]. However, many AF patients present with symptoms of fatigue and dyspnea even without impaired LVEF and without an excessive HR. It is reasonable to assume that both the irregular rhythm and the lack of active left atrial (LA) contraction in the late LV diastole associated with AF may result in reduced force of LV contraction. The most common measure of ventricular systolic function in clinical practice is the LVEF [5]. LVEF is a reliable and reproducible metric, but it has certain limitations, since it depends on the size and shape of the ventricle and on preload and afterload conditions in addition to contractility [6]. Furthermore, since LVEF does not take regional pathophysiological changes into account [7], it can best be described as a macroscopic measure of myocardial contractility that may neglect pathophysiological changes at a microscopic myocardial muscular bundle level. Myocardial strain and strain rate are measures of ventricular performance that have been proven to accurately assess LV myocardial contractility [8]-[10]. Systolic strain is a measure of the deformation of the myocardium that occurs with ventricular contraction, most commonly expressed as the change in base-to-apex longitudinal length of ventricular myocardial segments starting with the onset of ventricular contraction and ending with the closure of the aortic valve. Strain rate represents the speed by which myocardial deformation occurs and is derived from the first derivative of the strain curve [7],[11]. Strain rate is typically expressed as a global systolic and diastolic average with the former occuring at the peak systolic rate of change in ventricular shortening and the latter occuring at the peak rate of lengthening during early ventricular relaxation (corresponding to the E-wave).

The objectives of the present study was to examine the reproducibility of LV strain and strain rate measurements in patients with AF and determine to which extent these measurements are affected by AF independent of age, sex, HR, LVEF and LV mass.

Key Words

Atrial Fibrillation, Left Ventricular Systolic Function, Global Longitudinal Strain, Systolic Strain, Systolic Strain Rate, Diastolic Strain Rate.

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Material and methods

Study population

The study was conducted as a single-site retrospective analysis of echocardiograms and clinical data collected at the University of Rochester, Rochester, New York, between November 19th, 2007 and

May 30th, 2013. A total of 56,413 echocardiograms were performed during this time period. The inclusion criteria were ECG-documented AF at the time of the imaging procedure and adequate image quality in all standard views. Exclusion criteria included severe cardiac valvular disease, prosthetic valves, pericardial effusion, lack of an analyzable ECG and insufficient image quality (e.g. poor acustic window, frame rate < 45 frames/second etc.). The database of echocardiograms was queried to find two groups of patients depending on whether the codified variable, 'cardiac rhythm', was set to 'atrial fibrillation' (2,364 patients) or 'sinus rhythm' (24,189 patients). A total of 75 patients with AF and normal LVEF (LVEF ≥ 50%) and 75 patients with AF and reduced LVEF (LVEF < 50%) were randomly selected from the database. An identical-sized case-matched control group of 150 patients with SR was then created by matching patients from the SR group on a one-to-one-basis with the AF patients with respect to age, sex, HR, LVEF and LV mass. The study was approved by and conducted under the auspices of the University of Rochester's Ethics Committee. All personally attributable information was anonymized. The study was carried out in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Echocardiographic Measurements

Echocardiographic imaging was performed according to guidelines from the American Society of Echocardiography (ASE) [12]using equipment capable of storing digital information in RAW format (GE Vingmed Ultrasound AS, Horten, Norway) and analyzed by a core lab using commercially available software (EchoPAC 6.1, GE Vingmed, Horten, Norway). Measurements of traditional systolic and diastolic parameters and standard dimensions were made from the RAW images. In addition, LV diastolic and systolic volumes were measured using the modified Simpson's method averaging the results from the three apical views (apical four-chamber, apical two-chamber and apical three-chamber views). LVEF was calculated from the average LV volumes according to the formula:

LVEF = (end-diastolic volume – end-systolic volume) / end-diastolic volume.

LV mass was calculated using the ASE-recommended formula from LV linear dimensions in the parasternal long axis view[12] and was indexed to body surface area (BSA). Assessment of longitudinal LV strain and strain rate was performed using 2D speckle tracking technique averaging the results from the same 3 apical views that were used to measure LV volume and LVEF.

In patients with AF, echocardiographic data were assessed using the so-called 'index beat method', which has previously been demonstrated to be feasible in patients with AF [17]. Finding cycles with similar RR-intervals in AF patients was not difficult, since cine-loop recordings were available with many more cardiac cycles in AF patients (5 to 10 or even more beats) compared to SR patients (3 beats). The HR used in the analysis of the patients with AF was measured from the RR-interval preceding the analyzed beat and averaged over the 3 views used for LV analysis.

LV Strain Analysis

2D speckle tracking imaging was used to study LV deformation on standard grayscale images from the three apical views. Using the EchoPAC 6.1 software package, endocardial borders were manually traced on one frame in each view, after which the software automatically tracked the outlined area on subsequent frames by tracking patterns of acoustic markers ("speckles") throughout the cardiac cycle. Myocardial strain was assessed by the change in position of the speckles compared to the initial position. In each of the three apical views 6 segments were analyzed. Accordingly, global systolic strain (GLS) was calculated by averaging the peak systolic values derived from the resulting 18 segments. A positive value indicated myocardial lengthening and a negative value indicated shortening. Examples of the technique are shown in Figure 1. In addition, systolic strain rate (SSR) and diastolic strain rate (DSR) (expressed as 1/s) were calculated as the differential of the strain curve.

Statistical Analysis

Continuous variables are expressed as mean ± standard deviation (SD). Categorical data are summarized as frequencies and percentages. Due to matched pair study design, differences between continuous variables in the AF group and SR group were compared by paired Student's t-tests, and categorical data were analysed by X_2test or Fisher's exact test when appropriate. Interobserver and intraobserver variability of strain and strain rate parameters were determined by linear regression (calculating Pearson's correlation coefficients) and Bland Altman analyses. Intraobserver variability was assessed by repeating measurements of strain and strain rate in all segments of images from 20 randomly selected patients, providing 360 measurements of GLS and 60 measurements of SSR and DSR. Interobserver variability was assessed by making a second investigator perform strain and strain rate measurements on images from the same 20 patients.

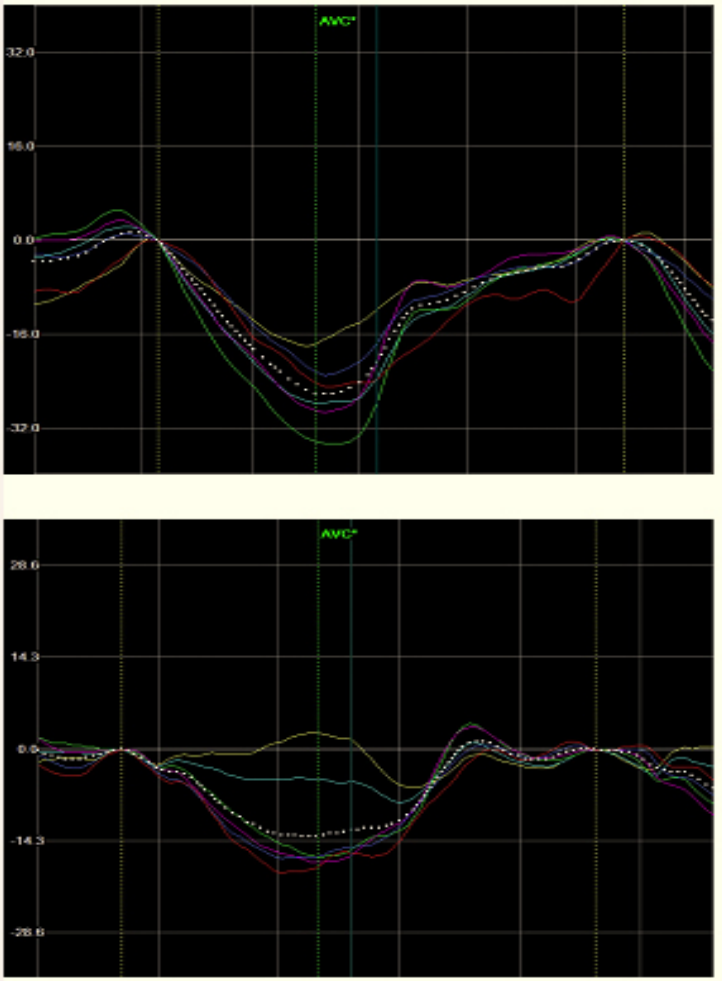

Figure 1: Left ventricular global longitudinal strain curves.

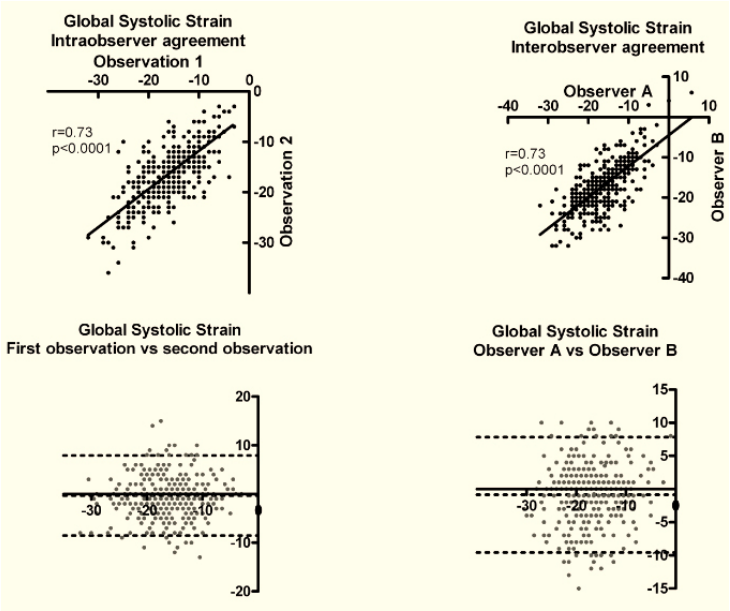

Figure 2: Intraobserver and interobserver variability. Upper panel: Linear relationship between measurements of Global Systolic Strain (GLS). Intraoberserver variability (left) and interobserver variability (right). Lower panel: Bland Altman plots for intraobserver (left) and interobserver variability (right) of GLS."

Statistical analyses were performed with the use of commercially available packages (SAS 9.3, SAS System, Cary, NC, USA and GraphPad Prism 4.0 GraphPad Software, San Diego, CA, USA). All p-values were two-sided, and a p-value < 0.05 was considered significant.

Table 1: Patient characteristics

	Preserved LVEF (LVEF>50%)			Reduced LVEF (LVEF<50%)		
	SR (n=75)	AF (n=75)	p	SR (n=75)	AF (n=75)	p
Age (years)	72.7± 12.6	72.7± 12.5	0.995	72.2 ± 13.1	72.8 ±13.1	0.762
Sex (% male) (n)	60.0 (45)	60.0 (45)	1.000	60.0 (45)	60.0 (45)	1.000
B M I (k g / m 2) Normal	28.5 ± 5.5	29.5 ± 6.2	0.364	27.4 ± 5.2	27.8 ± 5.1	0.780
BSA (m2)	1.92 ± 0.2	2.0 ± 0.3	0.050	1.92 ± 0.2	1.98 ±0.3	0.261
Heart Rate(bpm)	83.4 ± 15.9	86.7 ± 19	0.263	86.1 ± 18.5	87.9 ±20.4	0.579
Hypertension(% (n)	81.3 (61)	76.0 (57)	0.550	77.3 (58)	70.7 (53)	0.457
Diabetes (%) (n)	30.7(23)	32.0 (24)	1.000	36.0 (27)	32.0 (48)	0.731
Previous stroke/ TCI (%) (n)	14.7 (11)	24.0 (18)	0.214	10.7 (8)	16.0 (12)	0.472

Data are presented as mean ± standard deviation or as % (n) unless otherwise stated. BMI: body mass index, BSA: body surface area, TCI: transitory cerebral ischemia

Results

Patient characteristics are given in Table 1. Echocardiographic parameters of the AF and SR groups are given in Table 2. In the AF group mean duration of AF was 2.5 ± 0.8 years. In accordance with clinical expectations, the LA volume was significantly larger in the AF group than in the SR group. Linear regression analysis

Table 2: Echocardiographic parameters in the SR population and AF population

	Preserved LVEF (LVEF>50%)			Reduced LVEF (LVEF<50%)		
	SR (n=75)	AF (n=75)	p	SR n=75	AF (n=75)	p
LVEF (%)	57.2 ± 5.0	58.0 ± 5.1	0.428	37.5 ± 7.4	36.6 ± 7.9	0.247
LV mass index (g/m2)	121.0 ± 29.4	127.4 ± 36.4	0.2086	133.9 ± 31.1	138.0 ± 35.0	0.548
LVED volume (ml)	99.8 ± 42.1	112.3 ± 29.9	0.030	121.1 ± 46.0	142.3 ± 47.3	0.007
LAVI (ml/m2)	30.1 ± 10.4	49.4 ± 18.7	<0.0001	-12.85 ± 3.5	-10.10 ± 3.1	<0.0001
GLS (%)	-19.42 ± 3.1	-14.41 ± 3.9	<0.0001	-12.85 ± 3.5	-10.10 ± 3.1x	<0.0001
SSR (s-1)	-1.08 ± 0.3	-0.90 ± 0.2	<0.0001	-0.72 ± 0.3	-0.61 ± 0.2)	0.0002
DSR (s-1)	14.7 (11)	1.30 ± 0.4	0.113	0.88 ± 0.3	0.86 ± 0.3	0.587

Data are presented as mean ± standard deviation. LVED volume; left ventricular end diastolic volume, LVES volume: left ventricular end systolic volume, LVEF: left ventricular ejection fraction, LAVI: left atrial volume index, GLS: global longitudinal strain, SSR: systolic strain rate, DSR: diastolic strain rate

demonstrated good intraobserver and interobserver agreement for GLS, SSR and DSR. For intraobserver variability, the Pearson's correlation coefficients were 0.73, 0.70 and 0.89 for GLS, SSR and DSR, respectively, and Bland Altman analyses gave mean differences of –0.31 ± 4.19%, -0.05 ± 0.17 s^{-1} and 0.05 ± 0.23 s^{-1} for GLS, SSR and DSR, respectively (Figure 2).

In the overall study population, GLS was significantly impaired in the AF group compared to the SR group (-12.25 ± 4.1% vs. –16.13 ± 4.7%, p<0.0001) (Figure 3).

Similarly, in the subgroup of patients with preserved LV systolic function (LVEF ≥ 50%), GLS was significantly impaired in the AF group compared to the SR group (-14.41 ± 3.9% vs. –19.42 ± 3.1%, p<0.0001) (Figure 3), and the same was the case in the subgroup of patients with reduced LV systolic function (LVEF < 50%), where GLS was also significantly impaired in the AF group compared to the SR group (-10.10 ± 3.1% vs. –12.85 ± 3.5%, p<0.0001) (Figure 4). For SSR, absolute values were significantly lower in the overall AF population compared to the the overall SR population (-0.76 ± 0.2 s^{-1} vs -0.90 ± 0.3 s^{-1}, p<0.00001) [Figure 3]. The same was the case in the subgroups with preserved LVEF (-0.90 ± 0.2 vs. –1.08 ± 0.3 s^{-1},

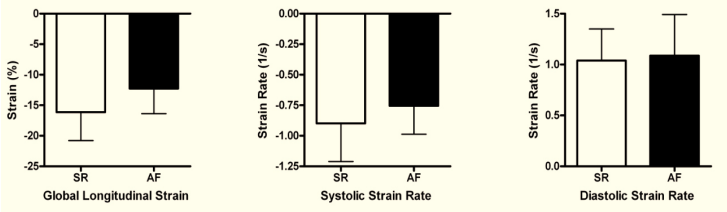

Figure 3: Atrial fibrillation vs. sinus rhythm. Comparison of strain and strain rate measurements in the overall study population.Differences in global longitudinal strain (GLS) (left), systolic strain rate (SSR) (middle) and diastolic strain rate (DSR) (right) between patients with atrial fibrillation (AF) and patients with sinus rhythm (SR) for all ranges of left ventricular ejection fraction (LVEF).

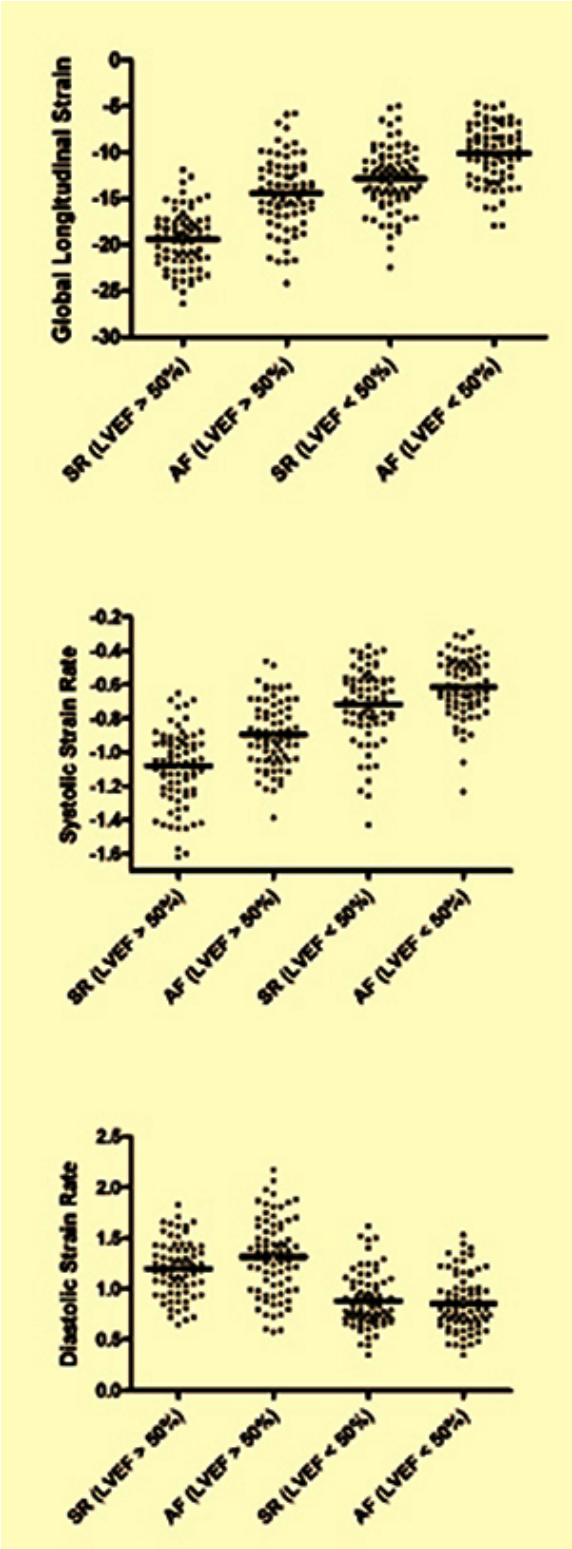

Figure 4: **Atrial fibrillation vs. sinus rhythm. Comparison of strain and strain rate measurements in subgroups with preserved and reduced left ventricular ejection fraction (LVEF), respectively.Differences in values of global systolic strain (GLS) (top), systolic strain rate (SSR) (middle) and diastolic strain rate (DSR) (bottom).**

p<0.0001) and the subgroups with reduced LVEF (-0.61 ± 0.2 s-1 vs. –0.72 ± 0.2 s^{-1}, p=0.0002) (Figure 4).

DSR values were marginally larger in the overall AF group than in the SR group, but the difference was not statistically significant (1.09 ± 0.41 s-1 vs. 1.04 ± 0.31 s-1, p=0.147) (Figure 3). Neither were the results significantly different between the subgroups with preserved LVEF (1.30 ± 0.37 s-1 vs. 1.20 ± 0.27 s-1, p=0.113) or the subgroups with reduced LVEF (0.86 ± 0.28 s-1 vs. 0.88 ± 0.27 s-1, p=0.587) (Figure 4).

Discussion

Assessment of strain based on 2D speckle tracking enables detection of more subtle abnormalities in LV contractility than can be appreciated by measuring LVEF. 2D strain assessment allows reliable distinction between active contraction and passive motion [13],[14]. Hence, it can be used to assess regional LV function in addition to global function. Due to the beat-to-beat variability associated with AF, analysis of myocardial strain has only been performed in relatively few studies of patients with AF [15],[17]. 2D speckle tracking strain imaging provides angle-independent evaluation of LV systolic function in 4 directions: radial, circumferential, longitudinal and rotational. The most reproducible of these strain measurements is longitudinal strain, which has been shown to be feasible in the early detection of contraction abnormalities in cardiac diseases such as hypertrophic cardiomyopathy with preserved LVEF [8].

The greater sensitivity of longitudinal strain compared to other strain modalities is thought to be caused by the fact that longitudinal fibers located in the subendocardium may be the most susceptible to pathological changes [18]-[20].

In the present study we have demonstrated that measurements of GLS and the derived parameters of SSR and DSR are reproducible even in patients with AF. Moreover, we have demonstrated that GLS is significantly impaired in AF compared to SR independent of age, sex, HR, LVEF and LV mass. These findings suggest that the extent of myocardial dysfunction is greater in patients with AF than in comparable subjects with SR, which indicates that the irregular LV filling associated with AF results in subclinical alterations in LV contractility that may precede deterioration of overall LV systolic function.

Limitations

Limited clinical information about the patients in the database was available, e.g. about the type of AF (paroxysmal, persistent, permanent) the patients had, as well as information about confounding factors, such as exposure to chemotherapy and/or radiation therapy. This lack of clinical information is an important limitation to the study, since these factors may well have had an impact on measurements of strain and strain rate. In addition, LA volumes were significantly larger in the AF group than in the SR group, which is consistent with clinical expectations and with findings from previous imaging studies [25]. However, these differences in LA volume imply that LA pressure was be higher in AF compared to SR, which combined with the lack of atrial contraction may have resulted in the finding of a slightly higher mean DSR value in the AF group compared to SR. Further investigation is needed to investigate the diastolic function abnormalities in AF patients taking the LA pressure and diastolic filling interval into account. Finally, differences in medication between the AF and SR group, especially in the use of beta blockers, could potentially contribute to the observed findings, since beta blockers are well known to alter preload and afterload conditions.

Conclusion

Measurements of GLS, SSR and DSR are reproducible in patients with AF. Patients with AF have significantly impaired values of GLS when compared to similar patients with SR independent of age, sex,

HR, LVEF and LV mass.

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Successful Denovo Implantation And Explanation of an Old Malfunctioning Micra™ Leadless Pacemaker

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Abstract

The use of leadless pacemakers is rapidly expanding. There is limited experience of extraction of leadless pacemakers. This case describes the successful extraction of an underperforming leadless pacemaker several weeks after initial implantation.

Conclusions: This case highlights the feasibility of extraction of Micra™ leadless pacemaker at an early stage post-implantation.

Introduction

Leadless pacemakers are advantageous since implantation is associated with fewer complications compared to a traditional transvenous pacing system. A recent multicenter experience has shown 99% implant success rate, with 48% fewer major complications than traditional pacemakers.[1] However, there is limited experience in the retrieval of leadless pacemakers.[2] This case report describes successful implantation of a new leadless pacemaker followed by extraction of a previously implanted device that had elevated capture thresholds.

Case report:

A 62 years old male with history of permanent atrial fibrillation, tachy-brady syndrome and right pectoral dual chamber pacemaker underwent extraction of transvenous pacemaker due to infection and bacteremia. Due to history of infected device at both right and left pectoral sites, the patient underwent implantation of a leadless pacemaker (Micra Transcatheter Pacing System, Medtronic, Minneapolis). Sensing and capture threshold was satisfactory at implantation but required multiple deployments to attain adequate thresholds. During subsequent follow up, the capture threshold increased gradually with eventual failure to capture at maximum output (5 V at 1 msec) at 3 months of implantation. A decision was made to proceed with extraction of the first device and implantation of a new leadless pacing device. A new leadless pacemaker was implanted in the high septal location (Figure 1). This figure shows that two leadless pacemakers in place. The newly implanted device is located in the high septal location while the older one is located in the right ventricular apex.

Key Words

Leadless pacemaker, Extraction..

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Extraction procedure:

After successful deployment of the new leadless pacemaker via right femoral vein access, a single-loop snare (EN Snare Endovascular Snare System, Merit Medical Systems, Inc) with an integrated protective sleeve was advanced via the delivery catheter into the right ventricle (Figure 2, left panel). The leadless pacemaker was successfully snared but this was cantered at its entry point into the delivery cup and came free(Figure 2, right panel). Due to concern for distal embolization, the delivery catheter was removed and a steerable sheath (8.5 F Agilis NxT™ Steerable Introducer, St. Jude Medical) with a triple-loop snare (En Snare, endovascular snare systems, Merit Medical Systems, South Jordan, Utah) was advanced into the right ventricle. A coaxial position was confirmed with multiplane fluoroscopy, but rather than using the retrieval loop at the proximal end of th e leadless pacemaker, the triple loop snare was used to entrap the entire body of the pacemaker(Figure 3, , right and left panel). With constant traction, the snare did not slip and successfully retracted the pacemaker from the myocardium (Figure 4, , right and left panel). The device separated smoothly without a pop. The device was then brought into the delivery sheath. The steerable sheath was pulled out of the delivery sheath; however, the leadless pacemaker could not be extracted from the delivery sheath due to the entrapment in the hemostatic valve (Figure 5). Continuing with constant traction to ensure that the pacemaker remained within the sheath, the entire sheath was then removed from the femoral vein and hemostasis was maintained with sutures. A follow up echocardiogram showed no pericardial effusion.

Discussion

This case describes the successful extraction of a leadless pacemaker after successful implantation of a replacement device. According to the manufacturer, nearly 50 such devices have been extracted to-date (personal communications). Due to size of the Micra™ (23 F), the delivery sheath (27 F) is necessary for extraction. Currently, there is no equipment designed specifically for Micra™ extraction. The usual equipment employed for extraction includes the delivery sheath,

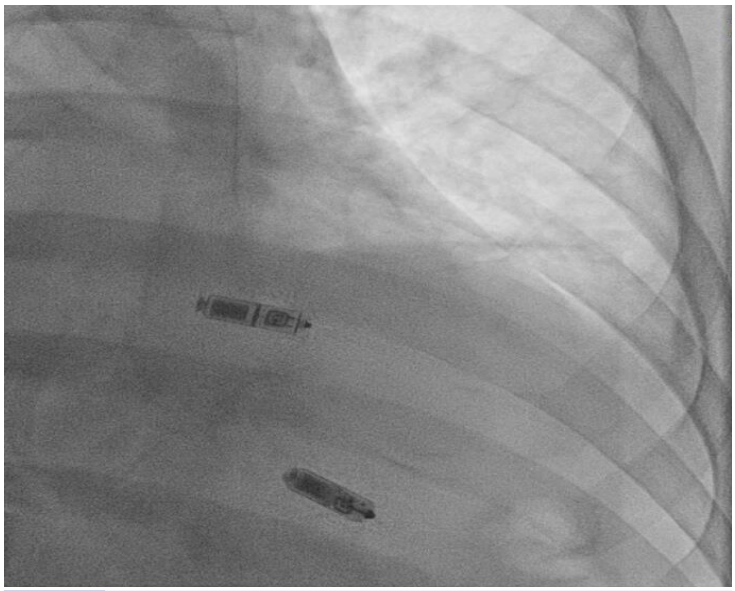

Figure 1: Implantation of a new leadless pacemaker in the high septal location in the presence of an underperforming pre-existing device located in the right ventricular apex.

This figure shows that two leadless pacemakers in place. The newly implanted device is located in the high septal location while the older one is located in the right ventricular apex

delivery catheter and a single or triple-loop snare. There are two recommended approaches for extraction of Micra™. First approach is to advance a single or multiple loop snare and an integrated protective

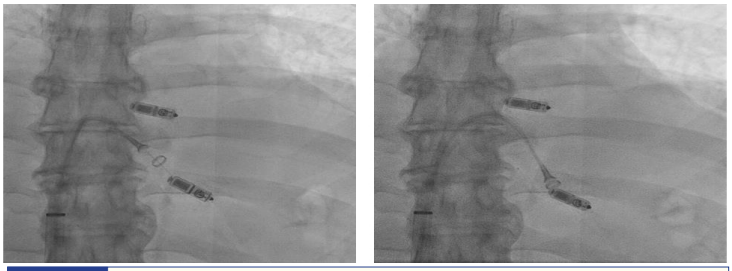

Figure 2: Attempted extraction of leadless pacemaker using the MicraTM delivery catheter

Left panel shows engagement of retrieval feature of the leadless pacemaker using the delivery catheter. Right panel shows the Leadless pacemaker was successfully snared but this was cantered at its entry point into the delivery cup and came free.

sleeve via the Micra™ delivery catheter (which requires removal of the pre-loaded device to load the extraction snare) and engage the

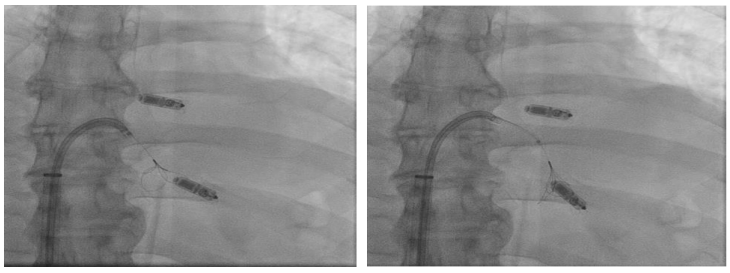

Figure 3: Use of steerable sheath and triple-loop snare to entrap the leadless pacemaker

Left panel shows a steerable sheath (Agilis, St Jude medical) and triple-loop snare in co-axial configuration with leadless pacemaker. The right panel shows that the triple-loop snare is encasing the entire body of the Leadless pacemaker.

proximal retrieval feature of the device (Figure 6). This proximal feature allows the distal cup of the delivery catheter to completely cover the proximal retrieval mechanism of Micra™. Once the delivery cup is snugged on the proximal part of the leadless pacemaker, the device is withdrawn from the tissue into the sheath. However,

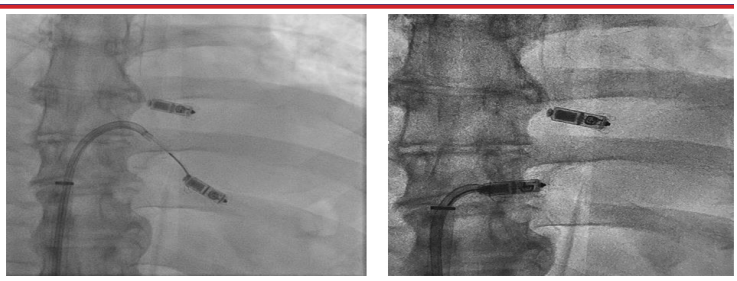

Figure 4: Successful extraction of the leadless pacemaker from the right ventricle using the snare via the steerable sheath

Left panel shows that the triple-loop snare is completely encasing the body of leadless pacemaker. The right panel shows retraction of the leadless pacemake from the myocardium.

engaging the proximal retrieval feature is sometimes challenging. The delivery catheter is unidirectional and steering is limited to only gross movements. The other approach is to use a steerable sheath for better

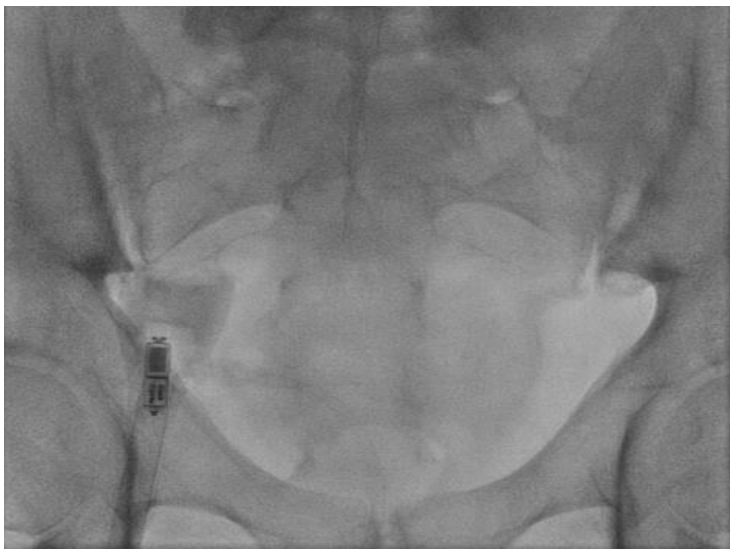

Figure 5: Leadless pacemaker entrapped in the hemostatic valve of the delivery sheath

This image shows the entrapped leadless pacemaker just beneath the hemostatic valve of Leadless pacemaker sheath.

co-axial positioning. A single or triple-lumen snare can be used via the sheath of multiple French sizes and diameters and allows the operator more flexibility. The latter was the successful strategy in this case.

Figure 6: Proximal retrieval feature of the device

This image shows the proximal retrieval feature of leadless pacemaker for deployment of snare. The sheath is outside the body and is upside down.

Factors responsible for inadequate thresholds:

The common reasons for a non-functioning leadless pacemaker device include inadequate insertion of the tines in the trabeculated tissue of right ventricle due to inadequate pressure at delivery. This problem can be circumvented by a radio-iodinated contrast injection to identify a septal region that will tolerate the forward pressure necessary for adequate engagement of the tines. Performing the tug test after implantation usually does confirmation of tine insertion. Per manufacturer, straightening of at least two tines is consistent with adequate implantation. Rarely, infarction of the tissue that includes the location of the leadless pacemaker implant can cause a rise in pacing thresholds as well. The recommended approach is to abandon the leadless pacemaker and place an alternative system. However, if the leadless pacemaker can be safely removed it will allow more area for subsequent implants and decrease the risk of implant infection or embolization as rare as that risk is.

Conclusions:

This case highlights the feasibility of extraction of Micra™ leadless pacemaker at an early stage post-implantation

Future directions:

As the experience with retrieval of LPs increases, these devices can be used in place of a temporary pacemaker in pacer dependent patients requiring prolonged course of antibiotics after extraction of an infected cardiac implantable electronic device. Further improvements in the proximal retrieval feature and extraction tools will facilitate this endeavor.

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Beating-heart Thoracoscopic Left Atrial Appendage Exclusion in a Patient with Left atrial Thrombus

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Abstract

Stroke remains a major complication of atrial fibrillation and third leading cause of death in Western Countries. [1] While Coumadin and novel oral anticoagulants have been efficient in reducing the stoke risk in patients with atrial fibrillation; there is a subset of patients who are not candidates for anticoagulation.[2] The management of these patients is clinical challenge.We describe a patient with history of permanent atrial fibrillation with contra-indication to anticoagulation presenting with and left atrial thrombus. She was treated with novel generation of epicardial left atrial appendage exclusion device.

Introduction

Management of left atrial thrombus in patients with significant gastrointestinal bleeding is a challenge for treating clinician.European guidelines recommend left atrial appendage exclusion for patients with an absolute or relative contraindication for oral anticoagulation. [3] The presence of a thrombus in the left atrial appendage is considered as a contraindication to percutaneous exclusion, as manipulation of catheters, guide wires, sheaths or devices in the left atrial appendage may lead to systemic embolization.

Clinical Summary

A 66-year-old female was presented with history of hypertension, ischemic cardiomyopathy with left ventricular ejection fraction of 29%, s/p PCI and Biventricular ICD implantation and permanent atrial fibrillation for 15 years, s/p atrioventricular node ablation. Her CHADSVASC score was 6 and her HASBLED score was 5. She was taken off dabigatranetexilate six months earlier due to two episodes of lower gastrointestinal bleeding requiring hospitalization and two united packed blood cells transfusion. Her workup by the gastroenterology was negative for any tumor, vascular anomalies or other sources of gastrointestinal bleeding. Subsequently, she was presented with left embolic stroke four months ago with right lower extremity paresis. Another trial of anticoagulation – this time with Coumadin – led to repeat hospitalization and lower gastrointestinal bleeding a month later, and therefore the Coumadin was stopped. Now, she is once again presented with recurrent left frontal embolic stroke and evidence of significant clot burden in left atrial appendage and computer tomography scan and transesophageal echocardiography [Figure 1],[Figure 2].

This patient was discussed in the multi-disciplinary conference. She was felt not to be a candidate for any endocardial or epicardial left atrial appendage exclusion by the interventional cardiology and electrophysiology team due to concerns of intra-procedural dislodgement of left atrial clot and recurrent episode of gastrointestinal bleeding. The only brainstorm adoption was to use thoracoscopic beating-heart approach using a hoopless open-ended surgical exclusion device. Everyone agreed that there is still significant risk of embolization of left atrial appendage thrombus during this procedure, and that risk of recurrent stroke without exclusion of the left atrial appendage is even higher. After discussing the risks and benefits with the patient as part of an informed consent, she decided to proceed.

The procedure was performed in the operating room under general anesthesia and double-lumen intubation. Two five mm ports and a twelve mm port was placed in left axillary line after the left lung was deflated and CO2 insufflation

The pericardium was opened two cm under the phrenic nerve and the entire left atrial appendage was exposed. Using atraumatic grasper the tip of the appendage was gently grabbed, the basis was sized to be 40mm.Through the12mm port, a 40mm AtriClip Pro-V (AtriCure, Mason,OH) was introduced and placed across the basis of the left atrial appendage with minimal manipulation, effectively exclude blood flow into the left atrial appendage. Under transesophageal echocardiography, complete exclusion of the left atrial appendage from circulation was confirmed. [Figure 3] All the instruments and ports were removed and the port skin incisions were closed under Valsalva maneuver. The patient tolerated the 25-minute procedure well, was extubated and transferred to postoperative care unit with no new neurologic findings, and discharged home two days later.

Key Words

Atrial Fibrillation, Left Atrial Thrombus, Left Atrial Appendage Exclusion, Left Atrial Occlusion.

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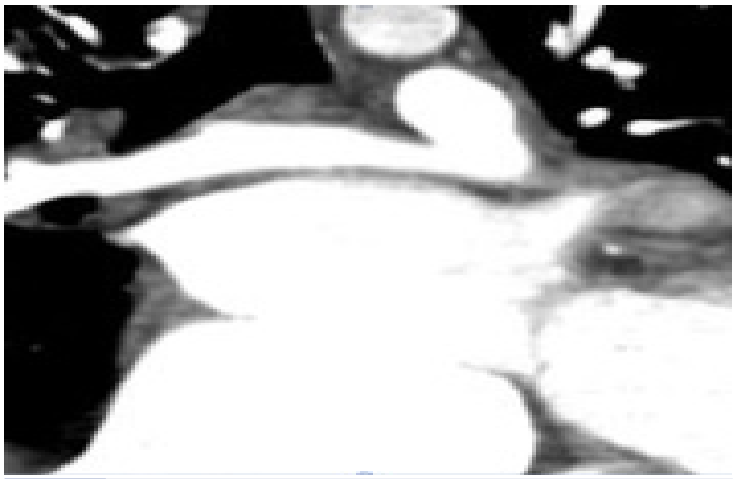

Figure 1: This figure illustrates presence of thrombus in the left atrial appendage on the preoperative cardiac computer tomography angiogram.

Discussion

Patients with high CHADSVASC score have a significant stroke risk without effective systemic anticoagulation.[2] These patients should be considered for endocardial exclusion of left atrial appendage. Management of patients with significant thrombus burden in the left atrial appendage and contraindication to anticoagulation is a challenging clinical condition. These patients are typically not candidates for any endocardial or epicardial closure techniques due to the risk of dislodgement and embolization. AtriClip has been evaluated and FDA-approved after the multi-center prospective EXCLUDE clinical trial (Exclusion of Left Atrial Appendage with AtriClip Exclusion Device in Patients Undergoing Concomitant Cardiac Surgery) assessed the safety and efficacy of left atrial exclusion.[4] In this patient, a novel version of AtriClip was used to exclude the appendage. This device is designed without a hoop end effector and the clip is also open-ended, allowing for minimal manipulation of the left atrial appendage during deployment. Given recent release, the experience with AtriClip Pro-V in this clinical setting is limited. There are recent reports of transcatheter exclusion of left atrial appendage in setting of left atrial clot using cerebral embolic protection. [5]-[6]

Although the use of cerebral protection systems is reasonable in this context, this type of device was not in this case for several reasons. Firstly, the use of such devices needs arterial vascular access and catheter and device manipulation in the aortic arch, and extends the duration of the procedure, which may increase the risk of perioperative complications and aorta-embolic stroke in this fragile patient. Secondly, embolic events can occur despite the use of the embolic protection devices.[7]

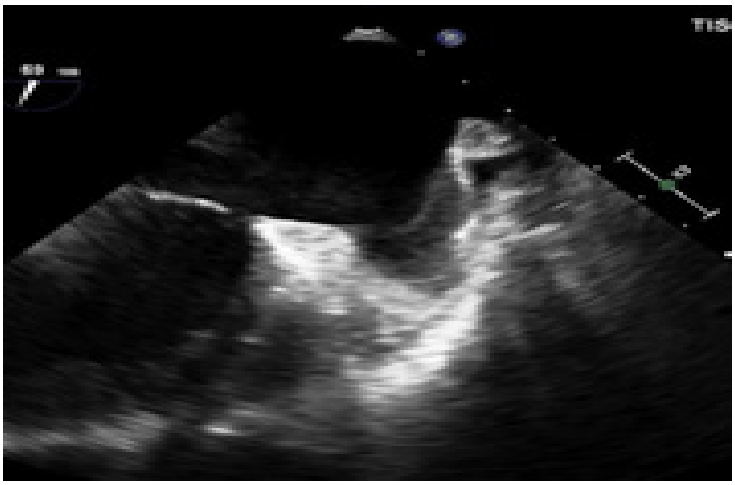

Figure 2: This figure confirms a large thrombus in the left atrial appendage on the intraoperative transesophageal echocardiography.

The rate of stroke in patients with left atrial thrombus is unknown. This case report, to our knowledge, is the first published report of the utility of an epicardial device in a patient with left atrial thrombus and absolute contraindication to anticoagulation, where there are no great alternatives.

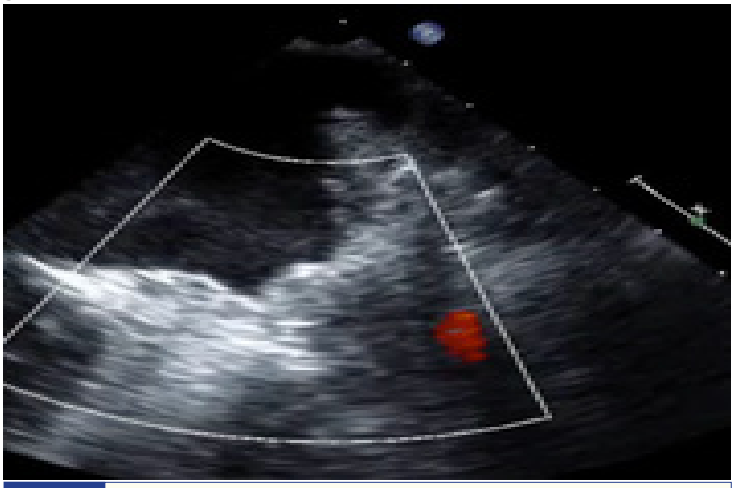

Figure 3: This image depicts postoperative transesophageal echocardiography images after placement of the AtriClip PRO-V.

Disclosures

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Tumor Or Thrombus? The Role Of Cardiac Magnetic Resonance Imaging In Differentiating Left Atrial Mass In a Transplanted Heart: A Case Report

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Abstract

Background: An unknown mass in the left atrium can be challenging to differentiate, especially after previous heart transplant. A precise diagnosis is clinically crucial because of the therapeutic implications. CMR is an useful, non-invasive tool to distinguish intra-cardiac lesions, thereby enabling clinicians to initiate adequate therapy.

Case Report

A 62-year-old male patient with a past medical history of myocarditis 6 years ago, resulting in highly reduced left and right ventricular function, received a biventricular assist device 8 months later as bridge to transplant. He was finally being transplanted two and a half years later. After transplantation the immunsupressive medication included tacrolimus, mycophenolat and prednisolone. Due to leucopenia mycophenolat was changed to everolimus two years after transplantation. The patient was now seen for an annual routine check- up three and a half yearsafter heart transplantation.

The patient was in good health without any sign of transplant rejection, infection or other pathologies.

The transthoracic echocardiographic (TTE) evaluation revealed a good left and right ventricular ejection fraction, no relevant valve pathologies. Strikingly, a left atrial (LA) mass was detected that had not been observed during routine echocardiography 12 month earlier.

Cardiac MRI (CMR) was performed and showed an inhomogenous tumor at the left atrial posterior wall on the transition to the left atrial roof with an isointens presentation in T1 and T2 imaging [Figure 1] and no enhancement on late gadolinium enhancement imaging. The mass resulted in a functional stenosis of the left inferior pulmonary vein [Figure 1]. The main differential diagnoses were a thrombus or a cardiac tumor (e.g. lymphoma due to immunosuppressive therapy or an atrial myxoma). Other but rather seldom alternatives were a rhabdomyoma or a fibroma. As the mass showed neither perfusion on perfusion imaging nor contrast enhancement on late gadolinium enhancement images, a vascularized tumor seemed unlikely. Considering the CMR characteristics an atrial thrombus was considered to be the most likely diagnosis.

For further evaluation a CT scan of the thorax, abdomen and pelvis was performed, where no invasion of the structures surrounding the heart, nor enlarged lymph nodes were seen.

Anticoagulation with Rivaroxaban was initiated and switched to a Vitamin-K antagonist because no reduction in size could be demonstrated on follow-up echocardiography 1 month later.

After a total of three month of oral anticoagulation, CMR was repeated and revealed a significant reduction of the LA mass [Figure 2], supporting the initial diagnosis of a LA thrombus.

Multiple holter ECG could not confirm atrial fibrillation (AF). We considered two possible etiologies of the left atrial thrombus. The first is that the thrombus originates from the suture scar after heart transplantation and the second is a possible AF in the residual recipient left atrium with a total electrical isolation and therefore no propagation of the arrhythmia in the transplanted heart, which results in a decreased blood flow at the posterior wall of the LA.

Discussion

A left atrial thrombus is a major risk for systemic embolization. Most likely a LA thrombus occurs in the left atrial appendage under atrial fibrillation. If a LA thrombus is located at different site, differentiating it from a potential malignant tumor can be tricky and challenging. Previous studies have shown the value of CMR in examining intracardiac thrombus [1], making this the reference imaging modality for differentiating intraatrial masses [2]. In the case presented here, CMR imaging was a helpful tool to differentiate the LA thrombus from other intracardiac tumors. Early gadolinium enhancement imaging would have complemented the diagnosis but unfortunately was not performed in this patient. This diagnosis

Key Words

Magnetic Resonance Imaging, Cardiac Imaging, LeftAtrialMass, Heart Transplantation, Left Atrial Thrombus.

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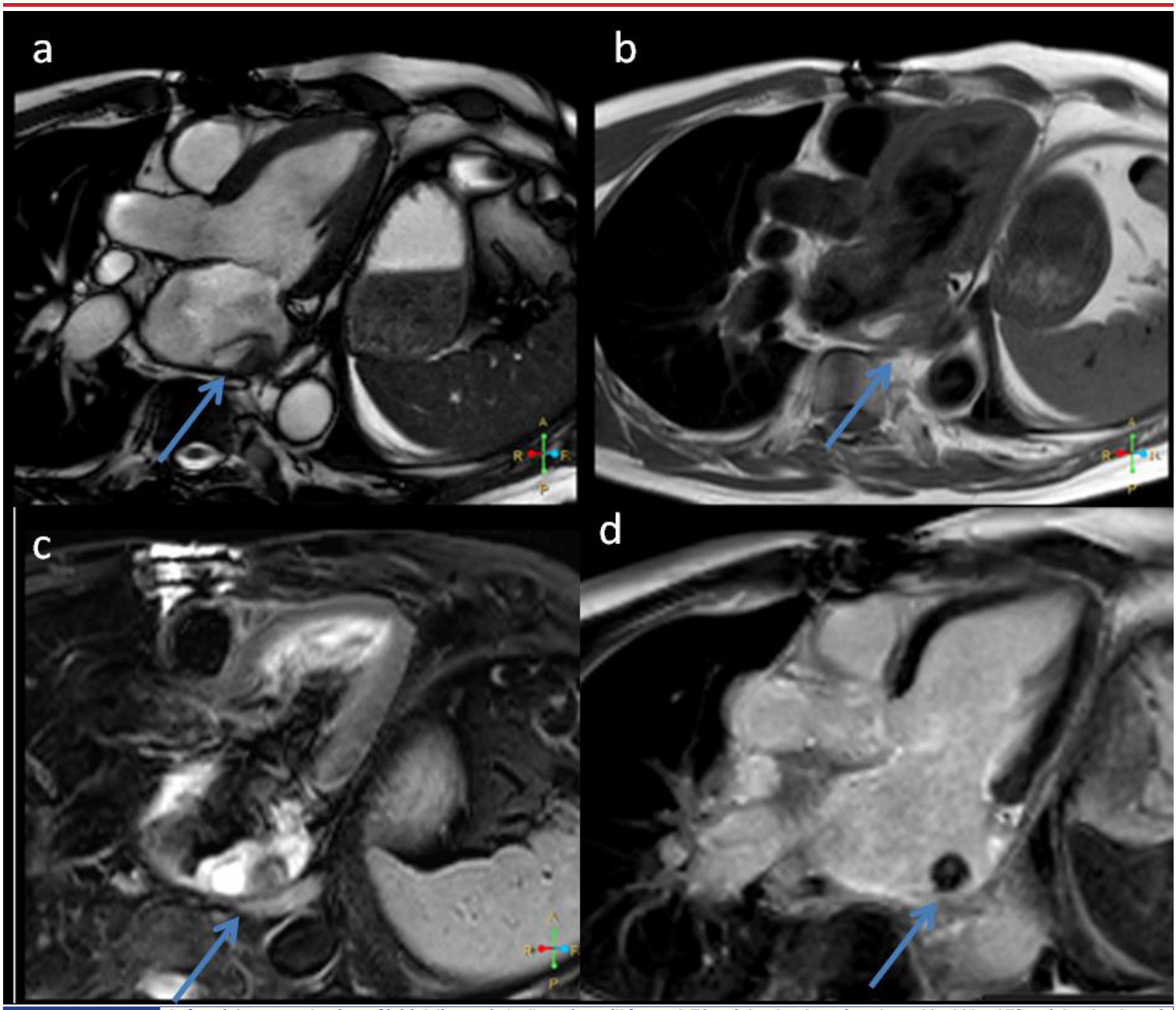

Figure 1: Left atrial mass at the time of initial diagnosis (a-d). a, cine still frame; b T1-weighted turbo-spin echo; c, blackblood T2-weighted turbo-spin echo; d, late-gadolinium enhancement imaging.

resulted in the initiation of anticoagulation therapy and saved the patient from more invasive and potentially harmful diagnostic measures such as biopsy. The exact cause of the thrombus remains unclear. Data on length of anticoagulation therapy in these cases is lacking. We decided to continue oral anticoagulation indefinitely. Unfortunately it was not possible to rule out atrial fibrillation in theresidual recipient left atrium.This is especially difficult as the suture scar provides a line of block which can constrain the atrial fibrillation to the posterior "old" atrial parts of the heart. Therefore atrial fibrillation can go missing from the ECG at rest which then only shows sinus rhythm of the transplanted heart.

Apart from an invasive electrophysiological study, esophageal ECG could be an option to further investigate this possibiliy.

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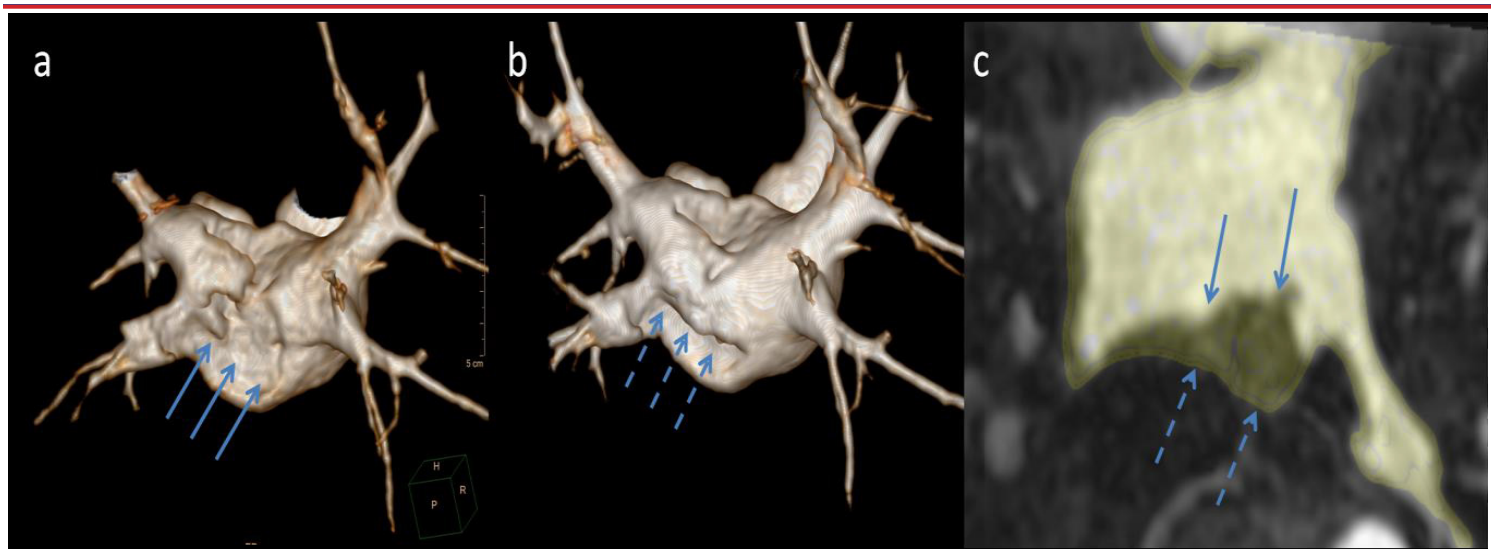

Figure 2:	Three-dimensional surface renderingof MR angiographic datasets at the time of initial diagnosis(a) after three months of oral anticoagulation with warfarin (b) and the merged image before and after oral anticoagulation(c); note the significant thrombus size reduction of the cardiac mass depicted as an impression of the contrast-agent filled left atrium (continousarrows: before oral anticoagulation and dotted arrows after oral anticoagulation).

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Electrocardiogram (ECG) for the Prediction of Incident Atrial Fibrillation: An Overview

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Abstract

Electrocardiograms (ECGs) have been employed to medically evaluate participants in population-based studies, and ECG-derived predictors have been reported for incident atrial fibrillation (AF). Here, we reviewed the status of ECG in predicting new-onset AF. We surveyed population-based studies and revealed ECG variables to be risk factors for incident AF. When available, the predictive values of each ECG risk marker were calculated.

Both the atrium-related and ventricle-related ECG variables were risk factors for incident AF, with significant hazard risks (HRs) even after multivariate adjustments. The risk factors included P-wave indices (maximum P-wave duration, its dispersion or variation and P-wave morphology) and premature atrial contractions (PACs) or runs. In addition, left ventricular hypertrophy (LVH), ST-T abnormalities, intraventricular conduction delay, QTc interval and premature ventricular contractions (PVCs) or runs were a risk of incident AF. An HR of greater than 2.0 was observed in the upper 5th percentile of the P-wave durations, P-wave durations greater than 130 ms, P-wave morpholyg, PACs (PVCs) or runs, LVH, QTc and left anterior fascicular blocks. The sensitivity , specificity and the positive and negative predictive values were 3.6-53.8%, 61.7-97.9%, 2.9-61.7% and 77.4-97.7%, respectively.

ECG variables are risk factors for incident AF. The correlation between the ECG-derived AF predictors, especially P-wave indices, and underlying diseases and the effects of the reversal of the ECG-derived predictors on incident AF by treatment of comorbidities require further study.

Introduction

Atrial fibrillation (AF) is a common arrhythmia, and the number of patients with AF is increasing in many developed countries. AF is associated with increased morbidity and mortality [1], and the prediction of AF development is expected to improve both health and clinical outcomes at the population level. Thus far, demographic and clinical variables have been extensively studied, and some have been shown to be risk factors for AF development [2]-[6].

Electrocardiograms (ECGs) are essential to diagnose AF and are used in population-based health examinations because of their ease of use and low cost. Recent advancements in high-quality signal acquisition and the availability of automated hardware ECG setups have facilitated the use of ECGs in mass examinations, and many ECG-derived markers have been confirmed as risk factors for incident AF. Here, we reviewed community-based cohorts that have confirmed ECG-derived risks for AF development.

Key Words

New atrial fibrillation, ECG-Derived Predictor, P-wave Indices, Atrial Remodeling.

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Studies treating incident AF

Mainly, studies treating incident AF in community-based cohorts were collected from the literature. Small studies of less than 100 participants were not included, except for those measuring P-wave duration or dispersion by signal averaged ECGs (SAECGs). SAECGs may present more accurate P-wave durations or dispersions in spite of the difficulty of using them in population-based examinations.

AF was diagnosed using ECG and Holter monitors. New AF was diagnosed when the participants had no AF at baseline ECG but had AF on an ECG during the follow-up period. Then, we included some paroxysmal AF (PAF), whereas some cases of PAF might have been undetected if the sinus rhythm had resumed.

Most ECG variables were automatically measured by the hardware ECG set-up, but some were confirmed by cardiologists in most studies.

Atrium-related ECG-derived predictors [Table 1]

P-rate (heart rate) and P-wave indices and PR intervals are considered to represent alterations of electrophysiological and/or structural remodeling of the atrium in association with or without demographic and clinical variables that are risk factors for incident AF. The appearance of premature atria contractions (PACs) or runs may trigger AF and can be another risk for incident AF.

P-rate

Bradycardia is known to be associated with AF, especially in

Table 1: Atrium-related ECG-derived predictors for new-onset AF

Author (Rf. No.)	Number of participants	FU time	Annual incidence	ECG finding	HR (95% CI, P-value)
P-wave duration					
Perez [13] Perez [13]	42,751	5.3 yrs	0.45%	>120 ms	1.6 (1.3-1.8, P<0.0001)
				per 20 ms	**1.1 4 (1.02-1.27, P=0.022)**
Soliman[14]	15,429	6.97 yrs	0.11%	>120 ms	1.94 (1.66-2.28) Model 1 1.79 (1.51-2.14) Model 2
			Upper 5%		5.23 (3.33-8.22) Model 1 4.07 (2.55 - 6.51) Model 2
Magnani[15]	1,550	15.8 yrs	1.46%	1.46%	Upper 5%	2.51 (1.13-5.57)
				per 1 SD	1.1 (0.90-1.47, P=0.27)
Nielsen[28]	285,933	6.7 yrs	0.49%	>89 ms	1.60 (1.41–1.81 P<0.001)
				100-105 ms	1.00
				112-119 ms	1.22
				120-129 ms	1.50
				≥130	2.06
P-wave dispersion					
Perez [13]				>80 ms	1.95 (1.7-2.3, P<0.0001)
				SD of P duration >35	**1.7 (1.3-2.1, P<0.0001)**
P-morphology					
Soliman[14]				95th% of PTFV1	1.23 (1.04-1.46)
Magnani[16]				PTFV1 >0.04 V•s	1.56 (1.24-2.00)
Enriquez[35]	122	30 mo	46.7%	P duration ≥120 ms	2.9 (1.02-8.6, P<0.04)
				Biphasic P in II,I II, aVF	
Abn. P axis					
Perez [13]				>95th%	1.21 (0.69-2.12, P<0.0001)
				>74° and <24°	1.52 (1.05-2.21, P>0.0001
PAC/runs					
Watanabe [51]	63,368	10 yrs	0.14%	Standard ECG, ≥1/10 sec	2.89 (1.80-3.35)
Perez [13]				Presence	2.1 (1.6-2.7, P<0.0001)
Murakoshi [52]	63,197	14 yrs	0.105%	Presence	4.87 (6.61-6.57) for men 3.87 (2.69-5.57) for women
Acharya[56]	1,357	7.5 yrs	11.4%	≥100/day	2.97 (1.85-4.80)
				couplets ≥50/day	3.11
				bigeminy	3.67
				3 PACs run ≥20 /day	2.94
				runs (≥10 beats/run)	1.73
PR interval					
Perez [13]				>200 ms	1.3 (1.1-1.6, P=0.003)
Nielsen[69]	288,181	6.7 yrs	3.8%	≥196 ms men	1.30 (1.17-1.44)
				≥204 ms women	1.18 (1.06-1.530)
				<129 ms men	1.09 (0.92-1.29) ‡
				<121 ms women	1. 32 (1.12-1.56)
Alonso[25]	262,288	5 yrs	6.8%	per 30 ms	1.03 (0.85-1.26, <0.0001) to 1.22 (1.01-1.42, 0.027)
Macfarlane[68]	5,680	3.2 yrs	9.4%	per 30 ms	1.19 (1.09-1.30, P<0.0001)

PAC: premature atrial contraction. FU: follow-up. HR: hazard risk. mo: months. yrs: years. Ref. No.: reference number.

athletes, but heart rate was not a significant predictor for incident AF after multivariable analysis [2],[5].

P-wave duration

The P-wave duration represents the time required for a sinus impulse to propagate from the sinus node to the entire atrium. A prolonged P-wave duration correlates with a slowed conduction velocity within the atria [7],[8], and fragmented local electrograms suggest the presence of fibrosis [9],[10]. P-wave duration (ms) was measured from the P-wave onset to its offset, and the maximum P-wave duration, defined as the longest duration observed on a standard 12-lead ECG, is most often used to predict incident AF in population-based studies and can be an intermediate ECG phenotype of AF [11],[12]. Perez [13] analyzed the data of 42,751 patients who were followed for 5 .3 years. New AF developed in 1,050 patients at an annual rate of 0.45%/yr. After correcting for age and sex, the maximum P-wave duration of >120 ms was predictive of AF, with a hazard ratio (HR) of 1.6

(95% confidence interval (CI): 1.3-1.8, P <0.0001). The ARIC study (15,429 participants), which had an annual rate of AF development of 0.11%/yr ([14]), and the Framingham Heart Study (FHS) (1,550 participants aged ≥60 years), which had an annual rate of AF development of 0.46%/yr ([15]), showed similar results. The HR per 20 ms or per 1 SD of the P-wave duration was also significant [13],[16]. In studies with smaller sample sizes, P-wave duration was a predictor of PAF in patients without [17],[21] or with heart diseases [22],[24].

The sensitivity, specificity and positive and negative predictive values for a P-wave duration ≥120 ms were 53.8%, 61.7%, 49.0% and 97.3%, respectively [25], and they were 7.2%, 94.5%, 34.6% and 76.4%, respectively, for a P-wave duration above the 95th percentile [16].

In studies with smaller sample sizes (n=50 to 371), a shorter P-wave duration was associated with AF development [26],[27]. In the Copenhagen ECG study, 285,933 participants were followed for 6.7 years [28]. The ECGs were digitally analyzed with clinically validated software (Marquette 12SL algorithm, General Electric Co., Fairfield, CT). AF developed at a rate of 0.49%/yr in this study. Compared to subjects who had a P-wave duration of 100-105 ms, both shorter and longer P-wave durations were associated with an increased risk of AF development [Table 1].

Using SAECG, the filtered P-wave duration (FPD) ≥125 ms as well as the root mean square value of the last 20 ms (RMS20) of ≤3.3 μV were independent predictors for incident AF [29],[32].

P-wave dispersion and variation

P-wave dispersion (PWD) is defined as the difference between the longest and shortest P-wave durations across 12-leads of the surface ECG. Although a precise electrophysiological role for AF development is only speculative, a P-wave dispersion of >80 ms was associated with an AF history ([13],[15]-[18],[26],[30],[33]) or new AF detection on Holter ECG recordings [23]. The sensitivity, specificity and positive and negative predictive values for a P-wave dispersion above the 95th percentile were 3.6%, 94.5%, 16.7% and 76.4%, respectively [15]. The standard deviation (SD) of the P-wave duration across 12 leads >35 ms was another risk factor for incident AF [13].

P-wave morphology and P-wave axis

P-wave duration ≥120 ms with and without inversion of the terminal part of the P-wave was defined as an inter-atrial block (IAB) [34], and an advanced IAB was defined as a P-wave duration ≥120 ms, with a biphasic morphology in the inferior leads shown to represent a block in the Bachman bundle with caudo-cranial activation of the left atrium. Association of an IAB with new onset of AF or recurrence of AF after cardioversion has been observed [35]-[38]. Following cavo-tricuspid isthmus ablation in 122 patients with typical flutter and no history of AF (mean age 63 years), advanced IAB was observed in 23% [35]. After a mean follow-up of 30 months, 46.7% developed new-onset AF. The incidence of AF was significantly higher in patients with advanced IAB than in those without: 71.4% vs. 39.4% (P=0.003) and a risk of new AF ([Table 1]). A recent meta-analysis included 18,204 patients (mean age 56±13, 48% male) with a mean follow-up period of 15.1 years [39]; advanced IAB was a significant predictor of new-onset AF with a pooled HR of 2.58 (95% CI: 1.35 to 4.96; P< 0.01), but the risk of new-onset AF for partial IAB (=P-wave duration ≥120 msec) did not reach statistical significance (HR: 1.42, 95% CI: 0.85 to 2.34; P=0.18).

The P-wave terminal force (μV•ms) was determined as the product of the negative P-wave deflection in the lead V1 (μV) and the duration (ms) from the onset of the negative deflection to its nadir (PTFV1). PTFV1 is considered to represent a volume or pressure overload of the left atrium [40], inter-atrial conduction delay [7] and fibrosis of the left ventricle as measured by MRI [41]. PTFV1 >0.04 mV•s and the upper 5th percentile of PTFV1 are risk factors for developing AF ([13],[14],[52]). Notching or deflection of the P-wave [30], P-pulmonale [43], the area of the initial portion of the P-wave [14] and pre-specified P-wave morphology were risk factors for incident AF [32]. The P-wave axis represents the electrical wave front propagation and the geometry of the atria, and it is altered under a volume or pressure overload of the atrium. A P-wave axis outside of 24°-74° [13] or <74° in the frontal plane was another risk factor for new AF [43].

Premature atrial contractions

The prevalence of PACs increases with advancing age and comorbidities, and PAC becomes a risk factor for AF. PAC may originate within pulmonary veins and precipitate PAF [44]. Prevention is difficult when it progresses to chronic AF [45]-[49], and catheter ablation is the only effective therapeutic modality thus far [50]. Watanabe analyzed data from a mass examination of a general population of 63,386 participants aged ≥50 years in the Niigata Preventive Medicine Study [51]. During a 10-year follow-up, new AF developed at a rate of 0.14%/yr. The presence of PACs in 10-second recordings of standard 12-lead ECGs was associated with AF, with an odds ratio (OR) of 2.89 (1.80-3.35). This result was confirmed later by Perez [13] and Murakoshi [52].

In Holter ECGs, supraventricular tachyarrhythmias have been shown to be a predictor of incident AF [53]-[59]. Frequent PACs, defined as ≥100 beats /day [56]-[57], ≥30 beats/hr [58] or PACs ≥102 beats/day [59], were a risk factor for incident AF. It has been found that subclinical atrial tachyarrhythmias detected by implanted devices within 3 months are a predictor of clinical AF, with an HR of 5.56 (95% CI: 3.78-8.17, P<0.001) [60]. The CHADS2 score and the count of PACs can predict incident AF independently and synergistically [59]. PACs have been shown to aid the detection of AF in patients with cryptogenic stroke or transient ischemic attack who had no AF at baseline [61]-[68].

The sensitivity was in the range of 4.1-29.0%, with a high specificity of >90%. The positive and negative predictive values ranged from 2.9-9.1% and 88.7-97.7%, respectively ([13],[51],[52]).

PR interval

The PR interval (ms) was defined by automatic measurement from the onset of the P-wave to the initiation of the QRS segment. It is composed of atrial conduction, conduction through the atrio-ventricular node and the His-Purkinje system, and it is affected by autonomic tones. A PR interval >200 ms or PR interval of ≥95th percentile (≥196 ms for women and ≥204 ms for men) was a risk factor for incident AF ([3],[66]-[71]). A significant HR was obtained for a 30-ms increment of the PR intervals [3],[25]. In a subgroup of patients with P-pulmonale (n=591), a PQ interval >150 ms was associated with a higher HR of 6.89 (95% CI: 2.39-29.15, P<0.0001) [43]. A short PR interval (≤121 ms for women and ≤129 ms for men) [69] or PR interval variation (maximum PR interval minus minimum PR interval) >36.5 ms [71] was another risk for AF development.

The sensitivity, specificity and positive and negative predictive values were 7.5%, 95.8%, 5.2% and 77.4%, respectively, for PR intervals >95th percentile in FHS [15] and were 13.2%, 90.1%, 4.8% and 96.6%, respectively, for PR intervals >200 ms compared with those ≤200 ms [25].

However, there was a study showing that a prolonged PR interval was not associated with increased incident AF and that a PR interval >200 ms could normalize to ≤200 ms in 30% of patients during follow-up [72]. The underlying mechanism of how a prolonged PR interval induces AF is not well understood.

Ventricle-related ECG-derived predictors ([Table 2])

Left ventricular hypertrophy (LVH), premature ventricular contraction (PVC) or non-sustained ventricular tachycardia (NSVT), ST-T abnormalities and the QT (QTc) interval or bundle branch block (BBB) have been examined in large studies.

LVH

LVH is usually diagnosed from ECG criteria, and ECG-derived LVH has been used in mass examinations [73],[74]. The Sokolow-Lyon, Romhilt-Estes, Cornell voltage criteria or Minnesota code were used. LVH reduces the compliance of the left ventricle and imposes a pressure overload on the atrium, leading to dilatation and remodeling.

LVH was a risk factor for AF development during a 10-year follow-up period in Japanese people [51] (OR: 1.43; 95% CI: 1.13-1.80). This was confirmed by subsequent studies ([13],[25],[67],[68]). The ECG-derived LVH measure of the Sokolow-Lyon voltage product had a risk similar to that of the cardiac magnetic resonance-derived LVH: 1.83 (95% CI: 1.06-3.14) and 2.04 (95% CI: 1.15-3.62), respectively [75]. The calculated sensitivity, specificity and positive and negative predictive values for LVH were 5.1-11.5%, 94.7-97.9%, 5.2-8.3% and 97%, respectively ([13], [15], [25]).

PVC and runs

Watanabe [51] and later, Perez [13], showed that the presence of a PVC on surface ECG recordings during examination was associated with incident AF. Any PVCs recorded for 2 minutes were risk factors for incident AF [76]. In studies from Taiwan [77],[78], non-sustained

Table 2: Ventricle-related ECG-derived predictors for new-onset AF.

Author (Rf. No.)	Number of participants	FU time	Annual incidence	ECG finding	HR (95% CI, P-value)
LVH					
Watanabe(51)				Sokolow-Lyon	1.43 (1.13-1.80)
Perez[13]				**Romhilt-Estes**	**1.3 (1.0-1.7, P=0046)**
Chrispin[75]	4942			Sokolow-Lyon	1.83 (1.06-3.14)
Alonso[25]					1.04 (0.99-1.10) to 2.96 (1.08-8.01)
Macfarlane[68]	117			Minnesota code, definite	2.51 (1.13-5.57)
	138			probable	1.1 (0.90-1.47, P=0.27)
	709			possible	1.35 (1.08-1.70, 0.010)
PVC/runs					
Watanabe[51]				presence	3.49 (2.40-5.08)
Perez[13]				presence	1.5(1.2-1.9, P=0.004)
Agarwal[76]	14,783	15-17yrs		**presence in 2 min**	1.56 (1.30-1.87)
Lin[77]	3751	10.1 yrs	0.68	multiform NSVT	1.546 (1.058-2.258)
Lin[78]	3367	10.1 yrs	0.68	NSVT (≥3 PVCs)	**1.716(1.243-2.368)**
ST-T abn					
Watanabe[51]				without LVH	1.89 (1.34-2.13)
Macfarlane[68]				Minnesota code 5-1/5-2	1.7 6(1.41-2.21, P<0.0001)
BBB					
Perez[13]				LBBB	1.7(1.2-2.5, P<0.0001)
Watanabe[51]				LBBB	0.96 (-)
				RBBB	0.84 (-)1.17(1.08-1.27, P<0.001)
				QRS width per 20 ms	1.17(1.08-1.27, P<0.001)
Macfarlane[68]	4,696	12.3 yrs	2.16%	LAFB	2.1 (1.1- 3.9, P=0.023)
QTc					
Macfarlane[68]				per 30 ms increment	1.31(1.20-1.42, P<0.0001)
Mandyam[83]	14,538		0.51%	per 10 ms increment	1.11(1.07-1.14, P<0.001)
				≥460ms (women)/≥450 ms (men)	1.99 (1.37-2.89, P<0.001)
Nielsen[84]				≤372 ms	1.45 (1.14-1.84; P=0.002)
				≥458 ms	2.32 (1.52- 3.54, P<0.001)
Nguyen[55]				≥460 ms (women) or≥450 ms (men)	2.5 (1.4-4.3, P=0.002)

From the pooled data of the Framingham study, the ARIC study3) and the Cardiovascular Health study40) for derivation and the Rotterdam study41) for validation in CHARGE-AF Consortium.25) BBB: bundle branch block or hemi-block. FU: follow-up. HR: hazard risk. LAFB: left anterior fascicular block. LBBB: left bundle branch block. LVH: left ventricular hypertrophy. NSVT: non-sustained ventricular tachycardia ≥3 beats. RBBB: right bundle branch block. PVC: ventricular premature contraction. Ref. No.: reference number. ST-T abn. : ST-T abnormality

ventricular tachycardia was a risk for new-onset AF.

ST-T abnormalities

ST-T abnormalities reflect the presence of hypertrophy, fibrosis or conduction abnormalities of the ventricle and ischemia of the ventricle, and these conditions can lead to diastolic dysfunction of the ventricle and atrial remodeling. In the general population, Watanabe [51] showed that ST-T abnormalities unrelated to LVH were risk factors for new-onset AF, and this was confirmed by the PROSPER study [68].

Bundle branch block (BBB)

Perez [13] has shown that left BBB (LBBB) is a risk factor for AF development, but neither right BBB nor left BBB was a risk factor for new-onset AF in the Niigata Preventive Medicine study [51]. In the PROSPER study [68], widening of the QRS complex was a risk factor for incident AF. A left anterior fascicular block (LAFB) was a risk for AF development [55], but cases with LAFB were found in only 2.3% of the 1,664 participants [79].

QT interval

An inherited abnormality of the QT interval is known to be associated with a high incidence of AF ([80]-[82]), and its pathogenesis is related to the ion channelopathy of the atrium. QT intervals were corrected by either the Bazett, Framingham study, Hodges or Fridericia formula. A QTc ≥460 ms for women or QTc ≥450 ms for men was a risk factor for incident AF in the ARIC studies [83]. The risk of incident AF increases for every 40 ms [62] or 10 ms [1]increment of QTc. A QTc interval lower than the first percentile (≤372 ms) was also associated with a significant HR for incident AF compared with that in reference individuals (411 to 419 ms) [84].

Discussion

In population-based studies, some ECG-derived variables are risk factors for AF development. P wave abnormality, such as prolongation of the P-wave width, its dispersion, and morphology, and the presence of PACs/runs are the ECG phenotype of electrical remodeling of the left atrium and triggers for AF initiation, respectively. The ECG markers of the ventricle were also predictors for incident AF. Most of these ECG predictors are associated with low sensitivity and low positive predictive values, which leads to difficulty in identifying patients who are likely to develop AF. However, the high negative sensitivity can be used to identify those who are unlikely to develop AF.The ECG-derived risk findings can be a result of the underlying diseases that cause remodeling of the ventricle and the atrium.

Measurements of ECG-derived variables

The ECG-derived predictors for incident AF can be easily and simply obtained in a population-based study and measured automatically by recent ECG hardware setups, with the exception of P-wave index measurements. P-wave durations were initially measured manually and more recently by a computer-assisted system, but it may still require confirmation by cardiologists. P-wave dispersion is defined as the difference between the longest and the shortest P-wave durations across 12-leads, but its electrophysiological significance and role in AF development need to be clarified. P-wave durations may be measured precisely using SAECG, but its use is impractical for screening mass examinations.

ECG-based LVH is associated with incident AF, and it can be measured easily and automatically. However, it is known that the ventricular mass is more accurately determined by echocardiography [85] or magnetic resonance imaging [86], although the use of such techniques is apparently limited in population-based screening. The number and runs of PACs and PVCs can be counted precisely, but we were unable to locate their origin from the surface ECG alone. The majority of PACs that trigger paroxysmal AF is known to occur within the pulmonary vein [44]. Of other ECG variables, the QT interval has been shown to be a risk for new-onset AF, but it was corrected differently by the formulas of Bazett, Framingham, Hodges and Fridercia. Uniformed measurements may be desired in screening candidates for incident AF in a population-based study .

Clinical risk variables and ECG-derived risks

There are well-known clinical predictors for new-onset AF (age, gender, hypertension, obesity, diabetes mellitus and heart failure) ([1]-[6],[79]), and all of these variables induce electrical and structural remodeling of the atrium and the ventricle. With advancing age, the heart increases in weight, ventricular wall thickness and valve circumferences, and the myocardium contains increased fat, collagen, elastin and lipofuscin [14]; these abnormalities all involve the LA. The age-related LA remodeling is accelerated by comorbidities, such as hypertension, diabetes mellitus or obesity. On the surface ECG, the maximal P-wave duration, P-wave dispersion and standard deviation of P-wave duration were observed to correlate with advancing age ([87]-[89]). LV dysfunction imposes a pressure overload on the left atrium and leads to electrical and structural remodeling of the atrium. P-wave durations showed a correlation with diastolic dimensions, ejection fractions and diastolic functions of LV ([28], [72]-[74]) and interstitial fibrosis as determined by MRI [75].

In hypertension, the conduction time is prolonged ([90]-[92]), and the P-wave duration is prolonged in the surface ECG [18],[93]. Furthermore, P-wave indices can be a marker of target organ damage [94]. P-wave indices are abnormal in type 2 diabetes ([95],[96]) and obesity ([93]) compared to those in healthy control individuals.

Reversal of ECG-derived risks

Treatment of hypertension induces reversed remodeling of the heart [97]. With the use of angiotensin-2 receptor blockers or angiotensin converting enzyme inhibitors, prolonged P-wave durations or dispersions were observed to normalize ([98]-[102]), but this was not the case with calcium channel blockers [99].

These findings are compatible with the results of our experiments. In spontaneously hypertensive rats (SHRs), olmesartan (OM), an angiotensin 2 type 1 receptor blocker, reversed hypertrophy and fibrosis of the atrium more effectively than azelnidipine, a calcium channel blocker [103]. OM decreased atrial oxidative stress and activation of Rac1. The structural remodeling of the atrium was prevented by OM and a mineral corticoid antagonist eplerenone in Dahl salt-sensitive rats [104]. They induced an attenuation of oxidative stress and an attenuation of the Rac1-oxidative stress/inflammatory axis. The regression was associated with prevention of AF induction by electrical stimulation [104].

Through intensified treatment of blood pressure in patients with type 2 diabetes mellitus, a composite endpoint of new AF and prolonged P-wave indices and incident abnormal P-waves were shown to decrease (P=0.02 for both) in the ACCORD Blood Pressure Trials [105].

A significant decrease of P-wave duration or dispersion was observed in patients with loss of their original weight ([106],[107]). Severely obese patients (n=40) who underwent bariatric surgery showed a significant decrease of P-wave dispersion after surgery [108]. Treatment of underlying diseases can correct the abnormal P-wave

indices, but their prophylactic efficacy for incident AF is yet to be determined.

Limitations

In the population-based studies, AF was diagnosed on ECGs recorded for approximately 10 seconds, and this may lead to the under diagnosis of PAF. The correlation between the ECG-derived predictors and clinical predictors for incident AF was studied in a small number of patients. It is unknown whether the reversal of ECG risk variables can prevent new-onset AF. Future study of a larger number of participants is needed. Recently, a genetic analysis has highlighted candidate genes or SNPs associated with AF development [109], but their relevance to ECG-derived predictors remains unknown.

Conclusions

ECG-derived variables have been confirmed as a risk for incident AF from large population-based studies. The correlation between these markers with underlying disease or clinical predictors of incident AF needs to be shown in a study with a larger number of participants. Whether AF can be prevented by treatment of comorbidities requires prospective study.

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Left Atrial Appendage Occlusion with Amplatzer Cardiac Plug and Amplatzer Amulet: A Clinical Trials Update

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Abstract

It has been over a decade since dedicated Amplatzer devices have been used for left atrial appendage occlusion (LAAO) in patients with atrial fibrillation. The first was the Amplatzer Cardiac Plug (ACP) that is now replaced in most countries by the Amplatzer Amulet device. Most of the clinical data for ACP come from the ACP multicenter registry that included 1047 patients from 22 sites, whereas the largest to date report on the Amplatzer Amulet is a recently published prospective multicenter study in 1088 patients from 64 sites. Two important randomized clinical trials the Amulet IDE trial and the STROKECLOSE trial are currently enrolling patients and expected to provide more data on LAAO with Amplatzer Amulet in the near future.

The Amplatzer Cardiac Plug (ACP) is the first Amplatzer device that was specially designed by Dr. Kurt Amplatz for percutaneous left atrial appendage occlusion (LAAO). [1] It acquired CE mark in December 2008. The Amplatzer Amulet is a second-generation LAAO device that became commercially available in Europe in January 2013 (AGA Medical, acquired by St Jude Medical, St Paul, MN, USA – now Abbott Vascular, Santa Clara, CA, USA). [2] Currently, the Amplatzer Amulet is one of the most widely used devices for LAAO worldwide but is not yet approved by the US Food and Drug Administration.

Most of the clinical data for ACP come from the ACP multicenter registry. [3] In this retrospective registry, prospectively collected data on 1047 consecutive patients from 22 centers were transferred in a common database and analyzed. Patients were treated between December 2008 and November 2013 so this analysis included the "learning curves" of all participating centers and operators. A total of 1001 patients who underwent LAAO with the ACP and had complete follow-up were included and were further analyzed for stroke and bleeding reduction by comparing their outcomes with the predicted risks by the CHA_2DS_2-VASc and HAS-BLED score, respectively. The most common indication for the procedure was previous bleeding (47%) followed by high bleeding risk (35%) and the avoidance of triple therapy for coronary artery disease and stenting (22%). The composite of previous bleeding (major or minor) and high bleeding risk was 73%. Therefore, this study was the first large "real world" report on LAAO in patients with contraindications to oral anticoagulation (OAC) therapy. The mean $CHADS_2$ score was 2.8±1.3 and the mean CHA_2DS_2-VASc score was 4.5±1.6. The mean HAS-BLED score was 3.1±1.2. A score of ≥3 was present in 742 patients (72%). Procedural success was achieved in 1019/1047 patients (97.3%). A total of 52 periprocedural major adverse events (4.97%) were reported, including 8 procedure-related deaths, 9 strokes, and 13 cardiac tamponades. The average patient follow-up was 13 months, resulting in a total of 1,349 patient years. It should be noted that LAAO with the ACP does not require OAC after the procedure. According to the device manufacturer recommendations, patients were prescribed dual antiplatelet therapy (DAPT) for 1-6 months (average 3 months) and single or no antiplatelet therapy thereafter. The annual rate of systemic thromboembolism in the study (periprocedural and follow-up) was 2.3% (31/1,349 patient-years), which is a 59.1% risk reduction [Figure 1]. The annual rate of major bleeding (periprocedural and follow-up) was 2.1% (28/1,349 patient-years), which is a 61.0% risk reduction. On transesophageal echocardiography (TEE) follow up that was available in 632/1001 of successfully implanted patients, a significant (3-5mm) peri-device leak was found in 12 patients (1.9%) patients, whereas a thrombus related to the device was observed in 28/632 patients (4.4%). This study had a few limitations: it was not randomized without a control group, the TEE follow-up was not available for all patients and the study results were self-reported, without independent adjudication. However, a written summary was provided for all major adverse events.

In order to address the lack of independent TEE adjudication in the ACP registry, a relevant sub-study was performed by Saw et al., entitled "Incidence and clinical impact of device-associated thrombus and peri-device leak following left atrial appendage closure with the Amplatzer Cardiac Plug". [4] A total of 344 follow up TEEs (performed after a median of 134 days), from 605 consecutive patients were submitted to a core laboratory and reviewed by 2 independent experts for peri-device leak, device-associated thrombus, device

Key Words
Left atrial appendage closure, Stroke prevention, Atrial fibrillation.

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embolization, device migration, left atrial appendage thrombus, and left atrial thrombus. Device-associated thrombus was observed in 3.2% and significant peri-device leak in 1.2% of patients. Neither device-associated thrombus nor peri-device leak was associated with an increased risk for cardiovascular events. Independent predictors of device-associated thrombus were smoking (odds ratio: 5.79; p=0.017) and female sex (odds ratio: 4.22; p=0.027). It should be noted that device-associated thrombus is a complex matter and other factors could be independent predictors but were not included in this analysis.

Patients with renal insufficiency and AF are usually difficult to manage with OAC therapy. Moreover, these patients are commonly not well represented in large randomized clinical trials. Therefore, Kefer et al. conducted a sub-group analysis of patients with chronic kidney disease (CKD) within the ACP registry. [5] Patients with CKD had at higher risk for stroke and major bleeding compared to patients without CKD (p<0.001 for both). Kaplan–Meier analysis showed a lower overall survival (84 vs. 96% and 84 vs. 93% at 1 and 2 yrs. respectively; p < 0.001) among patients with an eGFR <30 ml/min/1.73 m2. However, procedural success was similarly high (97%) in all stages of CKD, with no significant differences in peri-procedural major adverse events (MAEs; 6.1 vs. 4.5%, p = 0.47). The overall stroke and bleeding reduction was similar among groups (60-62%).

Another important group is patients with previous intracranial bleeding (ICB), who have often an absolute contraindication to OAC therapy. In the ACP registry, a total of 198 patients (18.9%) with previous ICB were identified and were compared with patients without previous ICB. [6] Patients were younger, more commonly male, and had a higher rate of previous stroke. The CHA_2DS_2-VASc score was similar between groups but the HAS-BLED score was higher in patients with previous ICB. There were no significant differences in peri-procedural MAEs. Patients with previous ICB were receiving more frequently aspirin and less frequently OAC at baseline. In addition, patients with previous ICB were more frequently on single aspirin therapy after LAAO (last follow-up visit: 74.5% vs. 61.3%; p < 0.001). At follow-up (average 1.3 years), the observed annual stroke/transient ischemic attack (TIA) rate (procedure and follow-up) for patients with previous ICB was 1.4% (75% relative risk reduction), [Figure 2]. The observed annual major bleeding rate (procedure and follow-up) for patients with previous ICB was 0.7% (89% relative risk reduction). This study concluded that in patients with previous ICB and AF, LAAO seemed to be a safe procedure and was associated with a significant reduction in stroke/TIA and a remarkably low frequency of major bleeding during follow-up. In a propensity score matched follow-up study from the Nordic countries, Nielsen-Kudsk et al. compared patients with AF and previous ICB who underwent LAAO using the Amplatzer Cardiac Plug or the Amplatzer Amulet to a matched group of 151 patients receiving standard medical therapy. [7] The primary endpoint was a composite of all-cause mortality, ischemic stroke and major bleeding. Patients with AF and a prior ICB treated with LAAO had a lower risk of the composite outcome as compared to patients treated with standard medical care (events/1000 years: 53.3 vs. 366.7; hazard ratio 0.16 [0.07-0.37]). The authors concluded that LAAO was suggested to be of major clinical benefit in AF patients having sustained an ICB. A relevant randomized clinical trial entitled STROKECLOSE (ClinicalTrials.gov Identifier: NCT02830152) started in May 3, 2017. The primary endpoint is a composite of stroke (ischemic or hemorrhagic), systemic embolism, life threatening or major bleeding and all-cause mortality, with a time frame up to 5 years after randomization. The study inclusion criteria are: a diagnosis of paroxysmal, persistent or long-standing NVAF with CHA_2DS_2VASc score >2, clinical and CT/MRI evidence of ICH within 6 months but not less than 4 weeks prior to enrollment, and age > 18 years. The study exclusion criteria are ICH secondary to vascular malformation or tumors, estimated life expectancy of < 1 year at eligibility assessment, modified Rankin Score > 3 at enrollment, contraindications to LAAO known at the time of enrollment, such as LAA thrombus or systemic infection, prior surgical LAA excision, and planned combined interventional procedures at the time of enrollment.

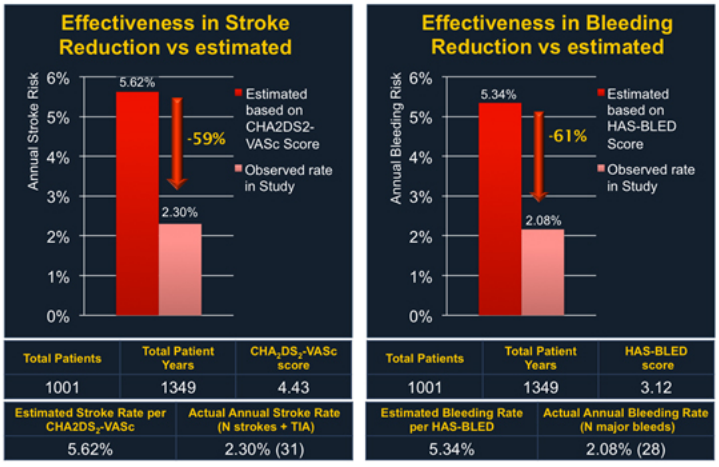
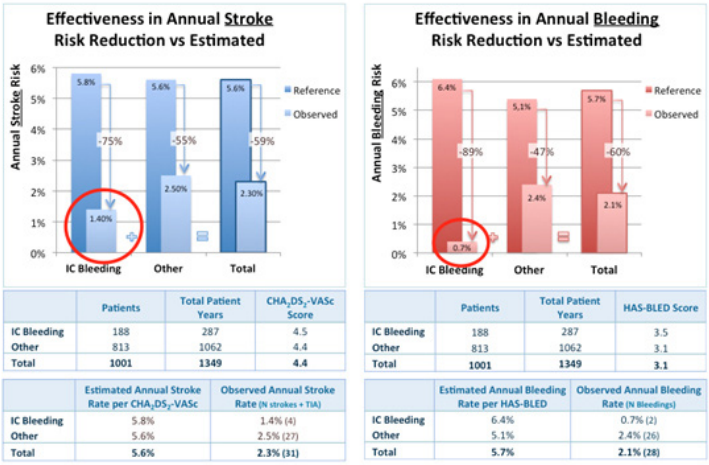


Figure 1: **Effectiveness of LAAO with the Amplatzer Cardiac Plug in reduction of thromboembolism and bleeding. Both periprocedural and follow-up events were included in the analysis.**

The severity of stroke related to AF is a matter of concern as these strokes result in death in 20% or major disability in up to 60% of patients. [8] Freixa et al. investigated all reported cerebrovascular events at follow-up from the ACP registry. [9] There were 9 strokes (0.9%), 9 TIAs (0.9%), and 0 intracranial hemorrhages (0%) at follow-up. After excluding the 2 patients with previous disability, functional assessment showed disabling cerebrovascular events in 3 (19%) of the remaining 16 patients. In the 2 patients with previous disability, no increase in the baseline, in-hospital, and 3-month modified Rankin Score was observed. The median time from LAAO to the cerebrovascular event was 420 days, and 17 patients (94%) were on single-antiplatelet therapy when the event occurred. The authors concluded that cerebrovascular events after LAAO with the ACP system were infrequent and mostly non-disabling. In another relevant analysis form the ACP registry, Freixa et al. investigated the impact of patient age in the overall LAAO outcomes. [10] In this analysis, LAAO with the ACP was associated with similar procedural success in patients aged < 75 and ≥ 75 years. Interestingly, older patients had a higher incidence of cardiac tamponade but at follow-up stroke and major bleeding rates were similar among groups.

An important subgroup of patients in the ACP Registry, those with previous major gastrointestinal bleeding (MGIB) as indication for LAAO, was studied by Lempereur et. al. [11] A total of 151 patients with previous MGIB were evaluated. Periprocedural major bleeding events were more frequent in patients with previous MGIB as compared to those without MGIB (4.0% vs 0.8%, p = 0.001).



	Patients	Total Patient Years	CHA_2DS_2-VASc Score
IC Bleeding	188	287	4.5
Other	813	1062	4.4
Total	1001	1349	4.4

	Estimated Annual Stroke Rate per CHA_2DS_2-VASc	Observed Annual Stroke Rate (N strokes + TIA)
IC Bleeding	5.8%	1.4% (4)
Other	5.6%	2.5% (27)
Total	5.6%	2.3% (31)

	Patients	Total Patient Years	HAS-BLED Score
IC Bleeding	188	287	3.5
Other	813	1062	3.1
Total	1001	1349	3.1

	Estimated Annual Bleeding Rate per HAS-BLED	Observed Annual Bleeding Rate (N Bleedings)
IC Bleeding	6.4%	0.7% (2)
Other	5.1%	2.4% (26)
Total	5.7%	2.1% (28)

Figure 2: **Reduction in stroke and bleeding after LAAO with Amplatzer Cardiac Plug. Patients with previous intracranial bleeding (IC Bleeding) are compared with patients without IC Bleeding.**

With an average follow-up of 1.3 years, the observed annual rate of stroke/transient ischemic attack and major bleeding for patients with previous MGIB were 2.1% (61.4% relative reduction according to the CHA_2DS_2-VASc score) and 4.6% (20.1% relative reduction according to HAS-BLED score), respectively. The study concluded that in patients with NVAF and previous MGIB, LAAO was associated with a low annual rate of stroke/transient ischemic attack. Periprocedural major bleeding events were more frequent in this specific population although the annual major bleeding rate showed a 20.1% relative risk reduction according to the HAS-BLED score.

A very important, partially unexplored field in LAAO therapy is the choice of antithrombotic medication after the procedure. Taking into account that some patients may not tolerate well DAPT, Korsholm et al. investigated the use of single antiplatelet therapy after LAAO with the ACP or the Amplatzer Amulet in 107 patients. [12] With a median follow-up of 2.3 years, device-related thrombosis was detected in 1.9% of cases. Annual stroke reduction was 61% compared to the predicted rate, and annual risk of major bleeding was reduced by 57%. Therefore, the authors concluded that LAAO with the ACP or the Amulet occluder could be safely performed with aspirin monotherapy after implantation, without an increased risk of device-related thrombosis or stroke.

In a study including 500 consecutive patients who underwent LAAO (408 treated with ACP – 92 treated with Amplatzer Amulet) published by Koskinas et al., overall early procedural success was 97.8%, and MAEs occurred in 5.8% of patients, with no effect of device type or size. [13] Independent predictors of MAEs were device repositioning and left ventricular ejection fraction <30%. It should be noted that this center follows fluoroscopy-only guidance for LAAO procedures.

The largest to date report on the Amplatzer Amulet is a global, prospective observational study that enrolled 1088 patients who were treated with this device in 64 clinical sites, worldwide. [14] The majority of patients (82.8%) had a contraindication to OAC therapy. Successful device implantation was achieved in 99.0% of patients. Major adverse events occurred in 3.2% of patients during the proce¬dure and the index hospitalization, including 2 deaths (0.2%), 26 major bleeding events (2.4%), and 2 strokes (0.2%). Patients were discharged on a single antiplatelet agent (23.0%), DAPT (54.3%) or OAC (18.9%). The TEE fol¬low-up 67±23 days post procedure that was available in 673 patients showed adequate (<3 mm jet) occlusion of the left atrial appendage in 98.2% of patients and device thrombus in 10 patients (1.5%), as evaluated by core laboratory analysis. The authors concluded that compared to other recent reports on LAAO, this study showed a high implant success rate (99%) and similar peripro¬cedural risk in a real-world all-comers cohort of AF patients at high risk of stroke and bleeding. Moreover, TEE follow-up data confirmed high closure rates at 1-3 months post implant. Long-term clinical outcome data are being collected and will be reported in the near future.

The Amplatzer Amulet device is currently being evaluated in a randomized controlled trial (Amulet IDE Trial; ClinicalTrials.gov Identifier: NCT02879448). The study is aiming to enroll 1600 patients from 150 centers (100 in the US and 50 worldwide). The Amulet device is compared to the Watchman device (Boston Scientific Inc. Marlborough, MA, US) in a 1:1 ratio. The primary safety endpoint is a composite of procedure-related complications, or all cause death, or major bleeding through 12 months. The primary effectiveness endpoint is a composite of ischemic stroke or systemic embolism through 18 months. A secondary endpoint is device closure, defined as residual jet around the device ≤ 5 mm at the 45-day visit documented by TEE. This study is the largest randomized study on LAAO and the first randomized comparison of two occluders.

An important remaining question in the field is the comparison between LAAO and NOAC therapy. A small, randomized clinical trial from the Czech Republic (PRAGUE-17 study) is currently recruiting patients, aiming to enroll a total of 400 subjects. Patients are randomized to undergo LAAO with either Watchman or Amplatzer Amulet or receive NOAC therapy. The primary endpoint is a composite of "stroke or systemic cardioembolic event or clinically significant bleeding or cardiovascular death or procedure or device-related complications" at one year.

One of the main limitations of LAAO-related clinical studies is the lack of universal definitions for parameters and endpoints to be assessed. A recent publication entitled "Percutaneous LAAO: the Munich consensus document on definitions, endpoints, and data collection requirements for clinical studies" aimed to address this issue. [15] This document proposes a consistent approach in the assessment and reporting of clinical results, including comparisons with other devices and with surgical or pharmacological therapies. It is endorsed by the European Heart Rhythm Association, the European Association of Percutaneous Cardiovascular Interventions, and other societies.

In conclusion, most of the clinical data on LAAO with the ACP and Amplatzer Amulet come from large retrospective or prospective multicenter registries and single center reports. Both devices have shown favorable results in terms of safety and efficacy. The vast majority of patients included in these studies have a contraindication to OAC therapy, which is alignment with the current real-world needs for stroke prevention related to AF. Nevertheless, it is important to collect more, good quality data coming from randomized clinical trials in order to confirm the so far promising results with this therapy.

Disclosures

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Reversal Agents in the Era of NOACs

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Abstract

The incidence and prevalence of atrial fibrillation (AF) is expected to more than double between 2010 and 2030. Accordingly, the use of non-vitamin K oral anticoagulant (NOAC) agents for thromboembolic stroke prevention is anticipated to increase. The development of effective and safe antidotes is needed to address the unmet need for rapid anticoagulation reversal. The immediate role for these novel antidotes is for reversal of NOAC activity in life threatening bleeding and urgent surgical intervention. In addition, reversal agents may play an important role in simplifying bridging protocols in the peri-procedural period for catheter ablation of AF and elective surgery. Currently, novel reversal agents are either decoy drug receptors or small molecule non-specific anticoagulant activity inhibitors. These agents are at various stages of FDA investigation and approval, with emerging prospective data for safety and efficacy. The purpose of this review is to outline the currently developed NOAC molecular antagonists, their potential clinical roles and future directions.

Introduction

The advent of NOACs has simplified the management of thromboembolic risk in non-valvular AF. Their use obviates the need for regular therapeutic monitoring whilst affording at least comparable efficacy and probably a superior safety profile, compared to traditional vitamin K antagonists (VKA)[1]-[4]. In the setting of catheter ablation of AF, uninterrupted VKA is an established strategy aimed at minimising the risk of peri-procedural thromboembolism [5], [6]. Likewise, the use of uninterrupted or minimally interrupted NOAC therapy in the peri procedural period has garnered traction, supported by case series and early prospective clinical studies[6]-[8]. However, the initial lack of reversal agents has been a hindrance in advancing the use of these agents in AF, both in general use and specifically in the ablation setting. A detailed understanding of NOAC molecular structure and function has enabled the design of antagonist drugs.

Overview of Non-vitamin K antagonists and the need for effective reversal agents

There are currently 4 NOACs available for clinical use. Dabigatran is a direct thrombin inhibitor while rivaroxaban, apixaban and edoxaban are factor Xa (FXa) inhibitors. Betrixaban is also a FXa activity inhibitor developed through the molecular iterative process, which has undergone phase II studies in AF[9]. An overview of the pharmacologic and pharmacokinetic characteristics of these agents is shown in [Table 1]

Between 2010 and 2030, the prevalence of AF is estimated to rise from 5 million to 12 million[10] . Correspondingly, between 2009 and 2014, the use of NOACs has increased to 4.21 million, and based on IMS Health Global Data, this figure is expected to continue to increase significantly [11] .The use of these agents in AF thromboembolic prevention is therefore expected to be accompanied by an increase in serious hemorrhagic complications. Rapid reversal of anticoagulation is particularly desirable in the event of intracranial haemorrhage and major gastrointestinal haemorrhage. TABLE 2 shows the incidence of life threatening hemorrhagic complications necessitating acute anticoagulation reversal in patients taking NOACs[1-4, 12, 13] . In addition, the annual acute care surgery rate is 1290 per 100,000 14 . These figures demonstrate a current and escalating future need for rapid, efficacious and safe NOAC specific reversal agents..

Pharmacology of Reversal Agents

Until recently, only bypass agents were available for bleeding on NOAC therapy. However, now direct molecular antagonists that inhibit the anticoagulant activity have been developed. The latter class of agents act by binding to and sequestering the active drug (Idarucizumab or Andexanet alfa) or occupying the anticoagulant drug's active site through non-covalent hydrogen bonding (Aripazine, Ciraparantag, [PER977]).

Bypass agents are pro-haemostatic clotting factors that can activate coagulation despite presence of coagulation inhibitors. Prothrombin Complex Concentrates (PCCs), activated PCCs (aPCCs) and recombinant FVIIa (rFVIIa) have been suggested for consideration within many local institutional bleeding management protocols. However it is important to note that efficacy testing for NOAC effect reversal has been limited to animal studies and small healthy

Key Words

Non-vitamin K antagonist anticoagulants, Reversal agents, Atrial Fibrillation.

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Table 1: Pharmacology and Pharmacokinetics of NOAC agents

	Dabigatran etexilate	Rivaroxaban	Apixiban	Edoxaban	Betrixaban
Mechanism of action	Reversible thrombin inhibitor. Indirectly inhibits thrombin-induced platelet aggregation	Competitive dose-dependent inhibition of free Factor Xa and prothrombinase activity as well as clot-bound Factor Xa. Indirectly inhibits thrombin-induced platelet aggregation			
Half-life (hrs)	7-9	5-9	~12	10-14	37
Time to maximum concentration (Tmax) (hrs)	1-2	2-4	3-4	1-2	3-4
Elimination	80% renally cleared unchanged; 20% active glucuronide-bound metabolites eliminated in stool	36% unchanged via renal secretion; 30% renal excretion of inactive metabolites; 34% hepatobiliary excretion	>50% excreted in stool; 12.5% recovered in urine unchanged; 12.5% inactive recovered in urine	60% excreted in stool; ~35% excreted in urine. >70% eliminated unchanged	<7% renal clearance; <1% hepatic metabolism. 82-89% unchanged hepatobiliary excretion via P-gp pump
Coagulation parameters (qualitative)	aPTT, TT	PT, anti-FXa	Anti-FXa	Anti-FXa	Anti-FXa

human volunteer studies[14]-[16] and to date there are no controlled clinical studies of reversal therapy in bleeding patients taking oral Xa inhibitors. Importantly, these agents carry an inherent pro-thrombotic risk and are expensive[17]-[19].

Ligand-specific and small molecule reversal agents are currently under investigation[20]. These agents are likely to be primarily used in life-threatening bleeding and emergent surgery. In addition, these agents may allow the safer implementation of uninterrupted or minimally interrupted NOAC protocols for elective surgery and catheter procedures. Notably, preliminary studies suggest that the ligand-specific reversal, idaracizumab, does not exhibit pro-thrombotic effects, in contrast to plasma protein derived bypass agents, and this may be important in pro-thrombotic states of AF and left atrial catheter ablation. However this observation requires confirmation by controlled trials. Aripazine (Ciraparantag, PER977) which potentiates FX activation by FIXa and platelet activation by adenosine diphosphate, may result in a pro-thrombotic state.

Idarucizumab is a monoclonal antibody that acts as a non-competitive irreversible inhibitor of unbound and thrombin-bound dabigatran and its active metabolites[21]. The compound has a high affinity and it is a specific inhibitor of Dabigatran action. The agent has a rapid onset mechanism of action and has been demonstrated to be safe and efficacious with a simple dosing regimen[22]. Laboratory evidence of reversal is observed within minutes. Idarucizumab has been approved by the FDA as well as the Australian and European regulatory bodies, and is widely incorporated into protocols for use in acute bleeding or emergent surgery[23].

Table 2: Incidence of serious hemorrhagic complications associated with NOAC use[1-3]

	Intracranial hemorrhage		Serious gastrointestinal hemorrhage	
	Incidence per year (%)	Estimated number per year	Incidence per year (%)	Estimated number per year
Dabigatran	0.3	900	0.4	1200
Rivaroxaban	0.5	4000	0.8	6400
Apixaban	0.4	2000	0.2	1000

Table 3: Bypass agents

Agent	Pharmacology	NOAC	Dosage and titration	Titration
3 factor PCC	Inactivated PCC (FII, FIX and FX)	Rivaroxaban, apixaban and Edoxaban. Variable evidence for Dabigatran	25-50IU/Kg	PT
4 factor PCC	Inactivated PCC (FII, FVII, FIX and FX)	Rivaroxaban, apixaban and Edoxaban. Variable evidence for Dabigatran	25-50IU/Kg	PT
Activated PCC	Activated FII, FVIIa, FIX and FX	Dabigatran, Rivaroxaban, Apixaban and Edoxaban	50 IU/kg. Maximum single dose of 100 Units/kg or maximum daily dose 200 Units/kg.	Not amenable to titration against standard coagulation assays
Recombinant FVIIa	Activated FVII	In-vitro data inconclusive for benefit in NOAC reversal	0.5-1mg/Kg	Currently not recommended due to poor in vitro efficacy and pro-thrombogenicity

PCC: Protein complex concentrate, F: coagulation factor, PT: Prothrombin time, NOAC: Non-vitamin K oral anti-coagulant

Andexanet-alfa is a recombinant modified human factor Xa decoy protein. It binds with high affinity to FXa inhibitors within 2 minutes of IV administration, but lacks enzymatic activity thereby neutralising the direct and indirect effects of FXa. A bolus dose is followed by an infusion with restoration of thrombotic activity being reflected by the change in thrombin generation and quantitative anti-FXa activity. Andexanet-alfa reverses the anticoagulant effects of small molecule anti-FXa agents (Rivaroxaban, Apixaban and Edoxaban) as well as low molecular weight heparin, and fondaparinux (the latter 2 being indirect FXa inhibitors)[24], [25].

Aripazine (Ciraparantag, PER977) is a small molecule non-specific antidote for all NOACs and heparins. The pan-antagonist has hydrogen bonding sites that bind NOAC agents' active moieties, heparin and LMWH (but not VKA), thereby preventing their anticoagulant function. Current phase II studies have employed a single IV bolus, with laboratory evidence of reversal observed by 30 minutes[26].

[Table 3] and [Table 4] detail the pharmacological properties of the currently developed pro-haemostatic reversal agents. [Table 5] summarises the key clinical data for the ligand-specific and small molecule NOAC reversal agents.

Current state of reversal agents and future directions

The projected AF epidemic will increase the use of currently available NOACs for thromboembolic prevention. Specific (Idarucizumab and Andexanet alfa) and non-specific small molecule (Aripazine) reversal agents may improve the safety profile of these agents particularly in the setting of acute hemorrhagic complications and emergent surgery. Idarucizumab approved by the FDA for the specific reversal of dabigatran, based on interim analysis of the first 90 patients in the REVERSE-AD study [27]. This was a cohort uncontrolled study as it was considered unethical to randomly assign patient to placebo. The results demonstrated rapid, effective reversal of dabigatran in 88 to 98% of patients with fixed dosage idaracizumab. Of note:

Table 4: Direct Reversal agents

Agent	Pharmacology	NOAC	Dosage and titration	Titration	Time to onset	Adverse reactions
Idarucizumab	Monoclonal antibody fragment with high affinity to Dabigatran (free and bound)	Dabigatran	2.5g IV x2 administered 15 minutes apart.	TT and serum dabigatran levels	2-3 minutes (TT). Initial half-life 45 minutes. Terminal half-life 10.3 hours. Renal clearance	Headache, hypokalaemia, fever, constipation, pneumonia
Andexanet alfa	Modified recombinant factor Xa (rFXa). Decoy receptor for oral FXa inhibitors devoid of enzymatic activity	Rivaroxaban, Apixaban, Edoxaban	Apixaban: 400mg IV bolus and 4mg/min infusion over 120 minutes Rivaroxaban: 800mg IV bolus and 8mg/min infusion over 120 minutes	Plasma FXa activity	2-5 minutes (FXa activity). Initial half-life 15 minutes Pharmacodynamic half-life ~1 hour	Thrombotic events in 18% however controlled studies are required
Aripazine (Ciraparantag, PER977)	Pan-antagonist small cation with multiple non-covalent binding sites	Dabigatran, Rivaroxaban, Apixaban, Edoxaban, Heparin and LMWH	Edoxaban: IV 100-300mg bolus (dose titration study)	Whole blood clotting time	Rapid onset within 10 min. Duration of effect 24 hrs. (WBCT)	Peri-oral and facial flushing. Dysgeusia.
Modified thrombin (T-S195A-IIa)	Trypsinized derivative of site mutated thrombin. Sequestration of dabigatran	Dabigatran	Proof of concept. 6mg/kg IV restored thrombus formation in dabigatran treated mice	Dabigatran reversal in vitro (bleeding time) and thrombus restoration in vivo (mice)	Investigational, pre-clinical	Investigational, pre-clinical

TT: Thrombin time, WBCT: whole blood clotting time, F: coagulation factor

the primary outcome in this trial was pharmacological reversal of drug with clinical outcomes as secondary endpoints. Among the 36 patients who underwent a procedure, normal hemostasis was reported in 92% with no pro-coagulant effects identified. Patients who were subsequently found not to have measurable dabigatran levels who received idaracizumab did not have adverse outcomes. Of note, five thromboembolic events that occurred in the study, were in patients who did not have anticoagulation restarted, highlighting the fact that the population requiring reversal has baseline high risk for thrombo-embolic events. Full recruitment has completed with the results expected to be published in 2017.

Likewise, recruitment for the ANNEXA-4 study evaluating

Table 5: Key clinical studies evaluating various NOAC reversal agents

Study	Design	Population studied	Key findings	Comments
Idarucizumab				
REVERSE AD (NCT02104947)	Prospective multi-centre cohort	Serious bleeding or urgent surgery. Dabigatran overwhelmingly for AF	Reversal achieved within 10 min. Median time to bleeding cessation 11.4 hrs. Clinical hemostasis evident at up to 48 hrs.	Laboratory hemostasis correction and diminished Dabigatran levels. No serious adverse reactions. Study currently ongoing
NCT01688830	Randomised, placebo-controlled, double-blind phase 1 study	Healthy male volunteers	Dose-dependent high efficacy immediate, complete and sustained Dabigatran neutralisation	Well tolerated. No clinically relevant adverse effects
NCT02815670	Open label uncontrolled safety trial	Paediatric population with serious bleeding or urgent surgery. Dabigatran for venous thromboembolism	Currently recruiting	Primary, drug-related adverse events. Secondary, bleeding parameters
Andexanet alfa				
ANNEXA-A (NCT02207725)	Prospective randomised double blind: Andexanet alfa vs placebo	Healthy volunteers taking Apixaban 5mg bid, 50-75 years of age	Sustained suppression of FXa activity and diminished unbound Apixaban levels	Bolus and infusion required for sustained suppression
ANNEXA-R (NCT02220725)	Prospective randomised double blind: Andexanet alfa vs placebo	Healthy volunteers taking Rivaroxaban 20mg daily, 50-75 years of age	Sustained suppression of FXa activity and diminished unbound Rivaroxaban levels	Bolus and infusion required for sustained suppression
ANNEXA-4 (NCT02329327)	Multi-center, prospective, open-label, single-group study	Major bleeding in patients taking FXa inhibitors. Mean age 77 years	Reduced FXa activity and effective clinical hemostasis in 79% of patients	Study currently ongoing.
Aripazine (Ciraparantag, PER977)				
NCT01826266	Double-blind, placebo-controlled trial	Healthy persons Edoxaban 18-45 years	100-300mg IV dose restored hemostasis within 10-30 minutes. Effects sustained for 24 hours	Phase II studies of re-anticoagulation with Edoxaban ongoing
NCT02205905	Phase I, open label	Single IV dose in healthy volunteers	Pharmacokinetics study, ongoing	C-14 radiolabelled Aripazine 200mg IV dose
NCT02206087	Phase I/II	Healthy volunteers. Reversal of standard UFH dose using PER977 or placebo	Dose escalation study for UFH dose	Dose determination for efficacy, safety tolerability and adverse events
NCT02207257	Phase II	Healthy subjects administered Edoxaban. Reversal using PER977 or placebo	Pharmacodynamic and pharmacokinetic study	Dose determination study for Edoxaban reversal, followed by re-anticoagulation with Edoxaban

F: coagulation factor, AF: Atrial fibrillation, UFH: Unfractionated heparin

Andexanet-alfa for reversal of FXa inhibitors including rivaroxaban, apixaban, edoxaban and enoxaparin is currently ongoing. The interim analysis of the first 63 patients was reported in 2016[28] demonstrating pharmacological reversal and achievement of haemostasis in 89% individuals. Drug was delivered as a bolus during a period of 15 to 30 minutes, followed by a 2-hour infusion with doses dependent on time since last dose of anti-FXa agent (within 7 hours of bolus or prior). The primary outcome demonstrated pharmacological reversal by anti-FXa levels during infusion, with partial return of anti-FXa levels to pre-treatment levels at 4-4.5 hours after infusion. Thrombotic events occurred in 18% of patients including myocardial infarction, ischaemic stroke and venous thromboembolism and it was noted at the end of the interim report that a controlled study would be required to assess whether the frequency of thrombotic events exceeded that expected in this at risk patient population.

Aripazine (Ciraparantag, PER977) has been granted fast track designation by the FDA.

Availability of these novel reversal agents will also facilitate protocols in the peri-procedural setting potentially adding an extra safety net for patients who proceed without interruption to NOACs during catheter ablation, however, the safety data will need to be carefully assessed.

While the availability of reversal agents is likely to further tilt the scales in favour of NOAC over traditional vitamin K antagonists, unresolved issues remain including clinical availability, cost and confirmation of efficacy and safety by large clinical trials.

Disclosures

None.

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Complications of Atrial Fibrillation Cryoablation

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Abstract

Catheter ablation either by using radiofrequency or cryo energy in symptomatic patients with atrial fibrillation (AF) has shown to be effective as compared to anti-arrhythmic drugs. However, all the techniques used during AF ablation are not free of complication. There are several well-known peri-procedural complications in which operators should be informed of the possible risks, cautious during the procedure and able to manage them when occurred. Herein, we aimed to review possible complications of AF cryoablation.

Introduction

Atrial fibrillation (AF) is the most common sustained arrhythmia and is associated with heart failure, thromboembolic events, hospitalizations and cognitive dysfunction [1]. Guideline-writing authorities recommend catheter ablation as a Class I indication in symptomatic paroxysmal AF to improve AF symptoms in patients who have symptomatic recurrences of AF under antiarrhythmic drug therapy (AAD) and who prefer further rhythm control therapy, when performed by an electrophysiologist who has received appropriate training and is performing the procedure in an experienced centre. Catheter ablation should be considered as first-line therapy to prevent recurrent AF and to improve symptoms in selected patients with symptomatic paroxysmal AF as an alternative to AAD and in persistent or long-standing persistent AF patients refractory to AAD, considering patient choice, benefit, and risk [2]

Radiofrequency ablation (RFA) is the conventional ablation procedure. It causes contiguous, transmural lesions due to heat energy. Major drawbacks of RFA have been "point- to- point" ablation and the resultant longer procedural and fluoroscopy time. Cryoballoon ablation (CBA) is the application of single-shot cryoenergy to pulmonary vein (PV) ostia and has emerged as an alternative to RF energy.

In August 2012, US Food and Drug Administration (FDA) approved the use of second-generation cryoballoon (CB-A) (Arctic Front Advance Cryoablation catheter, Medtronic, MN, USA), an updated version of the first-generation cryoballoon (Arctic Front Cryoablation catheter, Medtronic, MN, USA), which has a more uniform and distal cooling pattern. In May 2015, FDA and CE concurrently approved the use of third- generation CB (CB- ST) (Arctic Front Advance ST Cryoablation catheter, Medtronic, MN, USA). Balloon-tip of the novel CB-ST balloon has been shortened by approximately 40% when compared to CB-A for real-time recording of the PV potentials during freezing in a more reliable way.

There are several advantages of the use of cryoenergy when compared to RF energy during AF ablation. First, a single circular freeze can achieve PV isolation (PVI) rather than the application of many RF lesions. In case of incomplete PVI, bonus freeze cycles may be applied. Second, cryoenergy creates durable lesions preserving the structural architecture of the tissue [3], with less endothelial disruption [4]and accordingly, poses a reduced risk of thrombus formation [3]. It does not require three- dimensional mapping, therefore reduces procedural time and complexity. Furthermore, it allows increased catheter contact and stability, thus minimizes the fluoroscopy time. Overall, CBA is believed to have the potential to reduce the risk of complications compared to RFA. The major drawback of CBA for AF is the possibility of the presence of anatomical variants, such a common ostium or supernumerary PVs, which can make the procedure challenging and affect procedural outcomes [5]. Recently, Heeger et al. [6]. reported a multicenter experience in the role of second-generation CBA for left common PV in which there was a similar acute isolation rate and durability of PVI with the CB compared to RF ablation. Additionally, RFA seems more advantageous in persistent and long-standing persistent AF because of the need for additional ablation regions other than PV-triggers. However, very recent studies in such patient populations represented the feasibility and effectiveness of cryoballoon catheter during roof ablation or left atrial appendage and superior vena cava isolation [7–9].

Major complications of percutaneous catheter ablation for AF include pericardial effusion/tamponade, embolic events, PV stenosis, atrioesophageal fistula (AEF), phrenic nerve palsy (PNP) and vascular access problems. Although vascular complications are known to be the most frequent complication of the procedure, rare and life-threatening complications and their management should also be known by the electrophysiologists.

Fortunately, complication rates have shown a marked decline in time. A single- center study evaluating the complication rates in percutaneous catheter ablation of AF using both RFA and CBA [10]. have reported that complication rates have decreased over the study period from 4.67% in 2008 to 1.55% in 2014. This has been attributed to the technological advances and increased experience of

Key Words

Atrial fibrillation, Cryoablation, Complication.

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the operators and the nursing staff by the investigators. Since the conventional ablation strategy for AF has been RFA, data concerning the complications of CBA is often reported as in comparison with RFA in the literature. In this text, possible complications of AF ablation with cryoballoon technique will be reviewed.

Incidence Of Complications During Cryoablation Of AF

The major complication is defined as a complication that results in permanent injury or death, requires intervention for treatment, or prolongs or requires hospitalization for more than 48 hours [11]. The incidence of major complications during cryoablation has been reported to vary between 2.2-7.0% [12],[13]. The most recent study is a single-center prospective registry of 450 consecutive patients undergoing PVI using CB between 2011 and 2015 [12]. Major complications, namely persistent phrenic nerve injury (PNI), episodes of symptomatic pericardial effusion, deep vein thrombosis and arteriovenous fistula, occurred in 10 (2.2%) patients. In 49 (10.8%) patients, at least transient PNI was observed; only 5 persisted beyond the procedure (1.1%). All cases of PNI resolved eventually, with the longest time to the resolution being 48 days. There were no significant predictors of major complications [12]. Another study including 500 consecutive patients who underwent PVI using CB-A technology between June 2012 and February 2015 has reported the incidence of major complications as 2.0% [14]. PNP occurred in 7.2% of patients and was persistent in 2.2% of patients [14]. Therefore, although nearly all resolve eventually at least within the first year following the procedure, the most common complication associated with CBA is PNI/PNP.

Single Center Studies Comparing The Safety Of CB Ablation Vs. RF Ablation

Mugnai et al. [10]. have evaluated the complication rates in 1.233 patients who underwent AF ablation using either RF energy (n= 642) or CB (n= 591), between January 2008- December 2014. Authors have reported the incidence of serious adverse events as 2.9% (36/1.233): specifically, vascular complications requiring intervention or prolonged hospital stay in 14 (1.1%); cardiac tamponade in 13 (1.0%); a thromboembolic event in 4 (0.3%); and atrioesophageal fistula, PV intramural hematoma, retroperitoneal hematoma, pleural hematoma and persisting phrenic nerve palsy all occurred in 1 patient individually (0.1%). No deaths related to the procedure occurred. The complication rate did not significantly differ in the RF and CB groups (respectively, 3.6% vs 2.2%; p=0.1).

Chun et al. [15]. have recently published the differential risk of cardiac tamponade in AF ablation procedures undertaken from May 2010 to July 2015 at a single center. In total, 3.000 AF ablation procedures (RFA: 2.125, CB: 589, laser balloon: 286 patients) were performed. Cardiac tamponade was significantly lower in balloon-based ablation group than in RFA group (0.1 vs. 1.5%, p= 0.001). In addition, the authors have reported an increased complication rate (2.9% vs. 5.4%) beyond cardiac tamponade, which was driven primarily by PNP persistent at patient discharge (15 of 875 [1.7%]; 11 of 589 with CBs [1.9%] vs. 4 of 286 with laser balloon [1.4%]; p= 0.616) in the balloon-based ablation group.

Meta-Analyses Comparing The Safety Of CB Ablation vs. RF Ablation

The most recent meta-analysis [16]. has compared the safety and efficacy of CB and RF ablation for paroxysmal AF. It included a total of 38 eligible studies, 9 prospective randomized or randomized controlled trials (RCTs), and 29 non-RCTs, adding up to 15.496 patients (CB, n= 6218 vs. RF, n= 9278). CB ablation was shown to result in less complications when PNI was excluded [odds ratio (OR) = 0.79; 95% CI, 0.67–0.93; p= 0.004], however, the total complications of CB was higher than RF (OR = 1.37; 95% CI, 1.19–1.57; p < 0.0001)

Another meta-analysis published this year [17]. has included nine observational studies (2.336 patients) assessed the efficacy and safety of the CB-A compared with RF for paroxysmal AF ablation. The total complication rate showed no statistical difference (8.8 vs. 4.4 %, OR 2.01, 95 % CI 0.91- 4.43, p = 0.08). There was no report of PV stenosis or atrioesophageal fistula in the two groups. Almost all cases of PNP occurred in the CB-2 group except one which occurred in the RF group (6.6 vs. 0.1 %, OR 17.35, 95 % CI 6.57 to 45.85, p< 0.00001), whereas pericardial tamponade was seldom manifested in the CB-2 group (0.4 vs. 1.5%, OR 0.32, 95%CI 0.13 to 0.78, p = 0.01)

A meta-analysis [18] has aimed to compare the efficacy and safety of CB vs. RFA in patients with paroxysmal AF. The meta-analysis included a total of 6473 participants from 10 studies (CB, n= 2232 vs. RF, n= 4241). CB ablation was performed with 23–28 mm CB catheters, except for two studies [5], [19]. using only 28 mm CB catheters. The risk of procedure-related complications was found to be similar between patients treated with CB and those with RFA (4.7 vs. 4.3%; RR [95% CI]= 0.92 [0.66–1.28], p= 0.61). CBA has been shown to result in a higher risk of persistent PNP (RR [95% CI]= 13.60 [3.87–47.81], p< 0.01) and a lower risk of cardiac tamponade (RR [95% CI]= 0.48 [0.25–0.89], p= 0.02) compared with RF ablation. Although the risk of persistent PNP was significantly higher among patients receiving CB ablation, in all cases phrenic nerve palsy resolved within 1 year from the ablation procedure. Moreover, there was no significant interaction between the incidence of persistent PNP and the type of CB used

One other meta-analysis [20]. included 18 randomized or non-randomized cohorts that directly compared CB to irrigated RF catheter ablation for PVI in patients with AF with a total of 8.668 patients (CB, n= 3.706 vs. RF, n= 4.962). Pericardial effusion associated with PVI was significantly less common in patients who underwent CB (25/3.113; 0.8%) as compared to RF (84/4.004; 2.1%) (OR 0.44; 95% CI 0.28-0.69; p<0.01). There was also a significantly lower incidence of pericardial tamponade in CB ablations (7/1,922; 0.3%) when compared to the RF group (44/3,198; 1.4%) (OR 0.31; 95% CI 0.15-0.64; p<0.01). Conversely, PNP at discharge was exclusively observed after CB procedures (34/2,041 patients; 1.7%; OR 7.40; 95% CI 2.56-21.34; p<0.01). The vast majority of those cases resolved during short-term follow-up. PNP lasting >12 months was exceedingly rare, reported in only 4/1,716 (0.2%) patients in the CB group. Vascular complications (14 studies; 6.463 patients; 1.7% CB vs. 2.0% RF; OR 0.75; 95% CI 0.51-1.11; p=0.15) and major vascular complications (7 studies; 3.264 patients; 1.1% CB vs. 1.3% RF; OR 0.79; 95% CI 0.38-1.62; p=0.52) were not significantly different between groups. The incidence of stroke was exceedingly rare and not significantly different between CB (3/1.422; 0.2%) and RF (8/2.636; 0.3%) ablations (p=0.63). The incidence of pericardial effusions (11 studies; 5.821 patients; 0.8% CB vs. 130 2.1% RF; OR 0.45; 95% CI 0.28-0.75; p<0.01) and pericardial tamponade (7 studies; 5.020 patients; 0.3% CB vs. 1.3% RF; OR 0.30; 95% CI 0.14-0.65; p<0.01) was also lower with CB ablations in the subgroup of paroxysmal AF

Studies Comparing The Safety Of First , Second And Third Generation CB Ablation

Pandya et al. [21] have published a meta-analysis that included a total of ten published studies comparing the safety and efficacy of CBA for AF, with 2310 patients (CB-A: 957, CB: 1237 patients). They have found that PVI using CB-A resulted in a higher incidence of persistent and transient PNP compared to CB [OR=1.64 (95 % CI 1.19, 2.26), p=0.002, and OR= 2.38 (95 % CI 1.46, 3.88), p=0.0005, respectively]. The differences in the rate of pericardial effusion and incidence of access site complications were not statistically significant

On the other hand, a single center study [10] have shown no significant differences in complication rates among groups of CB (n= 145) and CB-A (n= 446). Although numerically higher in CB-A group, the difference between groups regarding the incidence of persistent PNP also did not reach statistical significance (2.5% vs 0%, p= 0.06), probably due to the low number of events, similar to a previous study [22].

A few studies comparing outcomes of CBA using CB-A and CB-ST balloon have reported similar complication rates between groups. Furnkranz et al. [23]. have evaluated 472 consecutive patients who underwent CB-PVI for AF (CB-ST: 49 patients, CB-A: 423 patients). There was no difference regarding the rate of transient (CB-A: 5.2% vs. CB-ST: 2.0%, p> 0.05) PNP, persistent PNP (CB-A: 1.9% vs. CB-ST: 2.0%, p> 0.05) or access-site complications (CB-A: 2.1% vs. CB-ST: 2.0%, p> 0.05) among groups. Mugnai et al. [24] have evaluated a total of 600 consecutive patients (100 CB-ST and 500 CB-A ablations). In the overall study population, major complications occurred in 12 of 600 patients (2.0 %). Most common complications were peripheral vascular complications requiring intervention or prolonged hospital stay (8 patients, 1.3 % per procedure), followed with transient ischemic attacks (TIA), pericardial effusion requiring intervention, retroperitoneal hematoma and symptomatic PNP persisting at final follow-up all occurred in one patient individually (0.2 % per procedure). No significant differences in major complications were observed between the two groups. Aryana et al. [25]. have also reported a similar incidence of PNP and procedure-related adverse events between the 2 groups

Possible Complication During Cryoablation For AF

A) Energy- Dependent Complication

Energy-dependent complications of CBA for AF include pericardial effusion/ tamponade, PV stenosis, AEF and thromboembolic complications. Cryoenergy is known to reduce this category of complications (See "Introduction").

Pericardial Effusion And Tamponade

Pericardial effusion can manifest itself from acute pericardial tamponade to asymptomatic effusion. A study has compared the incidence of pericardial effusion in a total of 133 consecutive patients undergoing ablation for paroxysmal AF (87 by RFA vs. 46 patients by CB-A) and no significant difference in the incidence of pericardial effusion between the cryoballoon and the RF groups were detected (11 vs. 16%) [26]. However, the incidence of cardiac tamponade has been reported to be higher following RFA [15]. A longer procedural time, coronary artery disease and arterial hypertension were found to be independent predictors of pericardial effusion during AF ablation [26]. Ablation technology (RFA), ablation strategy (PVI plus) and the number of procedures per patient were reported as predictors of cardiac tamponade [15]. Mugnai et al. [10]. have reported that 2 cases of cardiac tamponades occurred during PVI, respectively during freezes in the LSPV and in the RSPV, and the third one did occur 3 h after the ablation procedure. However, it may also occur following transseptal puncture.

How to manage it?

All patients should undergo routine transthoracic echocardiography prior to, after a transseptal puncture and at the end of ablation to assess the pericardial space. Furthermore, in case of suspicion (low blood pressure, tachycardia, narrowed pulse pressure), it should be repeated. Pericardial effusion usually resolves spontaneously, however immediate recognition and intervention is of vital importance in tamponade, since it may threaten life. The procedures should immediately be stopped and the drainage should be achieved by a percutaneous pericardial puncture in case of tamponade.

How to prevent it?

Successful one- shot transseptal puncture is essential for minimizing pericardial effusion/ tamponade. Safety of transseptal puncture lies in the recognition of the right atrial anatomy and in particular of the fossa ovalis. Some have reinforced the use of intracardiac echocardiography (ICE) or transesophageal echocardiography (TEE) in those procedures in which right atrial anatomy is unusual or in which fossa ovalis is difficult to engage [27]. However, TEE requires deep sedation or general anesthesia and ICE is associated with increased costs and needs a precise expertise. Furthermore, optimal anticoagulation management should be adopted before and after PVI [11].

-PULMONARY VEIN STENOSIS

Pulmonary vein stenosis is the constriction or narrowing of the PV ostium due to thermal injury to the vessel wall. This condition can restrict blood flow from the lungs into the heart. This had been a more common complication of RFA compared to cryoablation. In STOP-AF trial, CB therapy was associated with a 3.1% incidence of PV stenosis [28].

PV stenosis is often clinically silent. Symptoms may include a cough, dyspnea, chest pain, hemoptysis and recurrent respiratory infections. The severity of the clinical presentation depends on the severity of the stenosis and the number of PVs involved [29]. The severity of PV stenosis is generally defined as mild (<50%), moderate (50–70%) or severe (>70%), according to the percentage reduction of the luminal diameter.

How to manage it?

Pulmonary vein stenosis should be suspected in every patient presenting with one the above clinical symptoms after an AF catheter ablation. Cardiac computed tomography (CT) and magnetic resonance imaging (MRI) are diagnostic tools to make the definite diagnosis. Echocardiography might be useful to assess PV flows. Radionuclide ventilation/perfusion imaging may also serve as a screening tool in symptomatic patients and help to clarify the hemodynamic significance of PV stenosis [30].

Optimal treatment for PV stenosis is still unknown. Balloon angioplasty alone or in association with stent implantation seems to be efficacious in the acute setting but is also associated with restenosis in 30–50% of the patients.

How to prevent it?

Pulmonary vein stenosis may be minimized by not positioning the cryoablation catheter within the tubular portion of the pulmonary

vein. The balloon should not be inflated while the catheter is positioned inside the pulmonary vein. The balloon should always be inflated in the atrium and then positioned at the pulmonary vein ostia.

-ATRIOESOPHAGEAL FISTULA

An atrioesophageal fistula is a rare but fatal complication of the procedure. Despite the higher frequency with the use of RFA, it has been reported as case reports following cryoablation of AF [31-34]. Although its incidence has been reported to be approximately 0.01–0.2% [35], it has high mortality rates, up to 63% [36]-[37].

Very low temperatures (below -60°C), long freezing cycles and sharp temperature descent during first 30 seconds of the procedure are thought result in ulcer and fistula formation, respectively [38]. Heat is thought to affect esophageal endothelial cells directly or indirectly via damaging anterior esophageal arteries causing ischemia and ulceration of the mucosal layers [39]. In addition, pre-existing esophagitis due to gastroesophageal reflux is believed to exacerbate the esophageal injury by interfering with the repair mechanisms after esophageal injury [40]. Left atrial enlargement, persistent AF leading to left atrial enlargement and extensive ablation of the posterior wall have been proposed to be risk factors of AEF [30]-. Though unclear in underlying mechanism, general anesthesia has also been suggested to be a risk factor for AEF due to decreased esophageal peristalsis and swallowing during anesthesia and frequent use of orogastric/nasogastric tubes during the procedure [43].

How to manage it?

Atrioesophageal fistula typically develops within 1-4 weeks following catheter ablation. The signs and symptoms are non-specific and include fever, fatigue, malaise, chest discomfort, nausea, vomiting, dysphagia, odynophagia, hematemesis, melena, and dyspnea. Diagnosis should be kept in mind particularly in patients with the typical triad of infection without a clear focus, retrosternal pain, and stroke or TIA. Early recognition is important, as patients often develop endocarditis with septic emboli leading to neurological manifestations such as altered mental status, seizures, and coma within hours of symptom onset [44].

White blood cell count is an early and sensitive laboratory marker of an AEF [44]. Chest CT should be performed emergently. The test can be considered diagnostic if intravenous contrast enters the esophagus or mediastinum from the left atrium. Transthoracic echocardiography may demonstrate air in the left heart, pericardium or the presence of a pericardial effusion.

Esophageal instrumentation with endoscopy or TEE is not recommended as they theoretically may worsen the situation by increasing fistula size and also increase the risk of air embolism secondary to increased esophageal pressure with instrumentation and insufflation.

Available therapeutic options for AEF include surgical repair of the fistula (combined left atrial and esophageal repair) via thoracotomy [45], esophageal stenting [46] and conservative management with aggressive chest tube drainage and treatment of sepsis. Of these three approaches, conservative treatment of esophageal fistula remains controversial, as it requires frequent radiologic assessments and is associated with very high mortality rate. Data on stenting versus surgical treatment of AEF are conflicting and at the present, there is no consensus on the most effective treatment strategy for AEF. In addition, associated mediastinitis should also be treated. A multidisciplinary approach including cardiothoracic surgeons, infectious diseases specialists, neurologists and critical care physicians should be adopted.

How to prevent it?

Proton pump inhibitors should be initiated prophylactically prior to ablation [40].. Real-time luminal esophageal temperature monitoring by placing a temperature probe in the esophagus at the level of the ablation catheter may be beneficial to detect increases in luminal esophageal temperature and may alert the operator. Although its efficacy has been investigated for RFA, there are no studies evaluating the use of real-time esophageal temperature monitoring for cryoablation. However, several studies have reported incident AEF despite the lack of rising in esophageal temperature in the probes due to mismatch of the esophageal diameter relative to that of the probe [47], the phenomenon of thermal latency and difference between luminal and mural temperature in the esophagus [48]. And what is worse, Nguyen et al. [49]. have highlighted esophageal temperature probes may function as "lightning rods", attracting electrical current from the ablation catheter and potentiating heat transfer to the esophagus. Further research is necessary to confirm the safety of the esophageal temperature probes.

Another strategy for prevention of AEF is the mechanical deflection of the esophagus by using a TEE probe placed within the esophagus or endotracheal stylet within a thoracic chest tube [50],[51]. Feasibility of this method has been evaluated in patients undergoing RF ablation [50].,[51], however, there are no studies for CBA. Instrumentation of the pericardial space and introduction of a balloon catheter between the LA and esophagus has been suggested as an alternative approach to moving the esophagus away from the LA to reduce heat transfer to the esophagus during RFA [52].,[53].. However, it adds significant complexity to the procedure.

-THROMBOEMBOLIC COMPLICATIONS

Patients with AF undergoing catheter ablation have an increased risk for thromboembolic complications during, immediately following, and for days to months after procedure independent from pre-procedural thromboembolism risk [54].Despite the lower risk in cryoablation compared to RFA, CBA may also result in endothelial disruption and subsequent clot formation leading to thromboembolic complications. Maintaining optimal levels of anticoagulation and taking measures to prevent clot formation on sheaths and catheters (such as maintaining a constant heparinized flush through all long sheaths with access to the left atrium) are essential [11].

B) Procedure - Related Complications

Procedure-related complications include embolic (thromboembolism and air embolism) and vascular complications. These are related to the invasive nature of the procedure (sheaths, guidewires, manipulation) and the perioperative changes in anticoagulation, therefore it is unlikely that changes in AF ablation technology will completely eliminate these complications. Operator experience and optimization of periprocedural management might be the only way to reduce these inherent procedure-related complications.

-THROMBOEMBOLIC COMPLICATIONS

Thromboembolic complications include silent microemboli, transient ischemic attack (TIA) or stroke. Silent microemboli are asymptomatic white matter lesions detectable by cranial MRI and

have been observed in around 10% of patients treated with RF and cryoballoon ablation [55]. Their clinical significance is unknown. The incidence of TIA/ stroke has been reported to be <1% [55].

Activated clotting time >300 s and high-flow perfusion of the transseptal sheath are mandatory to reduce thromboembolic complications during AF catheter ablation. Furthermore, a continuation of oral anticoagulation at a therapeutic international normalized ratio at the time of ablation is recommended in patients under warfarin treatment compared with bridging strategies using heparin or enoxaparin [56]. Anticoagulation with NOACs is an alternative to warfarin [57]-[59]. No adverse effects have been reported in cohorts treated with uninterrupted NOAC therapy undergoing catheter ablation [58]-[60]. The RE-CIRCUIT study has been completed and published recently, which compared uninterrupted dabigatran vs. uninterrupted warfarin in patients undergoing AF catheter ablation. A total of 704 patients were randomized to these two anticoagulation strategies. The incidence of major bleeding events during and up to 8 weeks post-ablation among the 635 patients who underwent AF ablation was significantly lower with dabigatran than with warfarin [(1.6% vs 6.9%); absolute risk difference [RD] 25.3%, RR reduction 77%]. No strokes or other thromboembolic events occurred in the dabigatran arm compared with one TIA in the warfarin arm [61]. Ongoing studies compare uninterrupted VKA with NOAC therapy in AF patients undergoing ablation [e.g. AXAFA – AFNET 5 (Anticoagulation using the direct factor Xa inhibitor apixaban during Atrial Fibrillation Catheter Ablation: Comparison to vitamin K antagonist therapy; NCT02227550) [2].

HRS/EHRA/ECAS/APHRS/SOLAECE expert consensus statement on catheter and surgical ablation of AF is also reported some recommendations regarding peri-procedural strategies to prevent thromboembolic complications [54]. It is now evident that a strategy of performing AF ablation safely on patients receiving uninterrupted anticoagulation based on previous clinical trials. Performing TEE in patients with AF before catheter ablation depends on the clinical experience of operators. While some operators perform TEE in all patients presenting for AF ablation regardless of presenting rhythm and anticoagulation status, others perform TEE in patients with a CHA2DS2-VASc score of ≥2. Unfractionated heparin should also be administered prior to or immediately after a transseptal puncture during AF catheter ablation procedure and the dose is titrated to maintain an ACT of at least 300 seconds. Systemic anticoagulation with warfarin (time in therapeutic range (TTR) should be 65-70% on warfarin) or a NOAC is recommended for at least 2 months post-catheter ablation of AF. Discontinuation of systemic anticoagulation after 2 months post-ablation should be based on the CHA2DS2-VASc score.

-VASCULAR COMPLICATIONS

Vascular access site complications are the most common complications of AF ablation and include groin hematoma, retroperitoneal bleeding, femoral pseudoaneurysm or femoral arteriovenous fistula. Large-calibre [outer diameter of 15 French (Fr)] delivery sheath and maintained anticoagulation during the procedure may increase the risk of vascular complications. Furthermore, the additional 6Fr pigtail catheter in the aortic root in order to monitor arterial pressure and also to assess the radiological position of the aorta during transseptal puncture may contribute to femoral pseudoaneurysm formation [10].

Hematomas generally resolve spontaneously. Femoral pseudoaneurysms may be successfully treated conservatively by compression only, by percutaneous thrombin injection or by surgical repair. Arteriovenous fistulas are treated surgically without significant sequelae.

Operator experience is the main factor considering the incidence of vascular complications. Another critical point is the insurance of optimal hemostasis. Standard manual compression has already been used as an effective technique for access site hemostasis after AF ablation in most centers. However, it may lead to rebleeding, thrombosis or embolism. Besides, manual compression is time-consuming and exhausting for the qualified medical staff. Reversal of heparin-mediated anticoagulation by protamine sulfate prior to sheath removal has been shown to be useful for prevention of vascular access complications in patients undergoing CB ablation for AF (1.1 vs. 6.3%, p= 0.011) [62]. In an effort to reduce patient discomfort and other complications, application of "figure- of- eight" suture following removal of the sheath has been reported to be a safe and efficacious technique to achieve an immediate hemostasis in a cohort of patients undergoing CBA compared to conventional manual compression[63].

C) Device - Dependent Complication

-PHRENIC NERVE INJURY/ PALSY

Phrenic nerve injury (PNI) develops due to the close proximity to the right phrenic nerve with the right-sided PVs. The right phrenic nerve courses rightward and anterior to the right PVs, particularly closer to the RSPV (1.5–2.5 mm) than the RIPV (10–15.5 mm) [64]. PNI has emerged as the most common clinically significant complication of CBA of AF. Through a study conducted on animal models, Andrade et al.[65]. demonstrated that PNP and injury induced by CBA were axonal in nature and characterized by Wallerian degeneration, with potential for recovery. In addition, functional resumption of PNP was closely related to the degree of axon injury.

The incidence has been reported to be substantially higher in patients undergoing CBA [66]. when compared to RFA (11.2% vs. 0.48%) [67]. In a review [68]. that analyzed 23 articles using CBA for PVI, PNP incidence was 6.38% (86/1349 procedures) and 4.73% of patients had persistent PNP after the procedure. Among these, 0.37% of patients had persistent PNP lasting over 1 year [68].. PNP occurred in a much higher proportion of procedures that used the 23- mm CB compared with the 28- mm CB (12.37 vs 3.53%; p = 0.0001). A higher risk of PNP during CBA with CB- A has been reported [69]. Casado-Arroyo et al.[22]. reported that CB-A was more likely to cause PNP compared to CB ablation due to its larger cooling surface area and deeper damage foci. Compared to CB, CB- A has resulted in an approximate doubling of acute (from 12.6% to 19.5%) and persistent (from 5.4% to 7.3% [beyond discharge from the index procedure]) PNI [22],[70].Regression analysis identified 23-mm balloon use (16.3% vs. 5.2%, OR 2.94, p=0.011) and increased age (62.8± 7.7 vs. 58.7± 0.12 years, OR 1.058, p=0.014) as independent significant predictors of PNI in a recent study including 450 consecutive patients undergoing cryoablation [12]. 23-mm balloon as a predictor of PNI has also been reported in previous studies [13].,[71],[72]. An increased risk of PNI is likely when the balloon is positioned distal toward the vein, which occurs more frequently with the 23-mm balloon compared with the 28-mm balloon given its smaller size. Another hypothesis has been that the 28-mm balloon represents later cases in which the operator has gained experience.

Recently, various studies have compared the incidence of PNP between CB- A and CB- ST groups. Patients having undergone CB-A ablation experienced 36 PNPs (7.2 %) (5% transient and 2.2% persistent) and in the CB-ST patient group, there were six transient PNPs (6 %; p=0.6) and one persistent PNP (1 %; p = 0.7) which completely recovered within 1 month [24]. Another study reported lower incidence due to the application of preventive measures and the rates did not differ between groups (CB- A: 1.9%; CB- ST: 2.0%, p> 0.05) [23].

Phrenic nerve palsy is usually associated with dyspnea, cough, or hiccups; diagnosis is usually made with evidence of diaphragmatic elevation at the chest X-ray.

How to prevent it?

Phrenic nerve injury may be minimized by positioning the catheter as antral as possible and vigilantly monitoring the right hemidiaphragm contractions by pace-mapping during cryotherapy delivery. Pace-mapping is performed by pacing at a high output in the areas of presumable contact with phrenic nerves (usually right superior pulmonary vein, superior vena cava, and the roof of the left atrial appendage). Intermittent fluoroscopy is another practical method. Physicians should stop ablation immediately if evidence of phrenic nerve impairment is observed. However, intermittent fluoroscopy exposes the patient to an extra dose of radiation during the procedure. The palpation of the diaphragmatic excursion is a reliable method, but it requires an extra staff member to monitor the diaphragm. Furthermore, relying only on diaphragmatic contractions may result in long-lasting PN injury beyond 1 year [10],[73].

Electromyography of diaphragmatic contractions and auditory cardiotocograph can be used to monitor the phrenic nerve during cryoablation procedures. A diaphragmatic compound motor action potential (CMAP) can be recorded by two standard surface electrodes positioned across the diaphragm: one 5 cm above the xiphoid and the second along the right costal margin [74]. CMAP can also be measured by intravascular recording from the subdiaphragmatic hepatic vein [75]. The reduction in the amplitude of the CMAP precedes diaphragmatic paralysis and it may aid in early detection of phrenic nerve injury [75],[76]. A study of CMAP monitoring during CB-A ablation has reported a 24.5% incidence of CMAP changes that prompted early termination of ablation but only a 1.5% incidence of persistent PN injury with recovery [77]. A more recent case series of CMAP monitoring has found that 13.6% of subjects had CMAP-defined acute PNI leading to termination of cryoablation, and none developed persistent injury [78].

Regarding ablation technique, the exclusive use of the large 28-mm CB-A and shortening the delivery time to 180 s and avoiding "bonus" ablation after isolation is achieved may prevent PNI[79].. Combination of the use of a large 28-mm balloon, "single- shot" 3-min freezes with no "bonus" freezes, active balloon deflation, and CMAP monitoring has been reported to result in a persistent PNI incidence of 3%, with all patients recovering during follow-up [80]. Active and rapid deflation of the cryoballoon at the first sign of PNI [10],[71],[81], and terminating cryothermy ablation if there is a particularly rapid decrease in temperature to <- 38°C within the first 40 s [82]. are additional reported techniques. Another technique includes manipulation of the CB-A to avoid displacing the catheter into the RSPV by carefully disengaging the cryoballoon until a trivial leak around the balloon is visible before initiating freezing which then expands the balloon slightly to determine the freezing zone as near to the ostia-left atrium (LA) junction as possible.

Another approach for monitoring and diagnosing PNP is to use ICE during CBA of the right PVs. This monitoring technique has the advantage of continuous direct diaphragmatic visualization without the use of fluoroscopy, hence significantly minimizing radiation to both the patient and the operator. In addition, this technique does not require extra staff to monitor the diaphragm using manual palpation [83].

At last but not the least, the ability to predict patients are at risk for PNI using preprocedural imaging has been investigated in several studies. Although direct visualization of the PN with multidetector computed tomography (MDCT) can be difficult [84], a few studies [80],[85],[86]. have evaluated the predictive role of the distance between RSPV ostium and PN vascular bundle detected by MDCT on PNI development. In addition, another study has reported that ostial vein area and external RSPV-LA angle measurement had high predictive value for determining PNI at the RSPV in 41 patients undergoing PVI using 28- mm CB [87].

-COLLATERAL NERVE DAMAGE

Gastroparesis is one of the major complications that may occur due to collateral nerve damages during cryoablation due to the close proximity of nerves innervating the pyloric sphincter and stomach to the posterior LA wall and PVs [88]. It is defined as a syndrome characterized by delayed gastric emptying in the absence of any structural lesions in the stomach and usually manifests with nausea and vomiting. The incidence of asymptomatic gastroparesis following CBA at 24 hr documented with esophagogastroduodenoscopy has been reported to be 9% [89]. In another study by Furnkranz et al., 2 of 38 patients experienced symptomatic gastroparesis after cryoballoon ablation for AF, which healed in 1 week after conservative therapy [90].

D) Complications During Cryoablation Of Non-PV Triggers

Cryoablation of non-PV triggers include cryoenergy application to superior vena cava (SVC) and left atrial appendage (LAA).

Potential complications of SVCI using cryoenergy include pericardial tamponade, pneumothorax, venous stenosis, superior vena cava syndrome and right phrenic nerve palsy. Previously, the incidence of right PNI has been reported to vary between 0.17-2.1% [91],[92]. A meta-analysis which included 3 RCTs with a total population of 526 subjects has investigated the outcomes following empiric SVCI in AF ablation [93]. There were a total of 12 serious events in the study population (2.2 %). Two PNI (2/237 = 0.8 %) were seen in the PVI + SVCI arm; one of them was transient while the other had a partial recovery at the end of follow-up. A more recent study by Xu et al. [94]. has reported only vascular access complication in their study evaluating the role of SVC ablation in 102 patients with long-standing persistent AF ablation.

Careful observation of the diaphragm motion on fluoroscopy during isolation of the RSPV or SVC during spontaneous breathing or pacing of the right-sided PN and CMAP monitoring are useful for preventing right-sided PNP [95],[96].

Spasm of the left circumflex artery, left-sided PNP, and changes in mechanical functions of the LAA are specific complications for the cryoablation of the LAA [9]. The incidence of left-sided PNP has been reported to be 1% [9]. Spasm of the left circumflex artery is

relatively more common than PNP (4%) [9], it is asymptomatic and has been demonstrated to resolve following intracoronary nitrate administration. The left-sided PN should be paced from the LAA using circular mapping catheter throughout the freezing cycle as like pacing of the right-sided PN and PN capture is assessed by intermittent fluoroscopy and/or tactile feedback obtained from the patient's abdomen [9].

Impact of LAAI on LAA mechanics is complex. A study has reported a significant decrease in LAA flow rates without thrombus formation (mean LAA flow rates: 0.52± 0.19 m/s at baseline vs. 0.46± 0.15 at the 12th- month follow-up, p< 0.001) on 12th month follow-up TEE in patients undergoing LAA ablation in addition to PVI [9] and the only stroke case occurred at 5 months in a patient who discontinued oral anticoagulant for 10 days. Another study evaluating the impact of LAAI on LAA mechanical functions, which included 50 patients undergoing LAAI for the treatment of atrial tachyarrhythmias [97], has shown that during a median follow-up of 6.5 months, stroke occurred in 2 patients on OAC and TIA in one without OAC in the LAAI group. In the remaining 47 patients, LAA thrombus was identified on transesophageal echocardiography in 10 (21%) patients (OAC=9; no OAC=1). Another study showed that in 7/71 (10%) patients with previous LAAI who presented for a subsequent procedure, LAA thrombus formation was detected by pre-procedural TEE [98]. However, in BELIEF trial, although an impaired contractile pattern in LAA was observed in 35 (56.5%) patients, no thrombus was detected on TEE and no stroke or transient ischemic attack was reported [99].. Therefore, this ablation strategy may theoretically be associated with an increased risk of thrombus formation within the LAA and thromboembolic events despite optimal anticoagulation. Subsequent percutaneous LAA closure may be a solution in these patients.

Conclusions

Cryoballoon ablation for atrial fibrillation is a safe and effective strategy when compared to the conventional ablation strategy, RFCA, particularly when energy-dependent complications are taken into account. Phrenic nerve injury is significantly more common in CBA, however, this risk can be minimized and be comparable to RFA if preventive measures are taken. Rare but fatal complications of the procedure, such as atrioesophageal fistula and cardiac tamponade, should be immediately diagnosed and managed appropriately to avoid mortality.

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Management of Stroke Risk in Atrial Fibrillation Patients with Bleeding on Oral Anticoagulation Therapy-Role of Left Atrial Appendage Closure, Octreotide and more

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Abstract

Background: Bleeding complications especially gastrointestinal bleeding remains a major challenge associated with oral anticoagulation therapy (OAT) and often leads clinicians to withdraw oral anticoagulation therapy (OAT) . This exposes patients to risk of stroke and systemic thromboembolism (STE). Novel oral anticoagulants (NOACs) have proved no better when it comes to bleeding events and in fact studies have shown that overall NOACs are associated with higher incidence of gastrointestinal (GI) bleeding compared to warfarin [4].

Objectives: In this review, we describe the difficulties encountered in managing OAT in patients with bleeding and strategies to maneuver around these bleeding complications particularly gastrointestinal bleeding secondary to arteriovenous malformations (AVM) and other vascular abnormalities.

Findings: Left atrial appendage closure (LAAC) has emerged as a very elegant and promising tool for stroke prevention in non-valvular atrial fibrillation (AF) patients who are intolerant to OAT. But the need for OAT post procedure for a brief period is becoming a major hurdle for clinicians to pursue in this direction in patients with recurrent gastrointestinal bleeds. And in majority of cases, recurrent or refractory gastrointestinal bleeds are usually secondary to arteriovenous malformations/angiodysplasias (AVM/AD). We suggest that the problem has to be approached by decreasing or eliminating the acute bleeding risk and closing the LAA in the long term, to enable the patients to come off of OAT and minimize the risk of recurrent bleeding.

Conclusion: Recurrent GI bleeding, secondary to arteriovenous malformation (AVM), is one of the common reasons for OAT discontinuation in atrial fibrillation patients. Newer techniques of left atrial appendage closure (LAAC) offer some respite in such cases but we are in an era of transition wherein different options available for stroke prevention in atrial fibrillation patients are still interdependent on each other and therefore role of drugs like Octreotide (OCT) and other similar agents like steroids, hormonal therapy etc. becomes especially important and worth a trial in such cases. While we continue to work for future atrial fibrillation patients we should not forget about atrial fibrillation patients at present.

Introduction

Atrial fibrillation (AF) continues to remain a major cause of morbidity and mortality and a big challenge for clinicians around the globe for a variety of reasons. The most important being the stroke risk associated with atrial fibrillation, which tends to be more severe in patients with atrial fibrillation (AF) than in patients without AF [1]. At the same time the risk of bleeding especially life threatening intracranial hemorrhage (ICH) and gastrointestinal (GI) bleeding associated with oral anticoagulation therapy (OAT) significantly increases with OAT. And ironically the incidence of AF, the risk of bleeding and the incidence of strokes attributable to atrial fibrillation all increase with the age, making it a particularly difficult situation[2]. As for the above fact and the aging of our population, it is estimated that by 2020, 7.5 million individuals will have AF in the United States alone [3].

Novel oral anticoagulant (NOACs), despite having emerged as safer and more effective or equal alternative to vitamin K antagonists (VKA), still continue to have bleeding complications. The ground reality is that the risk of bleeding while being anticoagulated is always there for the simple fact that risk for both the thromboembolism and the bleeding are largely driven by an overlapping set of comorbidities [4]. Approximately 50 % of patients with AF who have guideline indication for oral anticoagulation therapy (OAT) end up not being on any form of oral anticoagulation therapy for various reasons with bleeding being the most common and obvious reason. [5]. This leads to a large population of AF patients who remain at risk for preventable stroke. Stroke is the leading cause of disability and third leading cause of death in United States with an estimated annual cost of around 60 billion dollars [6]. Left atrial appendage closure (LAAC) has offered some respite in a number of such patients in the long term. The LAAC devices have been used with varying OAT and

Key Words

Atrial fibrillation, Left Atrial Appendage, Arteriovenous malformations, Angiodysplasias, Octreotide.

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Antiplatelet Therapy(APT) protocols in different parts of the world with varied experiences. However, randomized controlled trials for LAAC have been done using intra and post-procedural OAT for 6 weeks and dual APT for 6 months. This presents a huge hurdle in pursuing endocardial LAAC in patients suffering from bleeding complications. Epicardial ligation or clipping of the LAA has been done with great efficacy with no need for post procedural OAT but has not been studied in a RCT.

Prevention of Thromboembolic phenomena in atrial fibrillation patients-Road bumps and detours-a brief background

OAT continues to remain the first line of therapy for prevention of thromboembolic events in patients suffering from AF. Current AHA/ACC/HRS guidelines recommend use of OAT in all AF patients with CHADSVaSc score greater or equal to 2, regardless of cardioversion/ablation or type of AF [7].

Warfarin with target INR of 2-3

It has traditionally been and is still being used for prevention of thromboembolic phenomena in AF patients with much success. However, bleeding complications associated with warfarin use have always been an issue. Typical bleeding rates reported in randomized trials are in the range of 1 to 3 percent per person-year, which tends to be an underestimation of the actual bleeding rates in practice. One of the recent studies showed that the rate of nonfatal and fatal bleedings for warfarin monotherapy were 3.6 and 0.2 percent per patient-year respectively with GI bleed accounting for a significant proportion of nonfatal bleeding events[8]. The bleeding rate significantly goes up when warfarin is combined with antiplatelet agents [Table 1].

Lowering target INR has been suggested in the past to offset the bleeding risk but studies did not show any effect on hemorrhage rate with such strategy. Low intensity warfarin was found to be less efficacious than conventional intensity warfarin with no reduction in the risk of clinically significant bleeding over time [9]. Low intensity fixed dose warfarin plus Aspirin was also studied but was found to be less efficacious than adjusted dose warfarin in preventing stroke in high risk patients[10]. Aspirin and Plavix combination was more effective than aspirin alone but less effective than warfarin [11]. Subcutaneous Idraparinux was also studied and was found to be more efficacious than warfarin but at the cost of substantially higher risk of bleeding [12]. Ximelagatran, a direct thrombin inhibitor, had equal safety and efficacy as warfarin but was found to be hepatotoxic [13]. Drug and food interactions, unpredictable daily variations in the INR, need for periodic checks has made warfarin relatively unpopular with both patients and physicians.

Table 1: Bleeding types and rates with different OAT regimens

	%per Patient-year Variable			
	Warfarin Monotherapy	Warfarin+ Aspirin	Warfarin+ Clopidogrel	Warfarin+ Aspirin+ Clopidogrel
Nonfatal bleeding	3.6	6.4	13.3	15.4
Fatal bleeding	0.2	0.4	0.6	0.2
Fatal and nonfatal bleeding	3.9	6.8	13.9	15.7
Intracranial bleeding	0.6	0.8	0.8	1.0
Airway bleeding	1.3	2.3	7.1	7.1
Gastrointestinal bleeding	0.9	2.1	3.8	5.1
Urinary tract bleeding	1.0	1.6	2.0	2.4

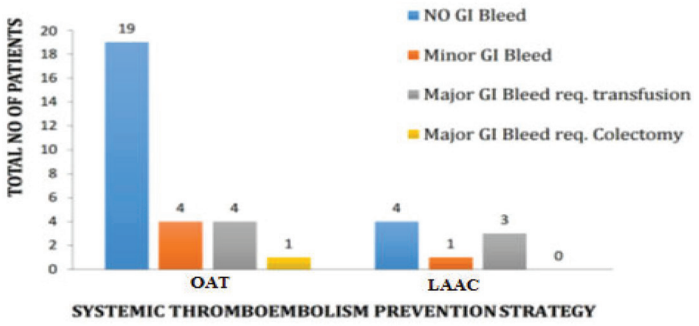


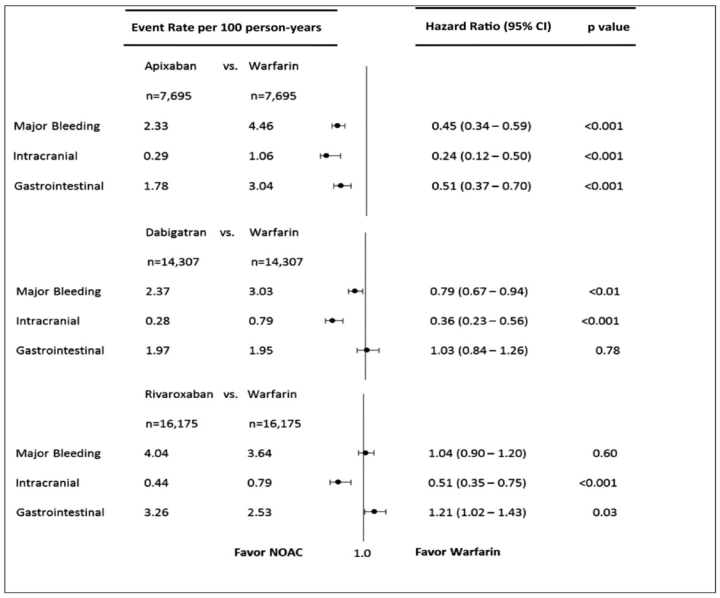
Figure 1: Showing the impact of OCT therapy on GI bleeding in patients on OAT

Novel Oral Anticoagulant agents (NOAC)

Continuous efforts to mitigate the problems of warfarin lead us into an era of Novel Oral anticoagulants. NOAC's target different parts of the coagulation pathway, have a more predictable anticoagulant effect, and do not require INR monitoring. This group comprises of direct thrombin inhibitors (e.g. Dabigatran) and direct factor Xa inhibitors (apixaban, rivaroxaban, edoxaban). Although NOACs were very effective in averting many of the downsides of warfarin like drug interactions, INR monitoring, unpredictability of anticoagulation, risk of bleeding while on NOACs stayed there. Studies showed that, in comparison to warfarin, apixaban was associated with lower risks of major bleeding, intracranial bleeding and gastrointestinal bleeding, Dabigatran was associated with lower risks of major bleeding and intracranial bleeding with no significant difference in the risk of gastrointestinal bleeding and Rivaroxaban was associated with similar risk of major bleeding but lower risk of intracranial bleeding and higher risk of gastrointestinal bleeding [Table 2] [14]. Overall, in comparison to warfarin, NOACs lower the risk for intracranial bleeding and probably also decrease the overall risk for major bleeding episodes but surprisingly increase the risk for gastrointestinal bleeding in atrial fibrillation patients [15]. And, with no FDA approved antidotes available except for Dabigatran, the issue of bleeding with NOACs got even more complicated especially for patients leading to non-compliance. Also, with no data for their use in the presence of mechanical heart valves or Valvular atrial fibrillation, a significant proportion of patients with atrial fibrillation are still dependent on warfarin for stroke prevention.

Despite substantial evidence about the risk of bleeding with NOACs, clinicians have been using them in patients who bled on warfarin as an alternative therapy without much success for obvious reasons. A recent multicenter real world study published by our group showed NOACs may not be all that much better in minimizing bleeding complications in warfarin ineligible patients. 265 warfarin ineligible patients who were started on NOACs were followed for a mean duration of 14 ± 4 months. Repeat major bleeding events (MBE) occurred in 63% of patients and incidence was significantly higher in patients with prior history of GI bleeding (74.5% vs. 30%, P <0.0001) than those without. HAS-BLED score, type of NOACs used or concomitant aspirin or clopidogrel use had no impact on repeat major bleeding event (MBE). However, subgroup analysis of the most challenging group of patients with left atrial appendage thrombus and intracranial hemorrhage on warfarin treated with a NOAC came up with some reassuring figures.13 out of 14 such patients had resolution of clot within 3 months but 50 % developed a

Table 2: Comparison of NOACs vs Warfarin in terms of bleeding



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repeat intracranial hemorrhage (ICH) or systemic thromboembolism (STE) on a NOAC. In patients who did not have another event (50% -7 of 14), majority of them 71% (five of seven) underwent successful left atrial appendage occlusion device implantation followed by temporary bridging with NOACs during the periprocedural period and 29% (two of seven) were continued on a NOAC with no further adverse events [4].

So the bottom line is that the risk of bleeding is always there no matter which anticoagulant is used and this leads to a large proportion of atrial fibrillation patients not being on any kind of anticoagulation despite having guidelines indications for the same. In this article we will review the strategies to maneuver around these bleeding complications and managing them.

Role of Left atrial appendage closure (LAAC) in stroke prevention and mitigating bleeding complications

Left atrial appendage closure (LAAC) has evolved to be a very promising solution in many of these patients who are high risk for long-term use but eligible for OAT. The PROTECT-AF and PREVAIL-AF studies have clearly shown the cumulative advantage of a LAAC over warfarin for major bleeding, stroke and death together. The benefit is more profound in mitigating the risk of major bleeding (including ICH and GI bleeding) and mortality. The stroke benefits are non-inferior to warfarin [16]. It is obvious that the warfarin group did exceptionally better in the study setting than what ones sees in a real-world setting. The ability of an OAT in preventing a LA clot and subsequent STE is expected to be superior to any other approach. However the associated bleeding risk is what makes these agents undesirable. At least in the current medical armamentarium there is no agent that can prevent stroke without the risk of bleeding. This exactly where LAAC devices fit in. Off label use of endo-epicaridal suture with the Lariat device and Atriclip has been seen in several OAT contraindicated patients.

Small registries on Watchman, Amplatzer Cardiac Plug and Lariat have shown 2-4 fold reduction in stroke rates in OAT contraindicated patients compared to their corresponding $CHADS_2$ score based stroke risk. The use of LAAC without post procedural OAT has been widely prevalent. It is probably hard to conduct a RCT in this specific subset of population. There are several larger ongoing registries that are addressing this specific issue. FDA approved the Watchman device in the United States in 2015 and has slowly gained momentum in clinical use. Current AHA/ASA Guidelines recommendations suggest closure of the left atrial appendage (LAA) for high-risk patients with AF who are deemed unsuitable for anticoagulation if performed at a center with low rates of periprocedural complications and the patient can tolerate the risk of at least 45 days of post-procedural anticoagulation (Class IIb; Level of Evidence B)[17]. European Society of Cardiology recommends LAAC for patients with non-valvular AF, who are either contraindicated or Unsuitable for long tern OAT-owing to high bleeding risk (HASBLED score greater or equal to 3) Or as an alternative treatment (Class IIb; Level of Evidence B)[18]. European Heart Rhythm Association (EHRA) and European Association of Percutaneous Cardiovascular Interventions (EAPCI), recommends LAAC in patients with AF and indication for OAT for stroke/embolism prevention (with CHA_2DS_2-VASc score > 1 point) and increased risk of bleeding (HAS-BLED score 3 points or more), contraindications for OAT, or refusal of treatment with OAT [19]. But the limitations of this intervention are that it can only be done in patients with non-valvular atrial fibrillation and no other indication for OAT and also patient needs to be able to tolerate intra-procedure and post-procedure anticoagulation as per the protocol. This requirement of uninterrupted post-procedure anti-thrombotic protocol for some months becomes a major hurdle in pursuing this procedure in patients at risk for bleeding.

Causes of gastrointestinal bleeding in atrial fibrillation patients on oral anticoagulation therapy (OAT)

The majority of atrial fibrillation patients are elderly with multiple comorbidities and are on multiple medications including antiplatelet therapy, NSAIDS, etc. leading to increased overall prevalence of mucosal erosions, gut dysmotility, peptic ulcer diseases, diverticulosis, polyps and arteriovenous malformations in this population. All these factors contribute to increased vulnerability of these patients to gastrointestinal bleeding while on OAT.

Arteriovenous malformations (AVM) are of particular importance due to varied reasons viz- accounting for 40-60% of lower and 5% of upper gastrointestinal bleeds respectively, often elusive, multiple and difficult to treat with conventional endoscopic methods [20]. Pathologically they are dilated, tortuous thin-walled communications between veins, venules and capillaries located in submucosa of the gut. They are usually located in small and large intestines and diagnostic studies include upper and lower endoscopies, wireless capsule endoscopy, double balloon enteroscopy and computed tomography (CT) or magnetic resonance angiography. Gastrointestinal bleeding has a huge impact on healthcare costs in US with mean cost/ hospital admission for lower GI blood loss being around $40,456 [21]. Use of OAT in this group of patients is particularly challenging. Endoscopic cauterization, mesenteric arterial coiling or embolization, surgical resection of the affected regions may be reasonable options. But a large number of these patients continue to have repeat bleeding as more than one site is typically involved. Perhaps a systemic pharmacologic intervention to affect these AVMs may provide an opportunity to temporarily use OAT in these unfortunate patients with a long term plan for LAAC.

Interventions for management of gastrointestinal bleeding in patients with atrial fibrillation

Non-pharmacologic interventions

The first line therapy for any patient with gastrointestinal bleeding on OAT is endoscopic intervention. This is both diagnostic and therapeutic except for capsule endoscopy (only diagnostic). If the source of bleeding is identified, it is usually subject to endoscopic therapy with argon plasma coagulation (APC), electrocoagulation or mechanical hemostasis using clips. Surgery with resection of the bowel segment, identified to be the source of bleeding, may be needed in life threatening hemorrhages. If no bleeding source is identified on endoscopies, angiography with embolization is usually the next step in management. Patients can subsequently be re-challenged with oral anticoagulation therapy. However advanced age and associated comorbidities in majority of atrial fibrillation patients makes these invasive interventions more challenging and risky. Above all, multifocal nature and inaccessibility of AVM lesions in some patients, results in overall recurrence rate of 30-40% despite all these aforementioned interventions [22]. And ultimately the end result is discontinuation of OAT.

Pharmacologic Interventions

Due to its recurrent nature and risks of invasive procedures in elderly patients, pharmacotherapy is particularly sought for lower gastrointestinal bleeding secondary to arteriovenous malformations (AVMs). There is some evidence, mostly from anecdotal case reports, that supports the use of different pharmacological agents in such situations, as we describe further .Their overall benefits in isolated cases of lower gastrointestinal bleeding who are not on OAT is still a matter of debate. However, in patients with obligate need for OAT the overall clinical benefit outweighs the risks associated with those medications, as we showed in our study.

Role of Octreotide

Octreotide (OCT) is a long acting somatostatin analogue which acts as a vasoconstrictor and thereby decreases splanchnic blood flow. Octreotide has long been used in the management of acute variceal upper gastrointestinal bleed. Its role in non-variceal bleeds particularly angiodysplasias was less well understood until recent times. However, there have been multiple case reports, prospective non-randomized studies and a meta-analysis that showed its promising role in patients suffering from angiodysplasias [23]. Its role becomes particularly important in patients who have refractory bleeding, inaccessible or multiple lesions, patients at high risk for interventions and patients on anticoagulants/antithrombotic therapies. These vascular lesions represent a relatively common cause of gastrointestinal bleeding, especially among the elderly people. Because recurrent gastrointestinal (GI) bleeds and drop in hemoglobin due to these angiodysplasias forces clinicians to withdraw OAT, its role in patients with several co-morbidities and in need of anticoagulation becomes particularly noteworthy. One of the studies showed that use of long acting Octreotide (Octreotide LAR-Once a month IM injection) was associated with less bleeding events and transfusion needs with improvement in hemoglobin levels during octreotide treatment and interestingly enough most patients had severe co-morbidities and that treatment with either anticoagulants or antiplatelets was not suspended [24]. Octreotide can play a very vital role in atrial fibrillation patients who are off of OAT secondary to recurrent gastrointestinal (GI) bleeds or drop in hemoglobin level. It can help reinitiate OAT in many of these patients. Now that we are in an exciting era where we have options of LAAC, NOACs and 3D-mapping assisted radiofrequency ablation (RFA), role of octreotide can be particularly explored in atrial fibrillation patients. As mentioned above, recurrent gastrointestinal (GI) bleeding is one of the main hurdles in pursuing these procedures due to the fact that patient are still exposed to anticoagulation for a brief period after the procedure. Octreotide, with its impact on hemoglobin level and gastrointestinal (GI) bleeding recurrence, can help resume OAT in such patient and thereby pave the way for further available management options. Octreotide has an excellent safety profile with risk of gallstones, pancreatic diarrhea or impaired glucose metabolism in diabetics on long term use.

Table 3: Showing the OAT+OCT regimen used and improvement in mean Hb level in patients with history of GI bleed on OAT

Outcomes	Patients
Type of OAT Continued	
Apixaban	15 (53.5%)
Rivaroxaban	11 (39.3%)
Warfarin	02(7.1%)
Recurrent of GI bleeding after restarting OAT+OAC therapy	09 (32.1%)
Minor bleeds	04 (14.2%)
Major bleeding requiring transfusion	04(14.2 %)
Major bleeding requiring Colectomy	01 (3.5%)
Hemoglobin(gm/dl)	
At baseline	7.49 (±1.07)
At 3 months follow up	9.33 (±1.12)
At 6 months follow up	11.10 (±1.50)

Outcomes in patients on OAT/OCT therapy at 6 months follow up (n=28)

In a small prospective observational study **[Figure 1]**, conducted by our group involving 36 AF patients not on OAT due to recurrent gastrointestinal (GI) bleeds from AV malformations in the small and large intestine. These patients received 100 to 300 mg of subcutaneous Octreotide injection twice daily and OAT was resumed 24-48 hours after OCT was started. The mean age was 69 ± 8.0 years with a mean CHA_2DS_2VASc score of 3 ± 1 and the HASBLED score of 3 ± 1. Before oral anticoagulation was discontinued, warfarin was used in 44%, apixaban in 22.2 %, rivaroxaban in 16.7%, and dabigatran in 16.7%. LAA clot was present in 5/36 (13.8%), and systemic thromboembolic events were reported in 8/36 (22%) patients before enrollment. Angiodysplasia was the most common identified cause of bleeding (76%) and one third of the patients (33.3%) had a prior endoscopic intervention with APC of identifiable lesions, prior to enrollment. Median follow-up duration was 8 months (range of 6 – 13 months). Among the study population, 8/36 (22%) patients underwent left atrial appendage closure for stroke prevention (LARIAT in 4, WATCHMAN in 3, and AtriClip in 1) with subsequent discontinuation of OAT and OCT therapy. But, while still on octreotide/anticoagulation therapy, 4/8 (50%) had recurrent GI bleeds with 3 of them requiring blood transfusion [Figure 1].

The remaining 28/36 (77.8%) patients were continued on oral anticoagulation with apixaban in 15 (53.5%), rivaroxaban in 11 (39.3%), and warfarin in 2 (7.1%). Among these 28 patients, 19 (67.8%) had no recurrent GI bleeds, while 4 (14.2%) had minor GI bleeds, and 4 (14.2%) had major GI bleeds requiring blood transfusion [Figure 1]. In those patients who remained on OAT throughout the study period (n = 28), the mean hemoglobin levels were significantly higher at three months (9.33 vs. 7.49 g/dl; $p < 0.001$)

and six months (11.10 vs. 7.49 g/dl; p < 0.001) compared to baseline [Table 3], [Figure 2]. In addition, successful cardioversion was done in 13/36 (36%) and were started on antiarrhythmic drugs (AAD) for maintenance of sinus rhythm and continued on oral anticoagulation along with octreotide. There were no reported events of systemic thromboembolism or intracranial hemorrhage during the study period. So overall, octreotide therapy enabled stroke prevention in patients with recurrent gastrointestinal bleeding by either continued oral anticoagulation use (78%) or left atrial appendage closure (22%). And 68 % of patients who resumed and were maintained on oral anticoagulation therapy had no episode of recurrent gastrointestinal bleeding during the study period. No side effects from octreotide use were reported.

Potential role of other pharmacologic agents

The agents that have been studied the most in arteriovenous malformations (AVMs) are the hormones, estrogen and progesterone. There have been case series reports about successful use of estrogen in epistaxis but a randomized controlled trial (RCT), which included only 2 cases of gastrointestinal (GI) bleeding, failed to show any benefit [25]. Subsequently combination of estrogen and progesterone have also been studies in patient with gastrointestinal (GI) bleed

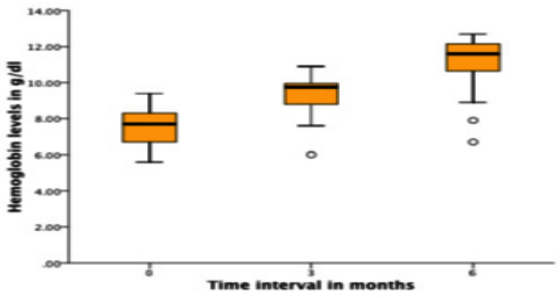

Figure 2: Boxplot illustrating the improvement in mean Hb at 3 and 6 months post OCT therapy

secondary to AVM (AD and HHT). There have been multiple case reports about successful use of estrogen alone in doses ranging from 0.035 mg to 0.05 mg, or estrogen 0.01 mg to 0.1 mg and progesterone 1 mg to 5 mg in patient with different AVM [26]. There was report of either bleeding stopped or reduction of transfusion requirements and an increase in hemoglobin for the duration of follow-up in most of these case reports. Subsequently two crossover trials both showed a significant impact on transfusion requirements in patients with AVM with combination hormonal therapy [27], [28]. One of the most recent Randomized double blind trial also failed to show any benefit of hormonal combination therapy over placebo [29]. However critics say that they used the lowest dose of estrogen reported so far which might have had an influence on the study outcome [30]. So overall, given the heterogeneity of results from different studies, there are no clear cut guidelines regarding efficacy of combination hormonal therapy in patients with AVM related gastrointestinal (GI) bleeding. Use of other pharmacologic agents like Prednisone, Danazol, Tranexamic acid (TA), Epsilon aminocaproic acid (EACA), Desmopressin, in patients with AVM related GI bleed, is mostly available from case reports [Table 4].

Interestingly enough, thalidomide-originally an anticancer drug, which made a comeback with its usefulness in Crohns disease, has also been reported to be useful in gastrointestinal (GI) bleeding related to angiodysplasias (AD). At low doses (100 mg/day to 200 mg/day),

Table 4: Pharmacological agents used for treatment of vascular malformations

Drug	Predominant diagnosis	Route and dose	Putative mechanism
Estrogen (E)	AD/HHT	0.035 mg–0.05 mg po	Vascular stability, improved coagulation, decreased mesenteric blood flow
E + progesterone (P)	AD/HHT	0.01 mg–0.1 mg po (E), 1 mg–2 mg po (P)	Vascular stability, improved coagulation, decreased mesenteric blood flow
Octreotide	AD/HHT, BRBNS	100 mg–500 mg sc bid, 10 mg–30 mg im	Multiple effects
Corticosteroids	WS	po	Increased vascular integrity
Prednisolone + cyclophosphamide	WS	po	Increased vascular integrity
Interferon	Hemangiomas	sc	Inhibits angiogenesis
Danazol	HHT	200 mg po tid	Weak androgen, direct vascular stability
Tranexamic acid	HHT	1 g po qid	Inhibits fibrinolysis
Aminocaproic acid	HHT	2 g po daily	Inhibits fibrinolytic system
Desmopressin	HHT	IV	Stabilizes vessel wall, increased platelet adhesion
Vasopressin	AD	IV/IA	Decreased splanchnic circulation
Diamino-8-D-arginine vasopressin	AD + VWD	IN spray, 300 µg	Increased vascular stability
Thalidomide	AD, HHT	100 mg–300 mg qid 400 mg po daily	Antiangiogenesis

^Reproduced from Can J Gastroenterol. 2006 Mar; 20(3): 171–180
AD Angiodysplasia; bid Two times per day; BRBNS Blue rubber bleb nevus syndrome; HHT Hereditary hemorrhagic telangiectasia; IA Intra-arterial; IM Intramuscular; IN Intranasal; IV Intravenous; PO Orally; QID Four times per day; SC Subcutaneous; TID Three times per day; VWD von Willebrand disease; WS Watermelon stomach

it has anti-angiogenetic effects. There are few case reports showing its positive impact in patients with refractory gastrointestinal (GI) bleeding secondary to arteriovenous malformations/angiodysplasias (AVM/AD). Patients showed improvement within 2 weeks which was sustained for more than 2.5 years with only minimal side effects of fatigue and transient peripheral neuropathy [31]-[34].

Conclusion

While research continues to strive in innovating new strategies to prevent cardio-embolic phenomena in atrial fibrillation patients with minimal complications, in future, we should not lose the focus of atrial fibrillation (AF) patients at present. Roughly around 50 % of atrial fibrillation (AF) patients with guideline indications for OAT end up not being on any kind of anticoagulation, which is of huge concern as stroke is the leading cause of disability and third leading cause of death in United States with an estimated annual cost of around 60 billion dollars. Bleeding complication remains one of the most common reasons for a patient or a clinician to discontinue warfarin and NOAC's are no better when it comes to bleeding events. We can approach this problem by actively addressing the source of bleeding and then coming up with a long-term strategy for stroke prevention. Systemic Octreotide can be reasonable option as a bridge to a more definitive therapy for stroke prevention.

Conflict Of Interests

DL – is the principle investigator for the Amaze Trial and Amulet IDE trial. He is also a consultant for St. Jude Medical

Disclosures

None.

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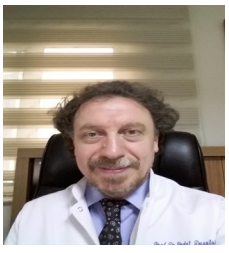

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