Issn : 1941 -6911

Apr - May 2019
Volume 11 - Issue 6

JAFIB

Journal of Atrial Fibrillation

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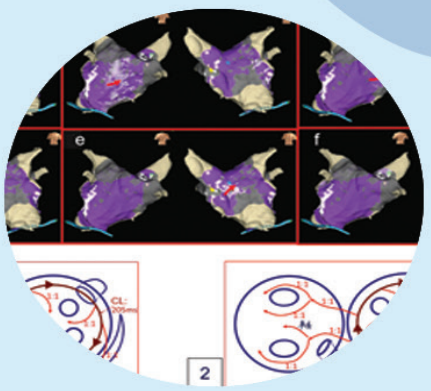
- The Impact of Repeated Cardioversions for Atrial Fibrillation on Stroke, Hospitalizations, and Catheter Ablation Outcomes.



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Apr - May 2019
Volume 11, Issue 6

JAFIB

Editorial

Journal of Atrial Fibrillation

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ISSN: 1941-6911 Volume 11 Issue 6 Apr - May 2019

Bracing a real hot summer!

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

Dear Colleagues

Welcome to the summer issue of JAFIB. Hope everyone had a chance to enjoy the short spring and a super-hot summer that has just begun. With half of Europe experiencing record temperatures, England has a crackling cricket world cup tournament on the way. Maybe it is time for the world to realize after all climate change is real and its not a creation of earth loving climatologists!

In this issue of the journal we have several interesting articles presented for your reading. We have several new editorial board members that have come on board. The journal website is being revamped to improve the workflow and user friendliness. The 11th iteration of Kansas City Heart Rhythm Symposium is due to happen August 17th and 18th. We welcome you to join us to celebrate the former Editor-in-Chief of JAFIB Dr. Andrea Natale receiving the Pioneer in EP award.

Have a great rest of the summer.

Best wishes
DJ Lakkireddy

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The Impact of Repeated Cardioversions for Atrial Fibrillation on Stroke, Hospitalizations, and Catheter Ablation Outcomes

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Abstract

Background: Long-term outcomes after direct current cardioversion (DCCV) in patients that receive anticoagulation have demonstrated to have no adverse sequela. Less is known about the impact on atrial fibrillation (AF) outcomes and resource utilization of repeated DCCVs that are often required for long-term rhythm control.

Methods: A total of 4,135 AF patients >18 years of age that underwent DCCV with long-term system follow-up were evaluated. Patients were stratified by the number of DCCVs received: 1 (n=2,201), 2-4 (n=1,748), and ≥5 (n=186). Multivariable Cox hazard regression was used to determine the association of DCCV categories to the outcomes of death, AF hospitalization, AF ablation, DCCVs, and stroke/transient ischemic attack.

Results: The average follow-up of the patient population was 1,633.1±1,232.9 (median: 1,438.0) days. Patients who underwent 2-4 and ≥5 DCCVs had more comorbidities, namely hypertension, hyperlipidemia and heart failure. Anticoagulation use was common at the time of DCCV in all groups (89.1%, 91.2%, 91.9%, p=0.06) and amiodarone use increased with increasing DCCV category (30.1%, 43.4%, 52.2, p<0.0001). At 5 years, patients that received more DCCVs had higher rates of repeat DCCVs, AF hospitalizations, and ablations. Stroke rates were not increased. Though not statistically significant, 5-year death was increased when comparing DCCV >5 vs. 1, (HR=1.32 [0.89-1.94], p=0.17).

Conclusions: This study found that the increasing number of DCCVs, despite escalation of other pharmacologic and nonpharmacologic therapies, is a long-term independent risk factor for repeat DCCVs, ablations, and AF hospitalizations among AF patients.

Introduction

Atrial fibrillation (AF) is a rising epidemic that will affect more than 12 million people in the United States by the year 2030.[1-4] AF is the most frequent clinical sustained arrhythmia and is increasing in prevalence as a result of improvements in diagnostic approaches, people living longer, and record growth of systemic co-morbidities associated with AF.[5,6] Direct current cardioversion (DCCV) is one of the modalities used for rhythm control in patients with AF.[7] Typically DCCV is performed if an individual experiences a recent onset of AF, significant symptoms related to AF, hemodynamic instability due to AF, or a high heart rate with myocardial ischemia or hypotension.[8] Therefore, DCCV is used primarily to improve symptoms or to achieve hemodynamic stability in a patient. Recurrences of AF after DCCV are common as arrhythmia provoking substrate persists despite rhythm restoration.[9] Antiarrhythmic medications can be used prior to a DDCV to assist in achieving better success in converting to and maintaining normal sinus rhythm (NSR).[10] Approximately 88% of DCCVs are successful in the restoration of NSR, however the long-term maintenance of NSR is impermanent in many patients and can require repeated DCCVs to achieve control of their arrhythmias. The factors adversely affecting the success of DCCVs include high body mass index, presence of cardiomyopathy, chronic obstructive pulmonary disease, and longer duration of AF.[8,11] Typically, patients with an increased number of co-morbidities are less likely to convert back to AF and require subsequent DCCVs to restore NSR. In addition, these same patients are also more likely to require more than one ablation procedure to sustain NSR. The purpose of this study was to determine differences in long-term outcomes among patients undergoing repeated DCCVs and the potential benefit of additional escalation of rhythm control therapies including repeating DCCV, ablation, and antiarrhythmic drug therapies.

Key Words

Atrial fibrillation, Cardioversion, Stroke, Heart failure, Ablation.

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Methods

Patients in this study underwent their DCCV procedures at the Intermountain Medical Center Heart Institute. Intermountain Healthcare provides medical care for approximately half of Utah residents, and has integrated electronic medical records for all hospitals within the system, stored in a data warehouse. Patients were included if they were >18 years old and underwent 1 or more DCCVs. The numbers of DCCVs were categorized as: 1, 2-4, and ≥5 for comparative analysis. For example, if the first category was changed to 1-2, 80% of the population would fall into it making further comparisons limited. The lack of use of more DCCVs likely reflects multiple centers within our healthcare network that perform

catheter ablation and are comfortable with the use and titration of antiarrhythmic drugs.

The population studied was primarily Caucasian (89%) with other races as follows: Hispanic 7%, Black 2%, Polynesian/Asian 1%, and Native American 1%. Baseline clinical variables were defined using International Classification of Diseases, Ninth and Tenth Revision (ICD-9 and 10) codes of inpatient and outpatient visits prior to or at the time of the first DCCV. Baseline characteristics included age, gender, hypertension, hyperlipidemia, diabetes, smoking history, prior myocardial infarction, cerebrovascular accident, heart failure, prior cerebrovascular accident, prior transient ischemic attack, prior thromboembolism, and cardiomyopathy. The use of HMG-CoA reductase inhibitors (statins), angiotensin converting enzyme inhibitors (ACE inhibitors), angiotensin receptor blockers (ARB), beta blockers, antiarrhythmic medications, aspirin, amiodarone, and all oral anticoagulants were documented.

A diagnosis of AF was determined by searching the hospital discharge summaries for ICD codes for AF (ICD-9: 427.31; ICD-10: I48.0, I48.1, I48.2, I48.91) at index and previous admissions to Intermountain Healthcare hospitals (Salt Lake City, Utah and its surrounding areas) and by searching the Intermountain electrocardiographic database. The electrocardiogram database stores electrocardiograms, ambulatory monitors, and event monitors from all Intermountain Healthcare facilities. These databases are updated daily with completion of the dictated medical reports and physician evaluation of the electrocardiograms.

Patients were followed for the 5 year and long-term outcomes of death, AF hospitalization, AF ablation, cardioversion, and cerebrovascular accident/transient ischemic accident. Patients were censored at the endpoint being evaluated, death, or last day of follow-up.AF hospitalization was defined as having a primary inpatient discharge diagnosis code of ICD-9: 427.31 or ICD-10: I48.0, I48.1, I48.2, or I48.91. Follow-up AF ablation and cardioversion were determined through procedure codes. Cerebrovascular accident/transient ischemic accident were determined using ICD-9 code 433. x1, 434.x1, and 435.x; and ICD-10: I63.x, I64. x., G45.0x, G45.1x, G45.8, G45.9x, and I167.848. Deaths were determined by telephone survey, hospital records, and Utah State Health Department records (death certificates) and were verified through Social Security death records. Patients not listed as deceased in any registry were considered to be alive.

The analysis of variance and the chi-square statistic were used to evaluate differences in baseline and clinical characteristics among the DCCV categories. The Kaplan Meier survival estimate, and the log rank test of survival were used to evaluate initial associations of DCCV categories to the endpoints. Multivariable Cox hazard regression analysis (SPSS, version 22.0) was used to evaluate study endpoints. Final models entered significant ($p<0.05$) and confounding (10% change in HR) covariables. Two-tailed p-values of <0.05 was designated as nominally significant.

Results

A total of 4,135 patients were included in this study. The distribution of patients in each DCCV category were: 1 DCCV: n=2,201; 2-4 DCCVs: n=1,748, ≥5 DCCVs: n=186. [Table 1] shows the baseline characteristics of the study population stratified by categories of DCCV. Age and sex did not differ between the groups. Those who underwent more DCCVs had more comorbidities (hypertension, hyperlipidemia, heart failure (HF), and cardiomyopathy). Patients who underwent >5 DCCVs were more likely to take amiodarone (52.2%), followed by flecainide (30.6%). The majority of patients received oral anticoagulation: 1 DCCV: 89.1%, 2-4 DCCVs: 91.2% and ≥5 DCCVs: 91.9% (p=0.06).

The average length of follow-up among the DCCV categories were: 1 DCCV: 1,718 ± 1,286 (median: 1,515) days, 2-4 DCCVs: 1,563 ±1,174 (median: 1,379) days, ≥5: 1,288 ±1,015 (median: 1,104) days ($p<0.0001$). The frequencies of 5 year and long-term outcomes are shown in [Table 2]. Data regarding the frequency of DCCVs, time to repeat DCCV, and escalation of antiarrhythmic drug therapies is shown in [Figure 1],[Table 2] shows the differences

Table 1: Baseline characteristics stratified by DCCV categories.

	1 (n=2,201)	2-4 (n=1,748)	≥ 5 (n=186)	p-value
Age (years)	67.2±11.0	66.9±11.1	66.8±11.7	
Sex (male)	62.4%	61.3%	66.7%	0.32
Hypertension	81.0%	86.6%	94.1%	<0.0001
Hyperlipidemia	65.9%	72.7%	82.3%	<0.0001
Diabetes	27.8%	31.8%	35.5%	0.005
Smoking	65.9%	72.7%	82.3%	<0.0001
Prior myocardial infarction	7.8%	8.2%	7.0%	0.81
Heart Failure	51.0%	56.3%	65.6%	<0.0001
Cerebral Vascular Accident	6.0%	6.4%	7.0%	0.76
Transient ischemic attack	7.4%	8.4%	9.7%	0.34
Cardiomyopathy	31.7%	38.2%	53.2%	<0.0001
CHADS2				<0.0001
0-1	36.7%	30.0%	19.9%	
2-4	57.8%	63.7%	73.1%	
>5	5.5%	6.2%	7.0%	
CHA2DS2-Vasc				0.001
0-1	15.8%	12.9%	7.5%	
2-4	50.5%	49.7%	50.5%	
>5	33.7%	37.4%	41.9%	
ACE Inhibitor	32.2%	34.3%	38.2%	0.14
Angiotensin receptor blocker	19.5%	21.2%	25.8%	0.08
Beta blocker	68.8%	67.8%	71.0%	0.62
Calcium channel blocker	32.9%	40.8%	38.2%	<0.0001
Amiodarone	30.1%	43.4%	52.2%	<0.0001
Dofetilide	4.8%	6.5%	12.4%	<0.0001
Flecainide	23.9%	29.5%	30.6%	<0.0001
Statin	44.0%	45.9%	51.1%	0.12
Propafenone	6.5%	7.6%	6.5%	0.38
Sotalol	18.4%	18.7%	23.1%	0.29
Anticoagulant	89.1%	91.2%	91.9%	0.06
ASA	43.5%	47.1%	43.5%	0.08

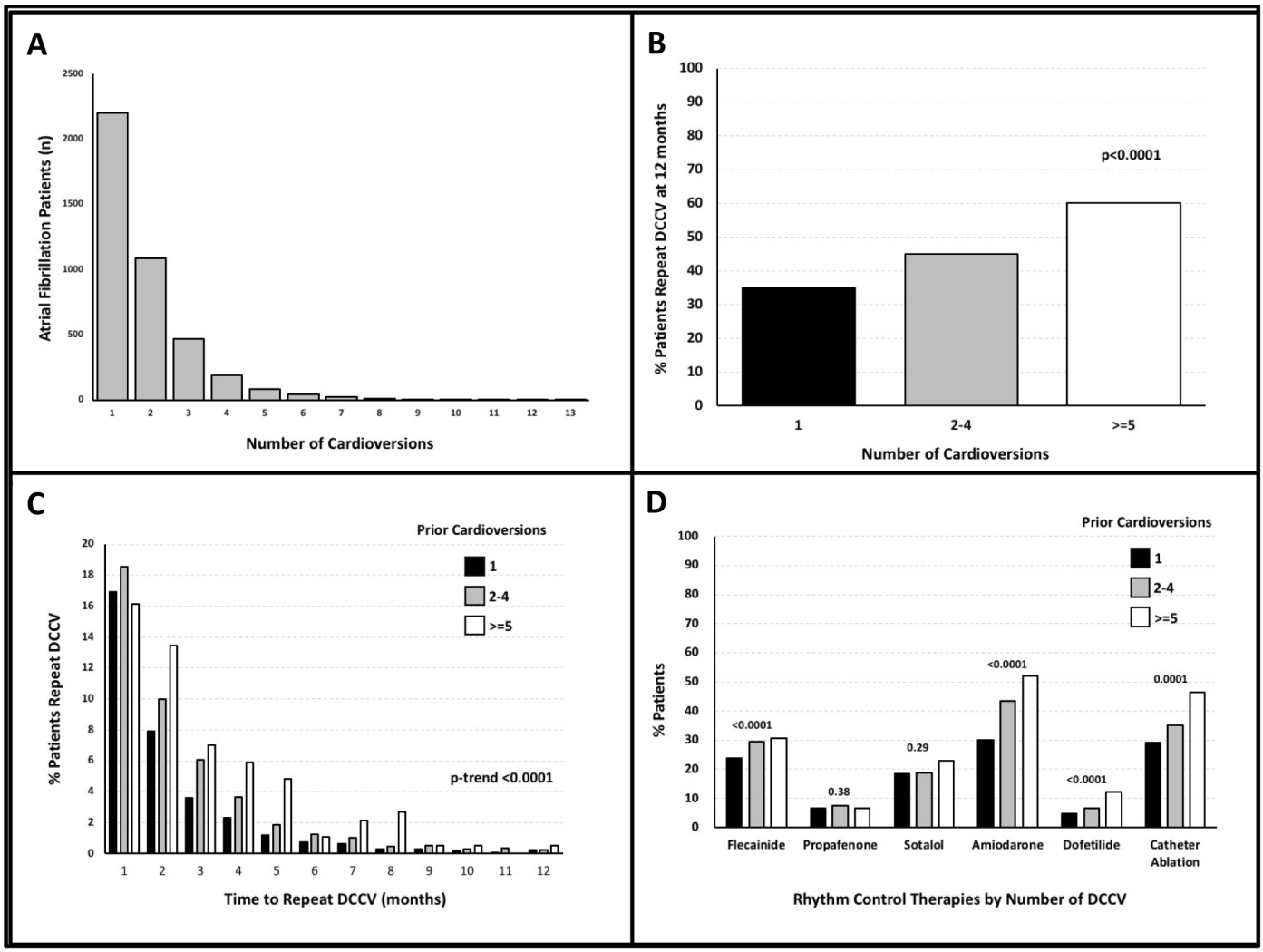

Figure 1: The distribution of cardioversions is shown in A, percentage use of cardioversions in the three groups studied B, time to repeat DCCV per DCCV group in C, rhythm control approaches both pharmacologic and nonpharmacologic per DCCV in D.

in outcome incidences at 5 years. Amongst the outcomes AF-related hospitalization, need for AF ablation, and need for repeat DCCV all significantly increased with higher initial DCCV category. [Figure 2] displays 5-year Kaplan-Meier survival curves among the DCCV categories. Multivariable hazard ratios for the 5-year outcomes are shown in [Figure 3]. After adjusting for comorbidities and medications, comparisons of 2-4 DCCVs and >5 DCCVs versus 1 DCCV were associated with increased risk AF ablations and DCCVs ([Figure 3]). Only the comparison of ≥5 DCCVs versus 1 DCCV were associated with AF hospitalization risk. [Table 3] displays mortality trends by AAD therapy. Across all 3 DCCV groups there was not an observed increase risk in those patients treated with AADs. In those patients with ≥5 DCCV there was a notable difference in mortality by AAD therapy, although the numbers in each group limited the significance. In regard to AF ablation, there was not a mortality difference noted in the different DCCV groups. However, in patient groups with 1 and 2-4 DCCVs, AF ablation positively impacted subsequent AF hospitalization risk [Table 4].

Table 2: Frequency of 5-year outcomes among DCCV categories.

	1	2-4	≥ 5	p-value
Death	17.9%	19.7%	25.4%	0.21
AF hospitalization	18.0%	21.3%	26.8%	0.05
AF ablation	29.1%	35.0%	46.5%	0.001
Cardioversion	40.7%	49.8%	64.8%	<0.0001
CVA/TIA	7.2%	6.3%	9.9%	0.43

Discussion

This study has several important associative findings. First, DCCV is an independent predictor of repeat DCCVs, ablations and AF hospitalizations. Second, patients who have undergone repeat DCCVs are less likely to maintain NSR despite escalating use of ablation and antiarrhythmic drug therapies. Third, changes in

Table 3: Antiarrhythmic drug use and 5-year mortality risk compared by DCCV use

	No Antiarrhythmic Drug	Antiarrhythmic Drug	p-value
1 DCCV	17.8% (67/377)	17.9% (149/833)	0.96
2-4 DCCV	24.5% (36/147)	18.7% (137/731)	0.11
≥5 DCCV	16.7% (2/12)	27.1% (16/59)	0.72

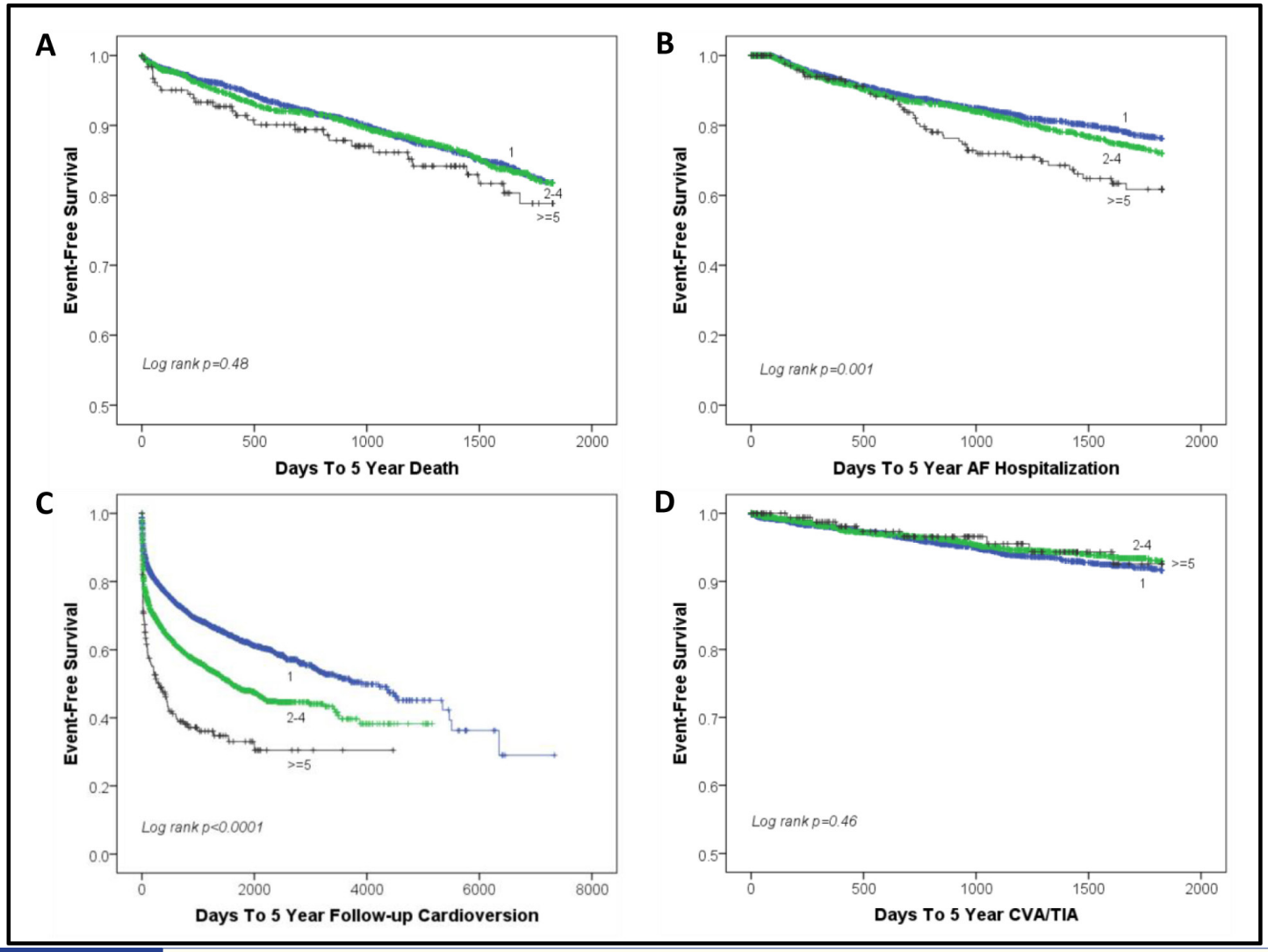

Figure 2: Kaplan-Meier survival curves for 5 year A. death, B. AF hospitalizations, C. repeat cardioversion, D. Cerebrovascular accident/transient ischemic accident among DCCV categories.

Table 4: AF ablation and risk of 5-year AF-related hospitalization compared by DCCV use

	No ablation	Ablation	p-value
1 DCCV	19.3% (190/987)	12.6% (28/223)	0.02
2-4 DCCV	22.9% (153/668)	16.2% (34/210)	0.04
≥5 DCCV	25.0% (12/48)	30.4% (7/23)	0.63

addressing multiple co-morbidities of AF patients may potentially decrease the need for multiple DCCVs and ablations.

AF in most patients is a progressive chronic disease associated with electrical and structural remodeling of the atrium.[12] These proarrhythmic substrate changes can influence the utility of rhythm control approaches. It is unclear the value adds and impact of augmenting both pharmacologic and nonpharmacologic therapies in an effort to restore sinus rhythm. DCCV is an upfront and immediate therapy to restore NSR and if often use with other pharmacologic and nonpharmacologic rhythm control approaches. In this study, DCCV is also a strong risk marker of a patient that will likely require escalation in other rhythm control approaches in the future and experience higher rates of AF-related comorbidities such as heart failure and death.

Central to these data and findings is the question of what drives AF recurrences beyond the local changes in the atrium of electrical and structural remodeling. If local atrial changes defined outcomes alone, then systemic outcomes such as death would not necessarily be impacted, and rhythm control approaches should result in better outcomes.[13] However, rhythm control approaches in general have consistently failed to lower risk of stroke and mortality. Clinical risk factors of recurrences are prevalent in AF patients such as aging, hypertension, coronary artery disease, obesity, metabolic syndrome, diabetes, cardiomyopathy, sleep apnea and these also contribute to AF-related comorbidities.[14] Within our population despite similar ages, the prevalence of many of these risk factors increased incrementally with the number of DCCVs performed. In support of systemic disease provocation of arrhythmia recurrence and worsening outcomes is that many biomarkers of inflammation, vascular, and cardiovascular disease are elevated in patients with AF recurrences. Amongst these biomarkers, C-Reactive Protein (CRP), natriuretic peptides, troponin, and pro-atrial natriuretic peptide (ANP) and

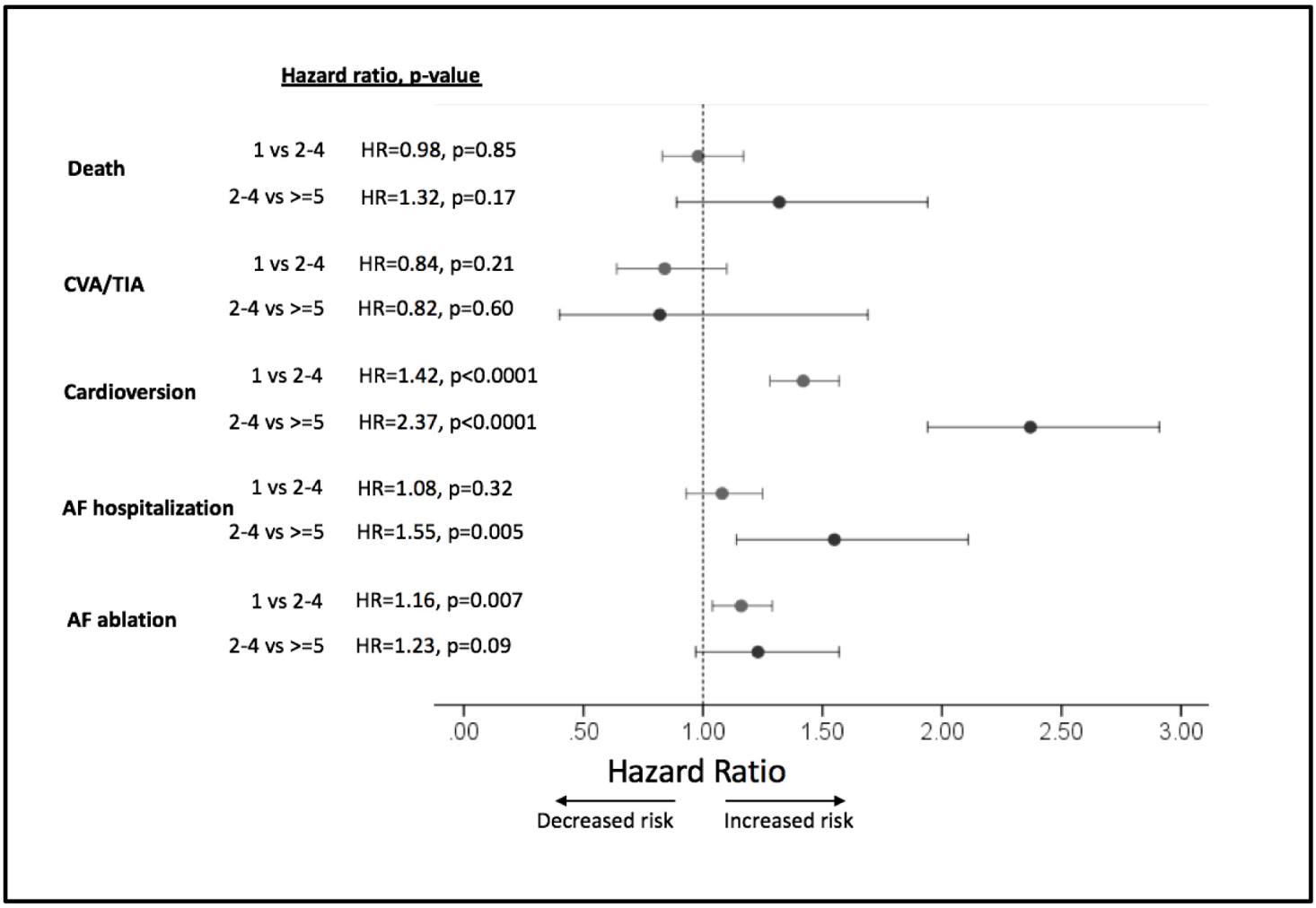

Figure 3: Overall representation of the multivariate adjusted hazard ratios results of: death, cerebrovascular accident/transient ischemic accident, cardioversion, AF and AF ablation.

pro-Brain natriuretic peptide (BNP) are all associated with AF recurrences.[15-17]

Next, current pharmacologic therapies are often poorly tolerated, lack efficacy (40-70%), and many are associated with significant side effects that can contribute to morbidity and mortality.[18] In this trial, use of class 1c agents and transition to a ratio of more class 3 agents is observed as DCCV use increased. Despite use of more potent antiarrhythmic drug therapies, AF recurrences were common and reflect the limitations with antiarrhythmic drug therapies as well as systemic disease state and atrium substrate changes that make the disease less amendable to pharmacologic rhythm control therapies.

Finally, although long-term outcomes in patients that underwent an ablation are generally favorable, those with recurrences have worse outcomes such as stroke, dementia, heart failure, and death.[19] In post-ablation patients the recurrence of arrhythmia is also a risk factor of adverse outcomes. Similar findings of improved outcomes are observed in patients that maintain sinus rhythm over time in the AFFIRM trial compared to those that do not independent of treatment strategy. [20] In the AF-Congestive heart failure (CHF) trial the presence of sinus rhythm trended towards lower rates of worsening heart failure (p=0.059), but not mortality.[21] In these studies, with and without ablation, sinus rhythm is a marker of a patient that is more likely to do well. As such, the need for DCCV a reflection of symptomatic AF recurrences is a marker of a worse substrate and risk. In this study, this morbidity and mortality risk persisted despite currently available therapies aimed to restore sinus rhythm (ablation and antiarrhythmic drugs).

Limitations

This study has some limitations to consider. It is observational and can only provide insight and associations, but not causality. Treatment was defined by the patient's physician and there may be some variability on treatment preferences, such as the use antiarrhythmic or performing additional DCCVs. Finally, some characteristics and outcomes were determined by ICD-9 and ICD-10 codes. Events may have occurred outside of our medical system and therefore unaccounted for in our data. However, Intermountain Healthcare is the majority provider within the state of Utah and nearby regions with an integrated system of hospitals and clinics, which improves longitudinal follow-up within the system.

Conflicts of interest

Victoria Jacobs: none Heidi T. May: none Tami L. Bair: none Brian G. Crandall: none Michael J. Cutler: none John D. Day MD: honorarium/consulting: Abbott Medical, Boston Scientific,

Medtronic Viet Le: None Charles Mallender: Jeffrey S. Osborn: honorarium/consulting: Abbott Medical, Boston Scientific, Medtronic, Spectranetics Peter Weiss: honorarium/consulting: Talon Medical, Stereotaxis T. Jared Bunch: research grants (no personal compensation): Boehringer Ingelheim, Boston Scientific.

Conclusions

DCCV is a long-term independent risk factor for; AF recurrence, catheter ablations and subsequent DCCVs in AF patients. DCCV is also a predictor for an increased incidence in the number of AF related hospitalizations, ablation and subsequent cardioversion needs. The risk association with DCCV was apparent despite increasing use of ablation and antiarrhythmic drug therapies.

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Transtelephonic ECG Monitoring to Guide Outpatient Antiarrhythmic Drug Therapy in Patients With Non-Permanent Atrial Fibrillation: Efficacy and Safety From a Single-Center Experience

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Abstract

Initiation of antiarrhythmic drug therapy (AADx) for atrial fibrillation (AF) on an outpatient basis requires intensive ECG monitoring in order to assess antiarrhythmic efficacy as well as ECG signals of potential proarrhythmia. Dronedarone (DRO) reduces cardiovascular endpoints in AF patients fulfilling criteria of the ATHENA trial [1]. In the present study transtelephonic ECG monitoring was used to guide initiation of AADx in AF patients fulfilling the ATHENA criteria.

In 19 consecutive patients (37% female; age 65+10 years; LVEF 62+7%; mean CHA2DS2-VASc score 2.9 + 1.6 (median=2), with symptomatic non-permanent AF and additional cardiovascular risk factors, DRO was prescribed as AADx of first choice. Initiation of therapy and follow-up were monitored by transtelephonic ECG recordings (VITAPHONE™100 IR; Vitaphone GmbH; Germany). In patients with persistent AF, electrical cardioversion was performed on an outpatient basis when DRO was started. Patients were followed for changes in QT intervals as well as AF recurrency. ECGs were transmitted according to a scheduled FU form as well as any time in case of pts symptoms.

Patients in whom DRO did not prevent AF recurrence were switched to alternative AADx, or to pulmonary vein isolation (PVI), respectively. At the end of long-term follow-up, DRO alone was successful in preventing AF recurrence in 5 of 19 patients (26%). When pts who responded to AADx of second or third choice or who underwent PVI were included, SR could be maintained in 17/19 pts (89%). No patient required discontinuation of AADx due to ventricular depolarization abnormalities, symptomatic bradycardia or pathologic QT prolongation.

In conclusion, transtelephonic ECG transmission is useful for close rhythm monitoring during initiation and follow-up of AADx, also during change from DRO to other AADx. DRO was effective to prevent AF recurrence in 26% of patients during a mean long-term follow-up of more than 30 months – which is well in line with data from the literature.

Introduction

Antiarrhythmic drug therapy (AADx) for restoration and/or maintenance of sinus rhythm remains a mainstay of treatment in highly symptomatic patients with non-permanent atrial fibrillation (AF), also in the era of interventional therapy of atrial fibrillation by means of catheter ablation [2-5]. However, AADx has potential pro-arrhythmic effects and its initiation requires intense ECG monitoring, particularly during the initial phase of treatment. Furthermore, pharmacologic therapy of non-permanent AF is characterized by a limited clinical long-term efficacy [3,6,7] and patients on AADx who were highly symptomatic prior to treatment may turn asymptomatic even in case of AF recurrence while on AADx [8]. Prolonged rhythm monitoring may thus be helpful in identifying patients with asymptomatic AF in whom modification of therapeutic strategies may be required.

Key Words

Atrial fibrillation, Transtelephonic ECG monitoring, Antiarrhythmic drug therapy.

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Recently, the multi-class AAD dronedarone has been added to the limited number of pharmacological armentarium of AF treatment. This drug is particularly an option in patients with additional cardiovascular risk factors such as atherosclerosis or hypertension [1]. The aim of the present study was to investigate the feasibility and clinical utility of guiding AADx by regular transtelephonic ECG monitoring in patients with non-permanent AF and additional risk factors who did not opt for pulmonary vein isolation (PVI) and in whom Dronedarone was prescribed as first line treatment.

Methods

In this prospective single-centre feasibility study at a cardiology outpatient office, consecutive patients with a history of symptomatic non-permanent AF and de-novo prescription of Dronedarone were offered to have transtelephonic ECG monitoring by means of a portable easy-to-use device instead of frequent in-office ECG registration during initiation and follow-up of AADx. Patients received a transtelephonic device (VITAPHONE 100 IR™, Vitaphone, Germany; [Figure 1] [Table 1]) on the day when Dronedarone was prescribed. The device can store a maximum of 3 episodes of a 30-second 1-lead ECG. After 3 registrations the

Figure 1: Transtelephonic ECG device used in the study (Vitaphone, Germany)

patients had to transmit the ECG data by telephone, after which the storage was cleared and the device ready for new ECG recordings. After transmission, a pdf with the ECG strip was generated and automatically sent to the investigator by e-mail. In order to ensure appropriate use of the device, the first ECG was registered immediately in-office. Also, the patient was asked to send additional 1 or2 ECGs from their home the same day and before the first dose of dronedarone. ECGs were analyzed with regard to the nature of rhythm, heart rate, and changes in QT interval, respectively. After start of AADx, patients were asked to record and transmit ECGs according to a pre-specified transmission schedule [Table 2]. Written informed consent was obtained from all patient with regard to the above mentioned study procedure. In particular, patients agreed that their ECG data were processed transtelephonically with the ECG tracings generated automatically and sent as pdf file per e-mail to the investigator. All electronic transmission and processing of ECG data were performed anonymously with the ECG tracing linked to the serial number of the ECG device.

Table 1: Technical data of the Tele-ECG device (VITAPHONE IR100, Vitaphone GmbH, Germany)

Leads	1 (bipolar)
A/D resolution	12 Bit
Frequency range	0.5 – 40 Hz
Max number of stored events	3
Duration of ECG event	30 sec

Table 2: ECG transmission schedule after initiation of AADx

Baseline ECG protocol		
Day 1-2	2 ECG/day	Additional ECG any time, e.g. in case of symptoms
Day 3-14	1 ECG/day	Additional ECG any time, e.g. in case of symptoms
Week 3-4	1 ECG / 2 days	Additional ECG any time, e.g. in case of symptoms
Beyond week 4	2 ECGs / week	Additional ECG any time, e.g. in case of symptoms
Beyond month 3	1 ECG / 1-2 weeks	Additional ECG any time, e.g. in case of symptoms
Additional recordings		
Change of AADx (see protocol above)		Additional ECG any time, e.g. in case of symptoms

(AADx=antiarrhythmic drug therapy; ECG=electrocardiogram)

Patients were followed for at least 6 months. Analysis of transtelephonic ECG recordings was performed as follows: number of episodes; quality of episodes; Heart rate and rhythm (SR vs AF) as from the electronic file. QT/QTc were measured from the ECG printouts with standard methods. The time of first AF recurrence was recorded. Changes in AADx as well as the total number of AADx used were recorded. The type of heart rhythm was recorded at each treatment step.

Data were analyzed using SPSS Vs 14. Descriptive statistical analysis was used. All patients still in SR at the time of data analysis were considered as Dronedarone responder. All patients in SR irrespective of the AAD used at the end of follow-up were defined as AAD responder.

Table 3: Patient characteristics

	N = 19
Females	7 (3177%)
Age (years)	65 + 10
LVEF (%)	62 + 7
Hypertension	17 (89%)
CAD	5 (26%)
No structural HD	2 (11%)
Previous AAD	1 (5 %)
Median CHADSVaSC (mean)	2 (2.9 + 1.6)

(AAD= antiarrhythmic drug; CAD=coronary artery disease; HD=heart disease; LVEF=left ventricular ejection fraction)

Results

Patient population

Between August 2011 and September 2012 a total of 19 patients were included in the study. Seven patients (37%) were female. Age averaged 65+10 years; mean LVEF was 62+7%. Median CHA2DS2-VASc score was 2 with a mean of 2.9 + 1.6. Mean follow-up was 36 + 21 months. Whereas the majority of patients had paroxysmal AF at the time of inclusion, 8 patients had persistent AF and underwent electrical cardioversion at the time of initiation of dronedarone therapy and inclusion into the study. All patients had at least one cardiovascular risk factor, most of them hypertension. [Table 3] depicts the clinical characteristics of the patient population.

Data collection and long-term follow-up

As already outlined above, patients were instructed to regularly transmit ECGs according to the protocol depicted in [Table 4].

Table 4: Follow-up and endpoints

Mean FU (months)	35 + 21
Sinusrhythm@ 6 months	16 (84 %)
Sinusrhythm@ 12 months	14 (74 %)
Sinusrhythm@ 24 months	11 (58 %)
No of AAD per patient during FU	
1 AAD (Dronedaron only)	6 (43 %)
2nd AAD	13(36 %)
3rd AAD	5 (14 %)
Subsequent PVI	6 (7 %)

(AAD=antiarrhythmic drug; FU=follow-up; PVI = pulmonary vein isolation)

Long-term follow-up was initiated. Only 2 patients decided to return their monitoring device prematurely; they were censored at the date of the last diagnostic ECG recording.

A total of 5258 ECGs were collected over time. These were 1-lead recordings of 30 sec duration. Patients showed a high adherence to the protocol and the quality of ECG recordings was high. Less than 5% of ECG recordings were not readable due to artifacts. Thus, nearly all ECG recordings were analyzable with respect to the underlying rhythm, conduction disturbances, and potential changes in repolarization. Each ECG was compared to the respective

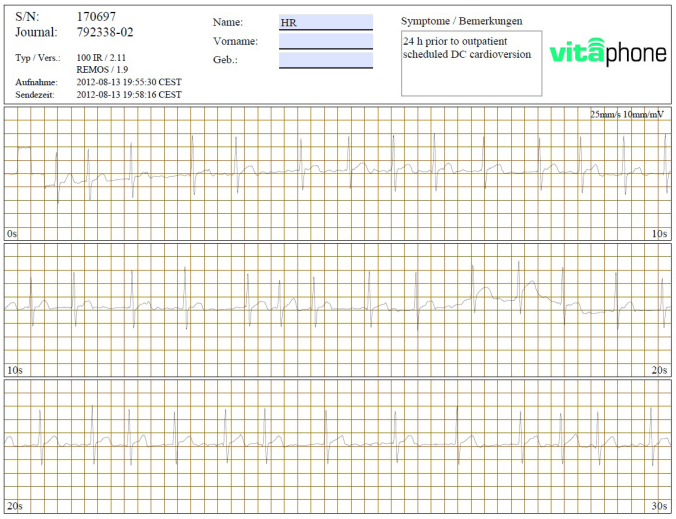

Figure 2A: Transtelephonic ECG in a patient with persistant AF prior to cardioversion and initiation of AADx with dronedarone

previous ECG. In case of changes – i.e. recurrence of AF – the patient was contacted and asked to increase the frequency of ECG transmission. In case of persistence of AF the patient was seen in the arrhythmia clinic to evaluate change in AAD therapy and / or to plan a cardioversion procedure. [Figure 2A+B] depict examples of transtelephonic ECG transmission in a patient prior to and after cardioversion of AF.

The mean duration of follow-up on regular ECG transmission was 36 + 21 months. A total of 5258 ECGs (28-792) were transmitted from 19 patients. The shortest follow-up was 3 months, the longest was 60 months. Fifteen patients (79 %) were followed 12 months or

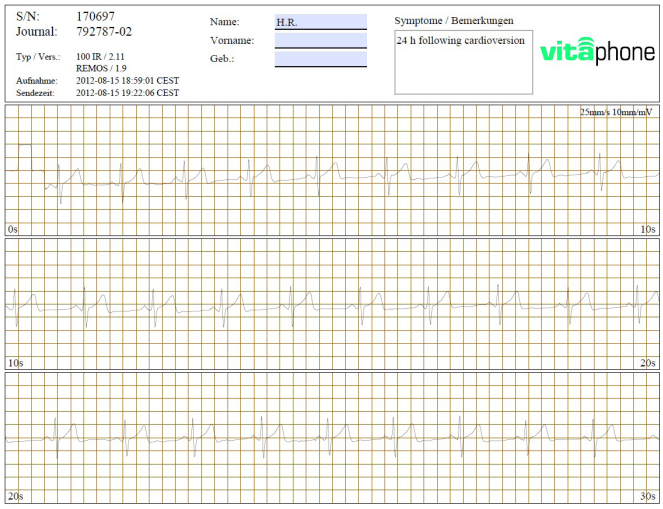

Figure 2B: Transtelephonic ECG on day 2 following cardioversion and on treatment with dronedarone

longer, 13 patients (68 %) sent regular ECG recordings for longer than 24 months, and eight patients (42 %) for 4 years or longer.

Monitoring results of antiarrhythmic efficacy

All patients could be guided safely and efficiently by transtelephonic ECG monitoring. Only one patient required an additional teaching with respect to appropriate use of the device. [Figure 3] depicts the efficacy result of AADx according to the findings of the transmitted ECG recordings. Therapeutic efficacy was defined as documentation of persistent sinus rhythm. As expected, a majority of patient had to change antiarrhythmic drug therapy over time, such as a 2nd choice or 3rd choice AAD or switching to PVI. The reason for changing antiarrhythmic therapy was either persistent AF, or no change or even an increase in paroxysmal AF episodes. Of the 13 patients who had to switch to a 2nd AAD, 11 (85%) did so within the first 10 months, 2 patients switched from dronedarone to another drug beyond 20 months of initially efficient treatment. Seven patients remained on dronedarone beyond 1 year of treatment. This 37% one-year efficacy rate is well in line with those described elsewhere [3,9]. Four patients (21 %) were still taking dronedarone after the end of the study (with

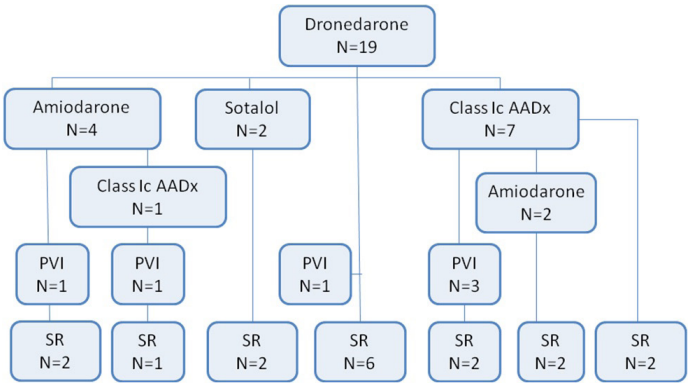

Figure 3: Flowchart: Treatment with AADx, including change to 2nd and 3rd choice drug, and catheter ablation, respectively. At the end of follow-up only 2/19 patients (11 %)had developed permanent AF.

(AADx= antiarrhythmic drug therapy; PVI= pulmonary vein isolation; SR = sinus rhythm)

follow-up times of 27, 38, 47, and 53 months). Regarding the 2nd choice AADx, these were Class Ic drugs in 7, amiodarone in 4, and sotalol in 2 patients. Of these, 2 class Ic patients were prescribed amiodarone as 3rd choice drug, 2 amiodarone patients were switched to class Ic drugs, and only 1 patient had a change within the AADx class Ic (from propafenone to flecainide). The main reason for stopping dronedarone was antiarrhythmic inefficacy (i.e. AF recurrence) in 11 patients. QTc-interval averaged 428 + 18 ms during the first TTEM recording, which was not different from QTc assessed from the last 12-lead ECG. No patient had a QTc > 470 ms at entry , or > 500 ms after 1 months on dronedarone. The number of PVC or PAC was not analysed since the recordings were too short for that purpose.

One patient developed bradycardia and diastolic heart failure, and underwent pacemaker implantation and subsequent change of AADx to amiodarone. As depicted in [Figure 3], six patients underwent PVI during follow-up, all due to symptomatic recurrent AF during AADx. All of these continued using the ECG monitoring device and four of them remained free from symptomatic AF during follow-up of the study.

Discussion

Initiation of AADx in AF patients requires regular ECG monitoring [1]. Recently, several approaches of screening for or rhythm monitoring in AF have been proposed, ranging from symptom-guided event recording to continuous monitoring through implantable devices [8,10-15].

The present study is the first to investigate a systematic protocol for patient-activated transtelephonic ECG monitoring (TTEM) in patients with symptomatic non-permanent atrial fibrillation undergoing de-novo AADx with dronedarone as first-line / de-novo medication. The results of the study demonstrate that TTEM is a feasible and effective means of rhythm monitoring in patients with non-permanent AF. The quality of recordings was extremely high with only 4 % of recordings being not diagnostic regarding the underlying rhythm (largely due to artifacts). Also, adherence to the prespecified protocol was high. Only 2 patients stopped rhythm recording prematurely for no specified reason. The second finding of the study is that – using a stepwise therapeutic approach – nearly 90% of patients were in persistent SR at the end of follow-up. In 26% of patients, dronedarone was effective throughout the very long follow-up period in maintaining SR; the efficacy rate during the first year was 37%. This proportion is well in line with efficacy data for dronedarone found in other clinical trials. For example, the ADONIS/EURIDIS programme demonstrated a 1-year efficacy rate of dronedarone of 30% [9]. The study by Freemantle depicts efficacy rates for different antiarrhythmic drugs and found similar antiarrhythmic efficacy rates [3]. Furthermore, TTEM is effective in observing ventricular repolarization changes in patients under AADx for non-permanent AF. In no patient, excessive QT prolongation was seen. TTEM thus proved to be an effective safety tool for guiding AADx.

TTEM by simple-to use Tele-ECG card has been described previously and has been found to be effective in documenting the underlying rhythm in patients with clinical suspicion of a cardiac arrhythmia [13]. So far most studies have addressed the value of such devices with regard to diagnosis making rather than assessing safety and efficacy of a specific AADx target to AF. The method of extended TTEM used in the present study has been described elsewhere. For example, in a study of Busch and colleagues, this system was used to identify AF patients in a population-based setting. The incidence of newly diagnosed AF was 2.6% as compared with only 1.3% with normal ECG registration [15]. To our knowledge, the present study is the first to use regular consecutive Tele-ECG registrations in order to monitor AADx safety and efficacy in AF. The quality of data was good in the present study. Gosciniak et al used TTEM to monitor heart rhythm after successful surgical ablation of AF. The quality of ECG signal was comparable to that in the present study. TTEM proved to be safe in rhythm follow-up in that patient cohort [12].

In summary, TTEM proved to be safe and efficient to guide patients even through a long-term follow-up after cardioversion of AF, including monitoring of subsequent changes of therapeutic strategy of AF treatment over time. Patient adherence was excellent. Complications did not occur.

The present study thus proves that TTEM may be helpful in improving patient care during initiation and follow-up of antiarrhythmic drug therapy for atrial fibrillation. It can be expected that automatic ECG monitoring, e.g. by implantable monitoring devices may further improve patient management following pharmacologic or interventional rhythm control strategies of atrial fibrillation [14].

Limitation

The present study has several limitations. One is the relatively small number of patients studied. This relates to the fact that these were highly selected patients with non-permanent AF in whom AADx was preferred over PVI as primary treatment choice. There is limited number of such patients in an era where PVI is considered the primary option in the majority of patients with non-permanent AF. Furthermore, patient-activated transtelephonic ECG monitoring is a clinical tool that – although being introduced for years – is yet far from being general clinical practice in many countries. Therefore the present study was designed as a feasibility and hypothesis-generating study. A larger trial comparing transtelephonic monitoring with regular care in patients with non-permanent atrial fibrillation is urgently warranted. Also, we did not test how long and by how many ECG transmissions patients should be followed optimally. We aimed to collect as much ECGs as possible in this feasibility study, however the use of shorter follow-up periods and different numbers of transmission may be sufficient. Another limitation is related to the fact that patients transmitted ECGs at predefined time-points, or when they felt symptoms. This probably caused underestimation of potential asymptomatic AF episodes. Such underestimation is however immanent to any patient-based event recording.

The inclusion of patients only with de-novo Dronedarone AADx was chosen in order to have a relatively "homogenous" patient population. The clinical efficacy of Dronedarone in this predefined population can be seen as secondary aspect of the study; the results are well in line with efficacy data for dronedarone from previous

clinical trials. In this context, another limitation relates to the fact, that QT- an QTc-measurement from transtelephonic 1-lead ECG strip carries the risk of inaccuracy. In all 19 patients, we compared the QTc from the first TTEM recording with the QTc from the standard resting 12-lead ECG before starting AADx. QTc was measured from all transmitted ECGs. We observed intraindividual variation in QRS morphology since patients sometimes used different positions for placement of the ECG device which made comparisons of QTc measurements difficult. However, the QTc did not exceed 500 ms in any patient.

The present study does not include patient questionnaires or economic analysis, since this was beyond the scope of this feasibility study. However, documentation of patient history during follow-up visits indicated a favorable acceptance and satisfaction with the ECG system. The cost-saving potentials of TTEM over regular care need to be assessed in a larger study in which both follow-up options are compared.

Ethics

The present study was conducted according to the Declaration of Helsinki. Informed consent was obtained from all subjects.

Conclusions

Transtelephonic ECG transmission is useful for close rhythm monitoring during initiation and follow-up of AADx, also during change from DRO to other AADx. DRO was effective to prevent AF recurrence in 26% of patients during a mean long-term follow-up of more than 30 months – which is well in line with data from the literature.

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Second Generation Cryoballoon vs Radiofrequency Ablation in Paroxysmal Atrial Fibrillation: Outcomes Beyond One-Year Follow-up

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Abstract

Aims : Pulmonary vein isolation (PVI) can be accomplished using radiofrequency (RF) or second generation cryoballoon (CB2). We aimed to compare the freedom from very late recurrence (VLR) defined as recurrence beyond one year in patients who were AF-free during the first post-procedural year after PVI using CB2 or RF.

Methods : Consecutive patients who underwent PVI by RF or CB2 ablation between August 2014 and December 2015 were included. The primary endpoint was the occurrence of VLR in follow-up after 12 months. Patients who experienced recurrence between the first 3 to 12 months after PVI and those who did not complete 15-month follow-up time were excluded.

Results: 139 patients were included: 68 underwent PVI by CB2 and 71 using RF. The global VLR rate was of 22.15%. The freedom from VLR beyond 12-month follow-up was of 84.5% (57 patients) for the CB2 group vs. 71% (50 patients) in the RF group (p=0.037). 15 patients underwent re-ablation (11 of the RF group and 4 of the CB2 group): all of the patients who had undergone PVI by RF in the index procedure were found to have vein reconnection, whereas none of the CB2 group had reconnected veins (3 cavotricuspid isthmus and 1 mitral isthmus).

Conclusions : In patients free of recurrence during the first post-procedural year after pulmonary vein isolation for the treatment of paroxysmal atrial fibrillation: second generation cryoballoon ablation showed a significantly lower very late recurrence rate compared to radiofrequency ablation.

Condensed abstract : The present study evaluates the freedom from very late recurrence (VLR), defined as recurrence in patients who were arrhythmia-free during the first post-procedural year after pulmonary vein isolation using second generation cryoballoon (CB2) or radiofrequency (RF). CB2 ablation had a lower VLR rate compared to RF.

Introduction

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia found in clinical practice and a global healthcare problem with a prevalence of near 3% in adults aged 20 or older [1-2]. Incidence increases substantially with age and therefore prevalence is expected to rise as the population grows older as a result of increased life expectancy, especially in developed countries. Complications of AF include ischemic events such as cardioembolic stroke, heart failure, hospitalization, impaired quality of life and elevated mortality rates therefore entailing a large economic burden for healthcare systems [3].

Since Haïssaguerre et al. [4] reported that the main origin of AF trigger is located at the pulmonary veins (PV), targeting them is the main strategy for AF ablation [5-6]. PV isolation (PVI) by catheter ablation provides an effective and safe treatment option for drug-refractory symptomatic paroxysmal AF (PAF) and it is a class I, level A recommendation according to the last expert consensus statements [7-8] as it has proven to be superior to antiarrhythmic drugs (AAD) as a rhythm control strategy. Yet, AF may appear again after PVI despite improvement in technology.

PVI can be accomplished using any of two available techniques: a point-by-point mode application of radiofrequency (RF) energy or a single-step procedure with second generation cryoballoon (CB2) using circumferentially applied cryogenic energy. Currently, both methods are approved by the US food and drug administration for the treatment of PAF.

Several small studies have compared these two methods of ablation, showing heterogeneous results. The trial by Kuck et al. was the largest multicenter, randomized, controlled trial to assess the safety and efficacy of PVI in patients with drug-refractory symptomatic PAF using either CB2 or RF ablation: the mean follow-up time was 1.5 years, and the primary efficacy endpoint was a documented clinical failure (recurrence of AF, atrial flutter, atrial tachycardia, use of AAD or repeat ablation), following a 90-day blanking period after ablation. CB2 ablation proved to be as safe and non-inferior with respect to efficacy compared to RF ablation [9].

Recurrence during the 3-month blanking period is not considered actual recurrence and therefore must be excluded when presenting

Key Words

Atrial fibrillation, Catheter ablation, Cryoballoon, Pulmonary Vein Isolation, Recurrence.

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ablation results [7-8]. Late recurrence is the occurrence of atrial arrhythmia beyond the blanking period and very late recurrence (VLR) refers to arrhythmia recurrence happening for the first time beyond one-year follow-up after PVI.

Although the two techniques have points in favor and against, it is still unclear if one of them is superior to the other in terms of efficacy beyond one year follow-up, specially regarding VLR.

We aimed to compare the freedom from VLR in patients free of AF during the first year after PVI using CB2 or RF.

Methods

Every patient participating in our study signed informed consent for the procedure and for the use of their medical records, information about procedure and follow-up. The present study was approved by the Institutional Committee on Human Research in our institution.

Study Design AND Patient Population

We determine ejection fraction and LA area, as well as multislice computed tomography (or cardiac magnetic resonance imaging if there was any contraindication for tomography) to evaluate the anatomic characteristics and number of PV.

Our primary endpoint was the occurrence of VLR in follow-up after 12 months. Patients who experienced late recurrence between the first 3 to 12 months (not considering recurrence during blanking period) after PVI and those who did not complete 15-month follow-up time were excluded, as well as patients who had previously undergone AF ablation and those with significant valvular disease.

Procedures

All procedures were performed under general anesthesia. Transesophageal echocardiography was performed only if the level of anticoagulation were inconsistent to exclude LA thrombi or to guide difficult transseptal punctures. The aim of the procedures was to achieve PVI. Anticoagulation was achieved by I.V. heparin infusion targeting TCA ≥ 350 ms throughout the procedure.

RF ablation: 12-lead electrocardiogram and intracardiac bipolar electrograms were recorded using electronic calibrators (EP-WorkMate 4.2 System, St. Jude Medical, Inc.) at a screen speed of 50 to 200 mm/s and were filtered at band-pass settings of 50 to 500 Hz. A non-fluoroscopic mapping navigation system was used in all cases (Ensite® Velocity® cardiac mapping system, St.Jude Medical Inc.). After both femoral veins were punctured, a decapolar catheter was placed in the coronary sinus. Under radioscopic guidance in the 40° left anterior oblique projection, two transseptal punctures were performed with Brockenbrough needles; then, two long preshaped introducers SL1 and SL2 (St. Jude Medical Inc.) were positioned. A circular duodecapolar Optima Plus® catheter and an irrigated-tip ablation catheter Therapy-Cool® (St. Jude Medical Inc.) were advanced through the introducers to deliver RF. The anatomical reconstruction was performed using the circular Optima Plus® mapping catheter which is capable of simultaneous recording from multiple points. The ablation catheter was used to identify the ostia and the antrum of the PV. The electric activity of each PV was obtained using the circular catheter. PVI started in the left superior PV and continued in the left inferior PV. The same sequence was used for the right PVs. RF energy was delivered at the anterior and posterior aspect of each PV with a power output of 40 W and of 35 W, respectively. The lesions were applied to the antrum but not the ostia of the PV. The electrograms recorded by the ablation catheter before and after applying the ablation lesion were analyzed in each patient. The target was a reduction of the potential amplitude by 75% and the elimination or dissociation between atrial and PV activity. Once the isolation was completed, the presence of persistent block in each PV was evaluated. If necessary, ablation was repeated to consolidate the line of bidirectional block. We used all the methods available to discriminate local or remote electrical activity. After PVI, other AF ablation techniques were used at the discretion of the treating physician: ablation lines at the cavotricuspid isthmus, venae cavae or coronary sinus, complex fractionated atrial electrograms mapping, and areas with intermediate voltage values (between 0.1 and 0.8 mV) in the LA (substrate).

CB2 ablation: After cutaneous antisepsis and by modified Seldinger's technique, puncture of the femoral veins was performed. A decapolar catheter was introduced into the coronary sinus to record the electrical activity of the AV groove. Transseptal puncture with Brockenbrough needle was performed using fluoroscopic guidance. Following that, a metal guidewire was placed in the LA and a Flexcath introducer (Arctic Front) was advanced. The CB2 system (Arctic Front Advance® 28mm) was then advanced, along with the circular mapping catheter (Achieve Mapping Catheter®) with which electrograms were obtained inside each of the PV. Each PV was then catheterized with the balloon catheter, adjusting it to the antrum until a good objective occlusion was achieved with retention of 50% contrast inside the PV and absence of drainage to the atrial cavity. Once this was verified, freezing was started keeping the pressure of the balloon on the PV until reaching 90 seconds; after this time, while the balloon remained completely adhered to the PV antrum, freezing was continued for a total time of 240 seconds. Once ablation of the left PV was done, the decapolar catheter was positioned in the superior vena cava for continuous phrenic stimulation (1000 ms) in order to monitor its integrity during CB2 ablation of the right PVs, especially the superior right PV.

Each PV was then catheterized with the balloon catheter, adjusting it to the antrum until achieving a adequate occlusion with retention of 50% contrast inside the PV and absence of drainage to the atrial cavity. Once this was verified, freezing was started keeping the pressure of the balloon on the PV until reaching 90 seconds; After this time, while the balloon remained fully adhered to the PV antrum, freezing was continued for a total time of 240 seconds. Once isolation of left PV was achieved (both superior and inferior), the decapolar catheter was positioned in the superior vena cava for continuous phrenic stimulation (1000 ms) in order to monitor its integrity during CB2 ablation of the right PV.

In every procedure, esophageal temperature monitoring was used, avoiding temperatures below 20°C. Immediate success was defined as the isolation of the PV with bidirectional block.

Follow-up after PVI

Every patient was systematically followed up with a 24-hour holter monitoring per month, two, three, six and twelve months after the PVI. And every 6 months thereafter. Symptomatic patients underwent extra 24-hour holter monitoring or 12-lead EKG in between the scheduled ones in an effort to document AF.

Patients continued under AAD treatment after PVI according to the criteria of each treating cardiologist.

We defined VLR as any documented episode of supraventricular atrial tachyarrhythmia (AF, atrial flutter or atrial tachycardia) at follow-up ≥ 12 months, both symptomatic and asymptomatic, lasting 30 seconds or more, observed in 24-hour Holter monitoring, 12-lead EKG or monitoring. All tracings were analyzed by a cardiac electrophysiologist..

Statistical analysis

All continuous variables were presented as mean (± standard deviation) or median (interquartile range) according to their distribution and categorical variables as percentage. Continuous variables with normal or asymmetrical distributions were compared using Student's t-test or Mann-Whitney U test respectively. Categorical variables were compared using Chi-square test or Fisher's exact test, as appropriate.

Kaplan-Meier plots were constructed to perform the survival analysis, and freedom from VLR between the CB2 and RF groups was compared by log-rank test. Patients who experienced recurrence between the first 3 to 12 months (not considering recurrence during blanking period) after PVI and those who did not complete 15-month follow-up time were excluded.

All statistical analysis was performed using SPSS software, version .24 (IBM Corp., NY, USA).

Results

A total of 102 patients underwent PVI using CB2 and 95 using RF in our center in the period analized. 3 patients lost follow-up and 139 patients that met the inclusion critaria were included: 68 underwent PVI by CB2 ablation and 71 using RF [Figure 1]. The mean (±SD) follow-up time was of 19 (±3) months. There were no differences in baseline characteristics between groups [Table 1]. The global VLR rate was of 22.15%. The freedom from VLR beyond 12-month follow-up was of 84.5% (57 patients) for the CB2 group vs. 71% (50 patients) in the RF group (p=0.037) [Figure 2]. There were no differences in the occurrence of early recurrence (ER) during blanking period between the two groups: 27% (3 patients) in CB2 vs 42% (9 patients) in RF (p=0.38). Finally, 15 patients underwent re-ablation (11 of the RF group and 4 of the CB2 group). In this second procedure, all of the patients who had underwent PVI by RF in the index procedure were found to have PV reconnection, whereas none of the CB2 group had reconnected PV (3 cavotricuspid and 1 mitral isthmus).

Discussion

In patients free of recurrence during the first post-procedural year after pulmonary vein isolation for the treatment of paroxysmal atrial fibrillation: second generation cryoballoon ablation showed a significantly lower very late recurrence rate compared to radiofrequency ablation.

Even though there is limited data comparing RF to CB2: there are a series of pros and cons of each approach. Although it demands extensive training and is time-consuming, RF ablation is still the

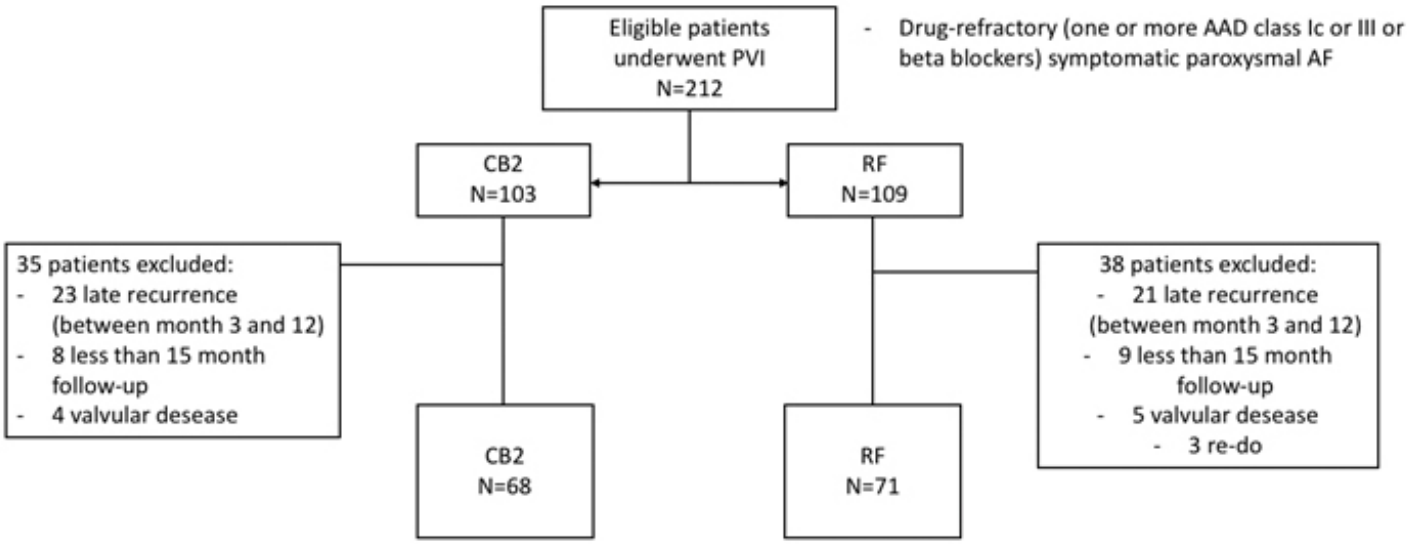

Figure 1: Patient selection

Table 1: Baseline characteristics

	CB2 (68p)	RF (71p)	p
Age, yr (mean, ±SD)	57.1 (±6.3)	63.8 (±8.2)	0.1
Male (%)	79.1	75.5	0.32
Hypertension (%)	42.4	56	0.25
Diabetes mellitus (%)	2.9	5.3	0.3
Stroke or TIA (%)	5.2	2.8	0.27
EF (mean)	62.3 (±6.9)	62.1 (±7)	0.74
LA area (cm2) (mean ±SD)	22.8 (±5.4)	23.7 (±5.6)	0.54
ER during BP (%)	27	42	0.38
CHADS VASC 2 score	1	1	0.8

CB2: second generation cryoballoon. RF: radiofrequency. TIA: Transient ischemic attack. EF: ejection fraction. LA: left atrium. ER: early recurrence. BP: blanking period.

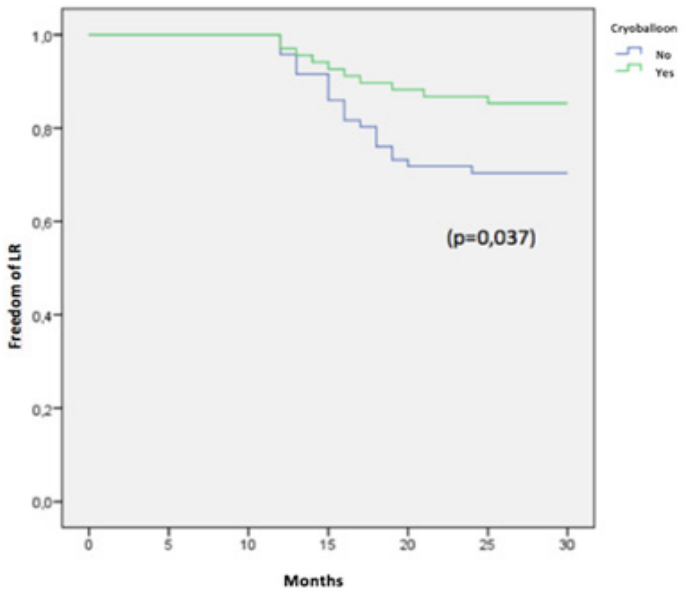

Figure 2: Freedom from very late recurrence in follow-up in patients free from atrial fibrillation 12 months post-PVI by Kaplan-Meier survival with log rank test.

most widely used technique to achieve PVI [10], its benefits include the use of limited time of fluoroscopy. In contrast, PVI using CB2 leads to longer fluoroscopy times. On the other hand, CB2 ablation is a simpler technique and has a short learning curve, and several additional benefits such as increased catheter stability due to tissue-catheter cryo-adhesion; it generates a uniform, more delimited lesion with low inflammation burden and less platelet and coagulation cascade activation. CB2 ablation is a shorter procedure compared to RF [9,11]. In an economic analysis of the FIRE AND ICE trial by Chun et al., CB2 ablation was even associated with a reduction in resource use and costs [12]. PV can have anatomical variants and this can determine a difficulty for CB2 ablation, but regardless of anatomy, PVI by CB2 has shown similar results compared to RF in patients with unusual anatomic features [13].

Episodes of recurrence are usually diagnosed within the first year after PVI. Regarding CB2 vs RF in one-year follow up time, there were no differences in late recurrence [9].

There is no published data on VLR in patients free of AF in one year follow-up after PVI using CB2 and only limited information about VLR in general. There are studies focused on patients who underwent PVI and experienced their very first recurrence after one year of being free of AF. For example, in the study by Bertaglia et al. patients who were recurrence-free at one year follow-up were seen to have a progressive increase in the risk of VLR (13% at 2 years, almost 22% at 3 years, 35% at 4 years, 47% at 5 years and over 54% after 6 years) [14] . In the study by Mainigi et al. [15] on patients undergoing PVI using RF, VLR was an uncommon event and re-connectivity of segments of the PV was demonstrated in 93% of isolated PV in the index procedure. In our study, although the number of patients was limited, 100% of the the patients who had undergone PVI by RF had reconnection of PV.

In the last years, several studies have aimed to determine scoring systems to predict the occurrence of recurrence in order to identify high risk patients [16-19]. Particularly, the MB-LATER (male gender, bundle branch block, LA ≥47mm, type of AF, ER) scoring system published by Mujovic et al. [17] aimed to identify predictors of VLR. However, none of these scoring systems included the technique used (CB2 or RF) as a variable.

Regarding the comparison between the two ablation techniques, long term outcomes of the FreezeAF published by Armin Luik et al. [20] provided data comparing the efficacy of CB2 ablation vs. RF showing that CB2 was non-inferior to RF. This was seen in our study, suggesting that those patients that underwent PVI using CB2 and had no recurrence during the first year, will not experience VLR due to PV reconnection at all. This can be explained by the fact that CB2 lesion is more stable and generate less local inflammation, therefore the isolation of the PV can be thought to be more effective than point-by-point application of RF.

Recent studies have demonstrated that technical aspects of lesions creation such as contiguity, stability and contact force are important for clinical results, therefore stating that cryoballoon ablation is more reproducible than RF [21-22]. Techniques such as pacing the ablation line [23] and adenosine testing after PVI [24] have also demonstrated utility to avoid reconnection after RF ablation. Overall, this translates in large between-center results after PVI using RF. These techniques, although useful are not a gold-standard of care in PVI and there is no evidence from large randomized trials supporting their use. In our study, none of this techniques were used, this may have translated in more favorable outcomes for the CB2 group.

Our study has an important clinical implication, further larger and randomized trials are necessary to confirm our findings but the fact that the patients who had undergone PVI using CB2 with VLR had no reconnected PV suggest these patients will not experience AF recurrence at all. The importance of our study relies on the fact that patients with no episodes of VLR could more likely be considered as "cured" by CB2 ablation, therefore long-term follow-up and rhythm monitoring could be optimized. This information can also determine the length of treatment, for example oral anticoagulation.

Although our research reached its aims, we are still aware there were

a series of limitations in its design. First, our study was a retrospective analysis and therefore we could be in presence of a selection bias, randomized and prospective studies are necessary to confirm our findings. Second, patient data were collected retrospectively. Third, the AAD treatment after PVI was not compared between the two groups. Fourth, our center is a monovalent institute, with a great number of patients and our electrophysiologists have vast experience in ablation procedures, therefore, results may not apply to the general population in our country. Also, there was no predefined criteria for choosing CB2 or RF for PVI, following each physitian´s judgement. Last, irrigated tip catheters were used, it can be thought that the use of contact force-guided catheters would have resulted in more effective ablation lesions and therefore better results.

We can conclude that in patients free of atrial fibrillation recurrence during the first post-procedural year after pulmonary vein isolation for the treatment of paroxysmal atrial fibrillation: second generation cryoballoon ablation showed a lower very late recurrence rate compared to radiofrequency.

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Outcomes of Hemorrhagic Stroke Patients with Atrial Fibrillation or Flutter

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Abstract

Introduction: Hemorrhagic stroke is a life-threatening complication, and may be particularly prevalent in patients with atrial fibrillation/flutter (AF/AFL) due to their need for anticoagulation. We sought to estimate in-hospital mortality, length of stay (LOS) and in-patient treatment cost of patients with AF/AFL admitted with hemorrhagic stroke.

Methods: We used the 2008-2011 National Inpatient Sample to identify adult AF/AFL patients with a principle discharge diagnosis of subarachnoid or intracerebral hemorrhage. Endpoints of interest included in-hospital mortality, LOS, and hospital treatment costs (2015 US$).

Results: In-hospital mortality for subarachnoid and intracerebral hemorrhage was 31.3% and 31.8%, respectively. Patients had a median LOS of 5 days and 25% of patients accrued costs in excess of $24,107/stay.

Conclusions: Admissions for hemorrhagic stroke among patients with AF/AFL were associated with substantial in-hospital mortality and treatment costs.

Introductio

Atrial fibrillation/flutter (AF/AFL) is a highly prevalent and important risk factor for stroke. Oral anticoagulation offers significant protection against AF/AFL-related thromboembolic events, but severe adverse events such as hemorrhagic stroke (i.e., subarachnoid and intracerebral hemorrhage) may complicate its use [1,2]. There is a paucity of recent data describing costs and consequences of such events. Thus, we sought to estimate in-hospital mortality, length of stay (LOS) and hospital treatment costs for hemorrhagic stroke admissions among United States (US) AF/AFL patients.

Material and Methods

This study used the Agency for Healthcare Research and Quality's (AHRQ's) National Inpatient Sample (NIS) database for the years 2008-2011. The NIS provides a nationally representative ~20% sample of US hospitals and their admissions [3]. We identified adult AF/AFL patients with an International Classification of Diseases, ninth-edition (ICD-9) code of 427.31 or 427.32 (any position) and a primary diagnosis code of 431 or 430 for subarachnoid or intracerebral hemorrhage, respectively. Patients not admitted through the emergency department or transfers from an outside facility were excluded. Endpoints of interest included in-hospital mortality, LOS and hospital treatment costs (in 2015 US dollars). Since all data were de-identified the study did not require institutional review board oversight.

Baseline patient (age, sex, race, primary payer, median household income for zip code and comorbidity status) and hospital characteristics (size, type and region) were descriptively summarized. Stroke and bleeding risk were calculated using congestive heart failure, hypertension, age, diabetes mellitus, prior stroke ($CHADS_2$) [4], and anticoagulation and risk factors in AF (ATRIA) [5] scores, respectively. Categorical data were reported as percentages, ordinal data as medians (25%, 75% range) and continuous data as means ± standard deviations (SD). We estimated the percentage (95% confidence interval) of patients with in-hospital mortality and median (25%, 75% range) LOS and costs for subarachnoid and intracerebral hemorrhage combined and separately. Charges were converted to cost using charge-to-cost ratios and inflated to 2015 US dollars using the Consumer Price Index for Medical Care. Descriptive statistics were performed using SPSS version 22 (IBM Corp., Armonk, NY).

Results

Among the 3,034,569 admissions for patients with a diagnosis for AF/AFL in the 2008-2011 NIS database, 7,897 (0.26%) had a primary diagnosis code for hemorrhagic stroke and met our inclusion criteria [Table 1]. Patients with AF/AFL experiencing a hemorrhagic stroke (70% white; 51% female) had a mean ± standard deviation age of 77.5 ± 11.0 years; median (25%, 75% range) CHADS2 score of 2 [2,3] and ATRIA score of 4 [3,4]. Most hemorrhagic stroke admissions (87.1%) were for intracerebral hemorrhage.

Key Words
Hemorrhagic stroke, Atrial fibrillation, Mortality, Length of stay, Cost.

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Table 1: Characteristics of atrial fibrillation/flutter patients admitted with hemorrhagic stroke

Characteristic	Total, n (%)	Subarachnoid hemorrhage, n (%)	Intracerebral hemorrhage, n (%)
	N = 7,897	N = 1,022	N = 6,875
Age, years, mean±SD	77.5 ± 11.0	72.9 ± 13.9	78.2 ± 10.4
Age, years (categories)			
18 – 40	37 (0.5)	22 (2.2)	15 (0.2)
41 – 65	1,040 (13.2)	251 (24.6)	789 (11.5)
66 – 75	1,692 (21.4)	228 (22.3)	1,464 (21.3)
> 76	5,128 (64.9)	521 (51.0)	4,607 (67.0)
Male sex	3,869 (49.0)	466 (45.6)	3,403 (49.5)
Race			
White	5,500 (69.6)	688 (67.3)	4,812 (70.0)
Black	523 (6.6)	67 (6.6)	456 (6.6)
Hispanic	464 (5.9)	53 (5.2)	411 (6.0)
Asian/Pacific Islander	295 (3.7)	44 (4.3)	251 (3.7)
Other	214 (2.7)	32 (3.1)	182 (2.6)
Not reported	901 (11.4)	138 (13.5)	763 (11.1)
CHADS2 score, median (25%, 75% range)	2 (2, 3)	2 (1, 3)	2 (2, 3)
ATRIA score, median (25%, 75% range)	4 (3, 4)	4 (2, 4)	4 (3, 4)
Number of AHRQ-29 comorbidities			
0	249 (3.2)	42 (4.1)	207 (3.0)
1	1,378 (17.4)	189 (18.5)	1,189 (17.3)
2	2,046 (25.9)	245 (24.0)	1,801 (26.2)
3	1,800 (22.8)	218 (21.3)	1,582 (23.0)
4	1,151 (14.6)	133 (13.0)	1,018 (14.8)
≥ 5	1,273 (16.1)	195 (19.1)	1,078 (15.7)
Primary Payer			
Medicare	6,350 (80.4)	709 (69.4)	5,641 (82.1)
Medicaid	281 (3.6)	53 (5.2)	228 (3.3)
Private (including HMO)	991 (12.5)	199 (19.5)	792 (11.5)
Self-pay	161 (2.0)	35 (3.4)	126 (1.8)
Other/Not reported	114 (1.4)	26 (2.5)	88 (1.3)
Median household income for ZIP code, $			
1–38,999	1,711 (21.7)	227 (22.2)	1,484 (21.6)
39,000–47,999	1,884 (23.9)	252 (24.7)	1,632 (23.7)
48,000–62,999	1,984 (25.1)	279 (27.3)	1,705 (24.8)
> 63,000	2,159 (27.3)	248 (24.3)	1,911 (27.8)
Not reported	159 (2.0)	16 (1.6)	143 (2.1)
Hospital size			
Small	619 (7.8)	70 (6.8)	549 (8.0)
Medium	1,667 (21.1)	185 (18.1)	1,482 (21.6)
Large	5,502 (69.7)	741 (72.5)	4,761 (69.3)
Not reported	109 (1.4)	26 (2.5)	83 (1.2)
Hospital type			
Rural	559 (7.1)	65 (6.4)	494 (7.2)
Urban non-teaching	3,257 (41.2)	347 (34.0)	2,910 (42.3)
Urban teaching	3,972 (50.3)	584 (57.1)	3,388 (49.3)
Not reported	109 (1.4)	26 (2.5)	83 (1.2)
Hospital region			
Northeast	1,689 (21.4)	203 (19.9)	1,486 (21.6)
Midwest	1,468 (18.6)	209 (20.5)	1,259 (18.3)
South	2,991 (37.9)	388 (38.0)	2,603 (37.9)
West	1,749 (22.1)	222 (21.7)	1,527 (22.2)

AHRQ=Agency for Healthcare Research and Quality; ATRIA=anticoagulation and risk factors in atrial fibrillation; CHADS2=congestive heart failure, hypertension, age, diabetes mellitus, prior stroke; HMO=health maintenance organization; SD=standard deviation

Table 2: Outcomes of atrial fibrillation/flutter patients admitted with hemorrhagic stroke

	Mortality, % (95%CI)	Length of stay, days median (25%, 75% range)	Cost, 2015 US$* median (25%, 75% range)
Any hemorrhagic stroke (N=7,897)	31.7 (30.7 – 32.8)	5 (2, 9)	$12,036 ($6,815, $24,107)
Subarachnoid hemorrhage (N=1,022)	31.3 (28.5 – 34.2)	6 (2, 14)	$17,314 ($7,945, $51,535)
Intracerebral hemorrhage (N=6,875)	31.8 (30.7 – 32.9)	5 (2, 9)	$11,677 ($6,715, $22,067)

CI=confidence interval *Charges were converted to cost using charge-to-cost ratios and inflated to 2015 US$ using the Consumer Price Index for Medical Care

Regardless of hemorrhage subtype, nearly one-third of patients died prior to discharge [Table 2]. The incidence of in-hospital mortality was 31.3% for subarachnoid and 31.8% for intracerebral hemorrhage. Patients had a median LOS of 5 days and 25% of patients accrued costs in excess of $24,107/stay.

Discussion

In our analysis of 2008-2011 NIS data, a small percentage of patients with AF/AFL had a primary diagnosis code for hemorrhagic stroke, with the majority of these patients having an intracerebral hemorrhage. In hemorrhagic stroke patients, in-hospital mortality was about one-third, median LOS and cost of hospitalization were 5 days and ~$12,000, respectively. Our analysis has shown that hemorrhagic stroke can be a fatal and costly complication in patients with AF/AFL, presumably on oral anticoagulation. As such, the risk and outcomes of this complication should be considered when selecting therapy for stroke prevention in atrial fibrillation (SPAF).

Alonso and colleagues [6] performed a similar analysis utilizing Market Scan 2009-2012 data to evaluate in-hospital mortality in AF patients on anticoagulant therapy (i.e., warfarin or dabigatran) with a primary diagnosis of intracranial hemorrhage (ICD-9 codes 430-432.x and 852-853.x). Patients were classified by the bleeding subtypes of subarachnoid/intracranial bleeding not otherwise specified (NOS) (n=410), intracerebral (n=748), and subdural (n=1,233) hemorrhage.

In-hospital death occurred in 23% of subarachnoid/intracranial bleeding, 34% of intracerebral, and 15% of subdural hemorrhage patients. While our intracerebral hemorrhage mortality rates are in agreement with Alonso et al. (32% vs. 34%, respectively), it is possible that our difference in subarachnoid hemorrhage mortality is a result of our larger sample size and exclusion of patients with intracranial bleeding NOS (31% vs. 23%, respectively). Our analysis was restricted to hemorrhagic stroke and subdural hemorrhage mortality was not evaluated.

Pharmacologic options for SPAF are often compared in cost-effectiveness models with the validity of such models dependent on their underlying data [7]. In a systematic review of 30 pharmacologic SPAF cost-effectiveness models, Limone and colleagues found that cost and event rate data were often from common sources and utilized data from the 1990s [7]. This concerning finding led Limone et al. to recommend that investigators use the most up-to-date inputs to avoid common flaws in SPAF models [7]. Our data can be used to provide contemporary inputs and to better predict outcomes of hemorrhagic stroke in economic models.

Although the NIS provides a large and nationally representative sample of data, its use has limitations. The NIS does not provide clinical data to calculate stroke severity or prescription use to confirm patients were on oral anticoagulation during the time of hemorrhagic stroke. We chose to avoid use of ICD9-code V58.61 for long-term (current) use of anticoagulants because we do not believe it to be accurate for our purposes. However, it is likely that a majority of patients in our evaluation were utilizing anticoagulant therapy. In an observational registry of newly diagnosed AF patients with at least one additional stroke risk factor, ~70% of patients receive anticoagulation and >80% of patients are on antithrombotic treatment (i.e., anticoagulants and/or antiplatelets) [8]. While the use of ICD-9 billing codes can cause misclassification and other biases if inaccurate, we feel confident in the hemorrhagic stroke codes used in our study as they have previously shown high specificity (>0.99) and positive predictive values (0.77) for event identification [9].

Conflicts of interest

All authors (SF, KL, AT, CIC, EN) have no conflicts germane to this manuscript to report.

Conclusions

We found that admissions for hemorrhagic stroke among patients with AF/AFL were associated with substantial in-hospital mortality and treatment costs. Our results provide data that can be used to inform economic models and decision makers.

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Selective Activation Re-Mapping Reveals the Mechanism in Apparently Unstable Atrial Tachycardias.

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Abstract

Following atrial fibrillation (AF) ablation procedures, patients may present with atrial tachycardias (ATs) that show remarkable stability for short periods of time but degenerate in unstable forms right afterwards. In order to map these types of ATs, we applied the sequential mapping capabilities only for time segments where ATs exhibited constant cycle length (CL) and activation sequence, excluding the segments with unstable recordings.

We herein describe two cases of ATs after AF ablation which were mapped with this technique that allowed for the successful identification and subsequent ablation of the tachycardia circuit.

Introduction

The evaluation of impulse propagation mapping during atrial fibrillation (AF) or unstable atrial tachycardias (ATs) requires simultaneous mapping, which is a subject of research and current clinical applications. Sequential mapping can only be used in stable ATs in order to disclose their mechanism. Advanced 3D mapping systems have the ability to perform reliable activation maps in a very short period of time in stable ATs. After AF ablation procedures, it is not unusual to be confronted with ATs that show remarkable stability for short periods of time, but degenerate in unstable forms right afterwards. In an attempt to map these types of ATs, we applied the sequential mapping capabilities only for time segments where ATs exhibited constant cycle length (CL) and activation sequence, excluding the segments with unstable recordings.

We describe two cases of ATs after AF ablation that were mapped using the EnSite Precision™ Cardiac Mapping System (Abbott Laboratories, Chicago, IL, USA) via the AutoMap module.

Case 1

A 69-year-old woman with paroxysmal AF and pulmonary vein isolation (PVI) plus cavotricuspid isthmus (CTI) ablation procedure 13 months ago, presented with symptomatic persistent AT and underwent electrophysiological study and ablation. In the EP Lab the patient was in AT and all the pulmonary veins remained isolated. The AT mapping procedure was performed with continuous movement of the circular catheter which was continuously collecting points. Unfortunately, the AT was not stable throughout this process. In the retrospective analysis, points obtained at time intervals where the tachycardia presented with unstable and complex sequence were discarded. Therefore, the propagation map was based only on points collected in stable AT intervals. A clockwise perimitral circuit was clearly discernible (Video 1). During mitral isthmus (MI) ablation the tachycardia terminated and the MI line block was proved in sinus rhythm [Figure 1]. The patient 14 months after the ablation was free from any atrial tachyarrhythmia off antiarrhythmic drugs.

Case 2

A 74-year-old woman 69 months after the initial AF ablation (PVI plus CTI ablation) was admitted for electrophysiological study due to persistent AT. In a similar manner to Case 1, after PVI confirmation, following sequential mapping of the tachycardia, we retrospectively rejected the segments where the tachycardia became unstable. We thus constructed a propagation map which clearly showed a counterclockwise circuit around the mitral annulus (Video 2). The patient received MI ablation and, notably, at the time of MI line completion, while the tachycardia remained unstable, eventually sinus rhythm was restored [Figure 2]. The patient had no arrhythmia recurrence after the procedure for 12 months off antiarrhythmic drugs.

Discussion

It is clear that in real time, an unstable AT could not be mapped with sequential mapping procedures due to disorganization and fibrillatory conduction. In this case, by failing to disclose the mechanism, we would probably be led to empirical complex fractionated atrial electrograms (CFAE) ablation. Probably, these

Key Words
Atrial fibrillation, Atrial Tachycardias, Pulmonary Vein Isolation.

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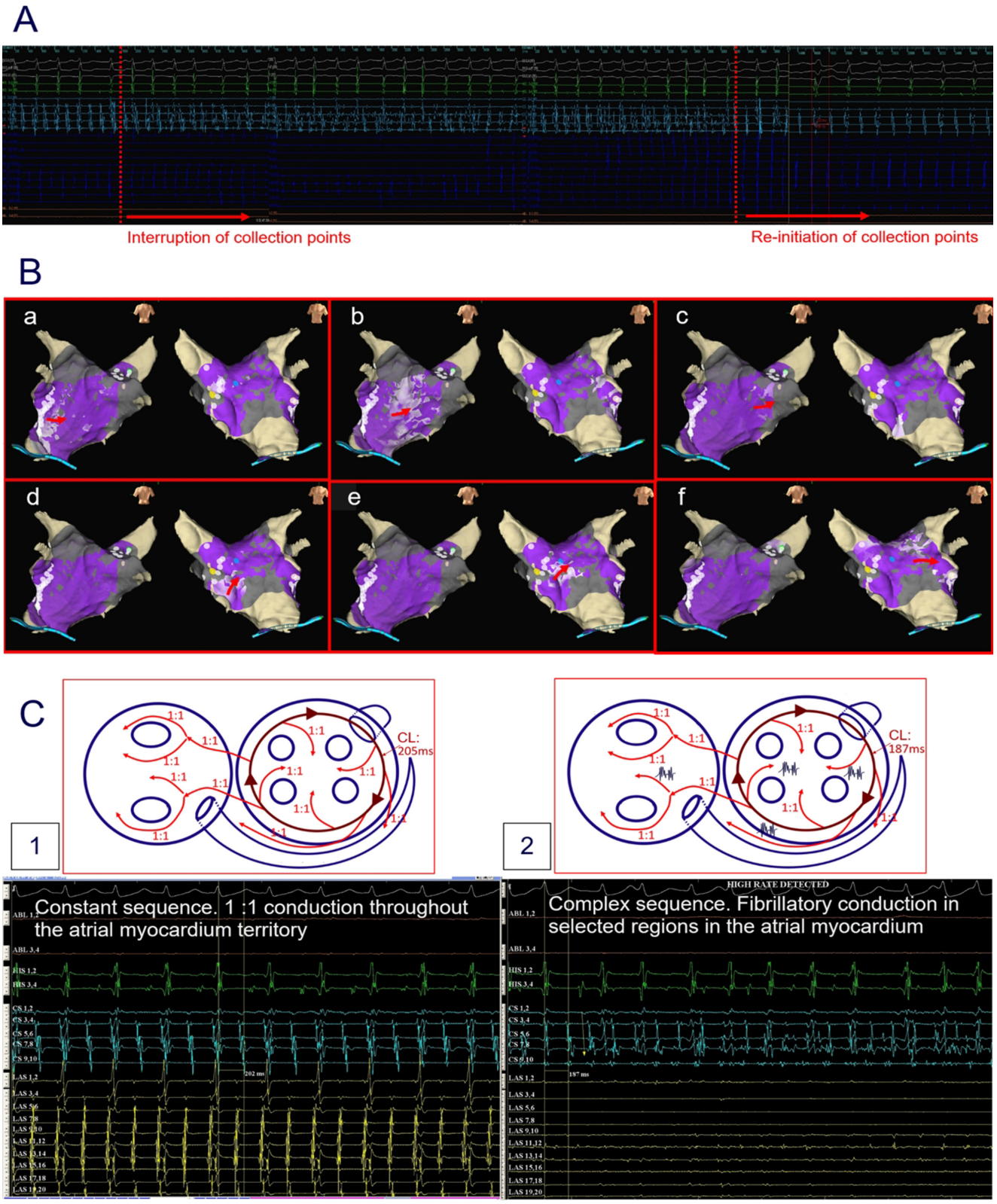

Figure 1: The selective activation mapping in the 1st case. The AT has initially constant sequence switching to an unstable form and inversely (A). The collection of points during the movement of the catheters occurs only for the periods that the tachycardia was stable. In the retrospective analysis of the entire recording, the points obtained at time intervals where the tachycardia presented with unstable and complex sequence (interval within dotted lines) were discarded. The propagation map obtained from this process showed a clockwise perimitral circuit (B) (video 1). It is worth mentioning that the AT initially has a CL of 205 ms (C1). When this slightly decreased to 187ms, the AT becomes complex and non-susceptible to sequential mapping (C2). Furthermore, in the tracing C2 we observe that the sequence in the coronary sinus (CS) for several beats remains the same (distal to proximal). Probably, the faster AT rate leads some parts of the atrial myocardium to conduct in a fibrillatory manner (schematic drawings), with different conduction velocities providing finally a completely disorganized AT appearance.

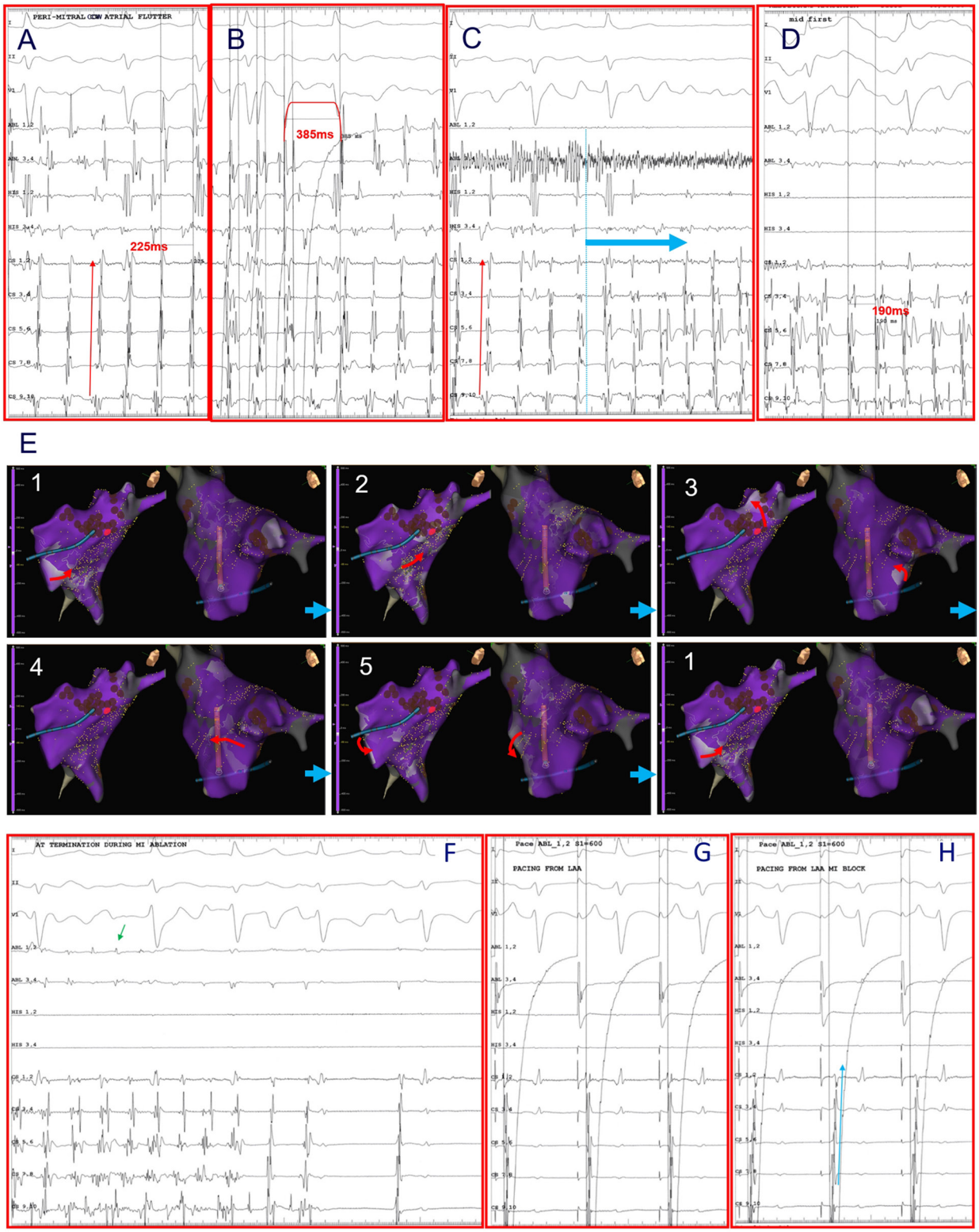

Figure 2: AT long after AF ablation in the 2nd patient, with CL of 225ms, and proximal to distal activation in CS (A). The tachycardia was mapped with rapid collection of points by moving the circular catheter to the LA. The entrainment mapping was negative from the CTI (B). The tachycardia after a few seconds lost its sequence stability (light blue arrow), with a small decrease in the CL at 190ms (C, D). In the retrospective analysis, the time segment where the tachycardia started to be unstable was rejected. Thus, the propagation map was based only at the points collected during the few seconds where the tachycardia showed CL and activation stability. The propagation map clearly showed a counterclockwise circuit around the mitral annulus (E, video 2). At the time of MI line completion, while the tachycardia remained unstable, eventually the sinus rhythm was restored (F). It is worth noting, that the tachycardia termination occurred in a non-fragmented atrial electrogram in MI (green arrow) (F). In sinus rhythm the MI line was completed with an apparent change in CS activation sequence during LAA pacing (G, H).

areas represent decremental and fibrillatory conduction not critical for AF-AT maintenance, while the initial tachycardia continues [1]. The fact that in both cases the tachycardia terminated during MI completion probably supports the hypothesis that a macro-reentrant circuit is the main maintenance mechanism of these arrhythmias.

Therefore, if the areas of decremental and fibrillatory conduction do not represent critical areas in the maintenance of the arrhythmia, attempting to eradicate them, apart from not having a successful effect, would take time out of the procedure, depriving the possibility of intervening to the responsible mechanism. Indeed, if all the areas that show decremental conduction characteristics were gradually eliminated, an organized tachycardia could be emerged that would be susceptible to sequential mapping. This phenomenon is not uncommon in clinical practice since the abolition of CFAEs leads to organization of the arrhythmia in certain cases. On the other hand, the inability to ablate all responsible areas will not probably reach this result.

These findings may be indicative that some unstable ATs appearing as AF, can be produced from the existence of one or more tachycardia sources [2,3]. It would be ideal if the future pursuit, insofar as simultaneous mapping is not technically feasible or absolutely reliable, to have a fast sequential mapping. This can be achieved by using special multipolar catheters that are capable to obtain high density maps. At the same time, it is technically feasible to create softwares that will facilitate the focusing, by manual or automatic capabilities, on time periods where the tachycardia exhibits stability in terms of CL and activation sequence.

By describing the above cases we underline the possibility that, in selected cases, specific macro-reentrant circuits may drive the maintenance of unstable ATs or AF. However, we do not overlook the fact that some other drivers can also contribute to the maintenance of an unstable AT or AF. Nevertheless, it is likely that the ablation of an existing and hardly disclosable macro-reentrant circuit could prevent arrhythmia recurrence.

Video Links :

Please click here for Video 1

Please click here for Video 2

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Evidence-Based Case Report: The Use of D-Dimer Assay to Exclude Left Atrial Thrombus in Patient with Atrial Fibrillation >48 Hours

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Abstract

Introduction: Patients with atrial fibrillation (AF) for >48 hours who are a candidate for cardioversion should have transesophageal echocardiography (TEE) performed to exclude left atrial thrombus (LAT) that may cause systemic thromboembolism upon conversion to sinus rhythm. However, TEE facilities were limited, especially in developing countries.

Case Illustration: A 50 years-old man presented with exertional dyspnea and palpitation for 72 hours prior to admission. Electrocardiography showed AF with a ventricular rate of 140x/minute. Cardioversion was decided to be the best approach. This patient has an AF >48 hours of onset, hence, LAT should be excluded by the use of TEE. Unfortunately, there was no TEE facility nearby..

Discussion: Upon comprehensive search on the use of D-Dimer assay to exclude the LAT in AF patients, we found seven studies showed increased D-dimer level in those with left atrial thrombus. In 4 studies, AUC was > 0.70, sensitivity and specificity varied from 75.9% to 89% and 73.1% to 95% respectively. However, there is no single cut-off point, due to the heterogeneity of cut-off points.

Conclusions: D-dimer assay combined with other variables of atrial thrombus exclusion score is valuable in excluding LAT. Previously, weeks of anticoagulation is more advisable before attempting cardioversion in the absence of nearby TEE facilities. With current evidence, a low D-dimer and ATE score of 0 is safe for cardioversion.

Introductio

Patients with atrial fibrillation (AF) for >48 hours who are a candidate for cardioversion should have transesophageal echocardiography (TEE) performed to exclude left atrial thrombus (LAT) that may cause systemic thromboembolism upon conversion to sinus rhythm. However, TEE facilities were limited mainly in developing countries and left atrial appendage may be a challenge to visualize by transthoracic echocardiography. In this article, we would like to discuss a patient that presented with AF >48 hours and is a candidate for cardioversion, however, there is no TEE at the facility. We performed a comprehensive search on whether d-dimer assay can be used to exclude LAT in this patient in order to perform safe cardioversion.

Case Illustration

A 50 years-old man presented with exertional dyspnea and palpitation for 72 hours prior to admission. There was no chest pain, episode of syncope, or edema. The patient was limited by symptoms but hemodynamically stable. Electrocardiography showed AF with a ventricular rate of 140x/minute. The patient has a history of hypertension on treatment with captopril. There was no history of stroke and heart failure. There was no apparent reversible cause of AF based on a panel of laboratory examinations (Including a D-Dimer <250 ng/ml DDU). Based on CHADVASC scoring, this patient has a score of 1, a 0 Wells DVT score for thromboembolic probability, and a HAS-BLED Score of 1 for bleeding probability while on anticoagulants. After considerations, it was decided that cardioversion into sinus rhythm would be the best approach in this patient. This patient has an AF >48 hours of onset, hence, LAT should be excluded by the use of TEE. Unfortunately, there was no TEE facility nearby. The patient was anticoagulated for weeks, cardioversion was performed, and AF was converted into sinus rhythm. On 6 months' follow-up, the patient remained in sinus rhythm.

Discussion

We The clinical question is whether d-dimer assay can be used to exclude the diagnosis of LAT in patients presenting with AF >48 hours without the use of TEE or should patients be anticoagulated for weeks before attempting cardioversion. To answer this question, two independent authors (E.Y and V.C) performed a comprehensive and systematic search on studies on the use of D-Dimer assay to exclude the left atrial thrombus in patients with atrial fibrillation

Key Words

Atrial Fibrillation, D-dimer assay, Left atrial thrombus, Cardioversion, Thromboembolism.

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presenting >48 hours with keywords ["d-dimer", "left atrial thrombus" and "atrial fibrillation"] and its synonym from inception up until June 2019 through PubMed, EBSCOhost, Cochrane CENTRAL, Proquest, EuropePMC, and hand-sampling from article references, discrepancies were resolved by discussion. Data extraction and quality assessment using appraisal tools from the Center of Evidence-Based Medicine, the University of Oxford was done by two independent authors (R.P and V.C). We included original articles and systematic reviews. We found a total of 182 unique results, 9 were relevant through screening of titles/abstract and the full-texts were assessed for eligibility [Figure 1] After excluding duplicate, applying inclusion criteria and performing critical appraisal using Oxford CEBM tools, we included seven studies [Table 1] and [Table 2] . All seven studies founded that D-dimer level significantly elevated in a group with LAT. Five were cross-sectional studies; one was a cohort and a systematic review. [Table 3].

Direct current cardioversion into sinus rhythm on patients with AF >48 hours may cause systemic thromboembolism due to the presence of LAT.[1] Thrombus formation leads to increased d-dimer products which means that D-dimer assay can possibly be used to exclude LAT in AF patients. Five included studies showed that d-dimer assay was elevated in those with LAT.

For D-dimer to have clinical implication, it is important to have a cut-off point that has satisfying diagnostic performance. Habara et al. showed that d-dimer assay at 1150 ng/mL had a negative predictive value (NPV) of 97% for LAT.[2] Somloi et al. found 600 ng/mL has a sensitivity: 89% and specificity: 75%, positive predictive value (PPV): 33% and NPV: 98%.[3] Tarnowski et al. found that d-dimer were significantly elevated in patients with AF and detected LA thrombus (0.13 ± 0.02 vs.0.69 ± 0.21, p=0.015); however, it is not significant at 500 ng/mL, which is the conventional cut-off value.[4] In contrast, Bejinariu et al. revealed that d-dimer assay failed to predict the LAT. [5] Wan et al. showed that elevated D-dimer was associated with left atrial spontaneous echo contrast/ LAT with moderate sensitivity and specificity. In 4 out of 5 studies, AUC was > 0.70, sensitivity and specificity varied from 75.9% to 89% and 73.1% to 95% respectively. [6] However, there is no single cut-off point, due to the heterogeneity of cut-off points.

The findings are congruent to Yasaka et al. study who evaluate the use of d-dimer to detect LAT in patients with mitral stenosis, they found that D-dimer at 300ng/mL has sensitivity= 61%, specificity= 93%, PPV= 79%, and NPV= 86%. In their study, 44 out of 63 subjects have AF. Several patients were found to have elevated d-dimer despite the absence of intra-atrial coagulation on echocardiography which may be explained by mobile thrombi undetected on TEE. This is a possible additional benefit of D-dimer assay.[7]

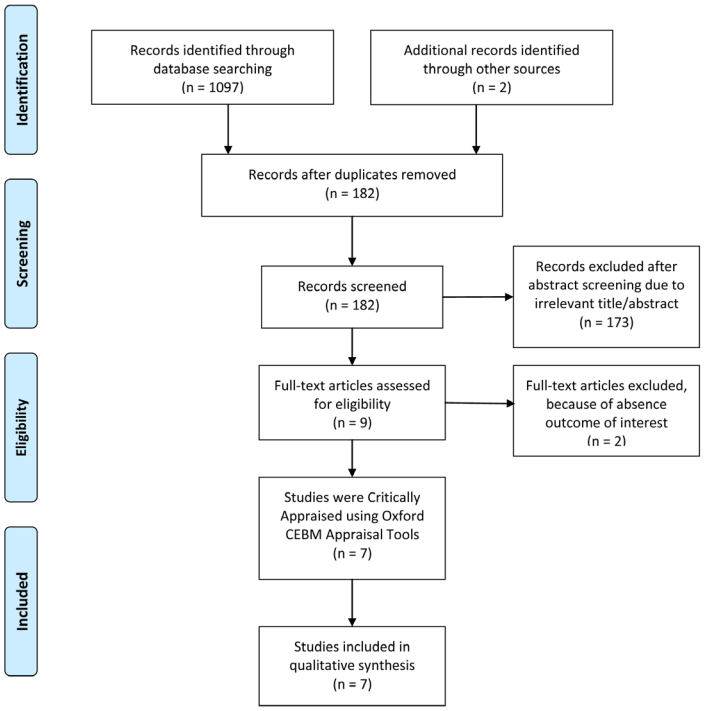

Figure 1: Flow Chart of Search Strategy

Table 1: Critical appraisal of six studies based on criteria by centre of evidence medicine University of Oxford

			Validity			Applicability	
Articles	**Year**	**Study Design**	**Representative Spectrum**	**Reference Standard Applied**	**Independent, blind Comparison**	**Applicability**	**Level of Evidence**
Milhem et al	2019	Cross-Section	+	+	+	+	1
Du et al	2019	Cross-Section	+	+	+	+	2
Tarnowski et al	2018	Cross-Section	?	+	?	+	2
Bejinariu et al	2016	Cross-Section	+	+	+	+	2
Habara et al	2007	Cross-Section	+	+	+	+	2
Somloi et al	2003	Prospective Observational Cohort	+	+	+	+	2

Table 2: Critical appraisal of a systematic review based on criteria by centre of evidence medicine University of Oxford

Article(s)	Year	PICO	Appropriate Searching	Relevant Study Included	Quality assessment of Trial	Heterogeneity	Level of Evidence
Wan, et al	2017	+	+	+	+	+	1

+ = Positive, - = negative, ? = Unclear. VIA was assessed using Oxford CEBM Appraisal Tools.

Table 3: Summary of studies included

Author	Year	Study Type	Sample (n)	Outcome of Interest	Results	Summary
Milhem et al	2019	Cross-section	2494	Plasma D-dimer levels and clinical data, to rule out a diagnosis of atrial thrombus before catheter ablation of AF.	D-dimer > 270 ng/mL was associated with adjusted OR of 2.29 (1.25–4.16) p=0.0070 The authors also proposed a score consisting of history of stroke, congestive heart failure, high plasma D-dimer level, and hypertension called atrial thrombus exclusion (ATE) score	D-dimers > 270 ng/mL combined with history of stroke, congestive heart failure, and hypertension is predictive of LAT
Du et al	2019	Cross-section	113	Plasma D-dimer levels and cardiac computed tomography angiography, to detect LAT	Age-adjusted D-dimer has sensitivity= 100.0%, specificity= 86.7%, PPV= 51.7%, NPV= 100.0% Combined with cardiac computed tomography angiography; sensitivity= 100.0%, specificity= 97.9%, PPV= 88.2%, and NPV= 100.0%	Age-adjusted D-dimer is reliable in predicting LAT especially when combined with cardiac computed tomography angiography
Tarnowski et al	2018	Cross-section	108	D-dimer level in patients with and without LAT in AF patients prior to electrical cardioversion or PVI	D-dimer (0.13 ± 0.02 vs.0.69 ± 0.21, p=0.015) were significantly elevated in patients with AF and detected LAT. In regard to the ROC, D-dimer showed an AUC of 0.77. However, D-dimer levels above the conventional cut-off of 5 mg/L (500 ng/mL) indicated LAT with a sensitivity of only 35% and a corresponding specificity of 95% (OR 4.41, 95% CI. 0.6–31.1, p = 0.14).	D-Dimer were elevated in presence of LAT but lost their quality as independent predictor using conventional cut-off value
Bejinariu et al	2016	Cross-section	372	D-dimer level in patients with and without LAA Thrombus in AF patients prior to cardioversion	1. multivariate logistic regression analysis predicting likelihood of thrombus formation in LAA → For D-Dimer (OR 1.055, 95% CI 0.783–1.420, p = 0.725) 2. Ordinal logistic regression → For D-dimer (OR 1.027, 95% CI 0.833–1.266, p = 0.806)	Biomarkers (Including D-dimer) failed to predict the outcome
Habara et al	2007	Cross-section	925	D-dimer level in patients with and without LAT in non valvular AF patients	1. D-dimer levels (OR 97.6, 95% CI 17.3–595.8, P,0.0001). LAA thrombi were detected in 21.8% of patients with higher D-dimer values, whereas it was detected in only 3.1% of patients with lower D-dimer values. 2. D-dimer > 1.15 μg/ml (1150 ng/ml); AUC: 0.80, 95% CI 0.75–0.85 At a cutoff level of 1.15 μg/mL, the sensitivity was 75.9% (95% CI 65–85), specificity 73.1% (95% CI 70–76%), PPV 21.7% (95% CI 17–27%), and NPV 97.0% (95% CI 95–98) for identifying thrombi in LAA.	D-dimer cutoff level of 1150 ng/mL had a negative predictive value of 97% for identifying LAA thrombi.
Somloi et al	2003	Prospective Cohort	75	D-dimer measured before TEE in 75 consecutive patients referred for TEE before cardioversion for AF or flutter >48 hours	ROC Curve, AUC 0.78 (95% CI: 0.63-0.93, p=0.007). Cut-off value of 0.6 μg/mL (600 ng/mL) yields a sensitivity 89% and specificity 75%. PPV 33% and NPV 98%.	D-dimer cut off value is 0.6 ug/mL
Wan et al		Systematic Review and Meta-analysis		D-dimer and presence of LAT or Spontaneous Echo Contrast	1. Pooled standardized mean difference (SMD) of D-dimer between patients with and without left atrial SEC and/or LAT was 1.29 (95% CI: 0.51, 2.08), with SMDs of 0.42 (95% CI: 0.08, 0.77) and 2.34 (95% CI: 1.01, 3.68) in SEC/LAT and LAT subgroups, respectively. 2. The combined RR of the presence of LAT among individuals between the top of the distribution of d-dimer levels and that in the bottom third was 3.84 (95% CI: 2.35, 6.28), associating with a mean difference of 0.78 ug/ml (1.10 vs 0.32 μg/ml). 3. D-Dimer for LAT → Sensitivity 0.75 (95% CI: 0.65, 0.83), specificity 0.81 (95% CI: 0.59, 0.93) and positive likelihood ratio 4.0 (95% CI: 1.7, 9.9] Range cut off 125 ng/ml – 4000 ng/ml	High plasma fibrin DD was associated with left atrial SEC/LAT, particularly among patients with LAT. DD levels have moderate sensitivity and specificity for diagnosing LAT

Description: AUC=Area Under Curve, LA=Left Atrium, LAA=Left Atrial Appendage, LAT=Left Atrial Thrombus, NPV=Negative Predictive Value, PPV=Positive Predictive Value, ROC=Receiver Operating Characteristic, SEC=Spontaneous Echo Contrast.

Currently, there is no recommendation on D-dimer use to exclude LAT; however, the NPV of D-dimer assay is comparable to TEE in excluding left atrial thrombi. D-dimer's effectiveness was shown to fall short to that of TEE (NPV= 98.7%; Hwang et al.) in studies performed by Habara et al. (NPV= 97%), Somloi et al. (NPV=98%), and Yasaka et al. (NPV= 86%). Thus D-dimer assay has the potential to be used to exclude LA thrombi[8]. Du et al. reported age-adjusted d-dimer assay has sensitivity= 100.0%, specificity= 86.7%, PPV= 51.7%, NPV= 100.0% for detection of LAT, the study included both valvular and non-valvular AF; an excellent diagnostic performance.[9] Du et al. study further combined cardiac computed tomography angiography to reach a sensitivity= 100.0%, specificity= 97.9%, PPV= 88.2%, and NPV= 100.0%. Hence, the combination may be valuable in the hospital without TEE but with cardiac computed tomography angiography.[9] The importance of d-dimer assay was further strengthened by a study by Milhem et al. whom suggested a d-dimer >270 ng/mL along with the history of stroke, heart failure, and hypertension formed a reliable atrial thrombus exclusion (ATE) score.[10] Milhem et al. demonstrated that an ATE score of 0 has a 0% atrial thrombus in 911 patients. While ATE score of 1 and 2 had 2.3% (out of 988 patients) and 2.9% (out of 481 patients) incidence of thrombus.[10] An ATE score of 3 and 4 had 9% (out of 111 patients) and 33.3% (out of 3 patients) incidence of atrial thrombus.[10] The ATE score is ideal in a rural hospital with limited facilities, needing only d-dimer assay and other variables that can be obtained by history taking and physical examination.

The patient in previous case illustration may benefit from cardioversion; however, those with AF >48 hours have a high risk for thromboembolism. The current recommendation is to rule out the LAT by the use of TEE. We conclude at that time (the year 2017) that there was not enough evidence to routinely recommend

measurement of plasma D-dimer to rule-out LAT; hence, the safest option is to administer anticoagulation to patients for weeks before performing cardioversion in the absence of TEE facility nearby. However, with the advent of ATE score proposed by Milhem et al. in 2019; measurement of D-dimer assay in the evaluation of patient requiring exclusion of LAT is reasonable. This patient has an ATE score of 1 having a 2.3% risk of stroke, hence low but null risk of cardioversion. D-dimer assay (and ATE score) in addition to transthoracic echocardiography may be of use, especially in those with a risk score of 1 to 3, hence, we recommend further studies to evaluate this possibility.

Limitations in this study are selection bias in which only positive studies are published, hence, may lead to overestimation of diagnostic performance. These studies also have varying cut-off point, to have a clinical impact, there has to be a single cut-off point.

Conflict of Interest

The authors declare no conflict of interest.

Authors Contribution

Raymond Pranata conceived and designed the study and drafted the manuscript. Emir Yonas and Veresa Chintya acquired the data and drafted the manuscript. Raymond Pranata and Emir Yonas interpreted the data and performed critical appraisal. Alexander Edo Tondas and Sunu Budhi Raharjo performed extensive research and critically revised the manuscript. All authors contributed to the writing of the manuscript.

Conclusions

D-dimer assay is valuable in excluding LAT; especially combined other variables of ATE score. Previously, weeks of anticoagulation is more advisable before attempting cardioversion in the absence of nearby TEE facilities. With current evidence, a low D-dimer and ATE score of 0 is safe for cardioversion. Further investigations on diagnostic performance by the combined use of transthoracic echocardiography and ATE score further risk stratify those with a score of 1 to 3 may further delineate the risk of cardioversion in hospitals with limited facilities.

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Pulmonary and Paradoxical Embolism after Slow Pathway Ablation: A Thrombotic Disorder Unmasked by a Rare Complication.

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Abstract

Cardiac electrophysiology study (EPS) and catheter ablation procedure are established diagnostic and therapeutic procedures for cardiac arrhythmias.

Pulmonary embolism (PE) is a relatively rare but potentially fatal complication of cardiac electrophysiology study (EPS). The paradoxical embolism (PDE) occurs due to an intracardiac defect with a right to left shunt with patent foramen ovale (PFO) being the most common cause. The simultaneous occurrence of PE and PDE is rare.

Here we present a case of PE and PDE after EPS and radiofrequency catheter ablation (RFCA) of the slow pathway in a patient with recurrent supraventricular tachycardia (SVT) due to atrioventricular nodal reentry tachycardia (AVNRT). To our knowledge, such a case of PE and PDE has not been reported after SVT ablation.

Introduction

Cardiac electrophysiology study (EPS) is an established diagnostic and therapeutic procedure for cardiac arrhythmias.[1] The catheter ablation procedure is a well-established treatment option for patients with supraventricular tachycardia (SVT) and has a high efficacy rate.[2] EPS procedure-related major complications occur in 1.1% of patients depending on the procedure type, patient's age, and concomitant comorbidities. However, a higher complication rate of 3.1% is reported in patients undergoing radiofrequency catheter ablation (RFCA).[3] EPS major complications may include vascular damage, deep venous thrombosis (DVT), pulmonary embolism (PE), systemic or paradoxical embolism (PDE), AV block, cerebrovascular accident, tamponade, cardiopulmonary arrest, and rarely death. EPS minor complications include bleeding, hematoma, pericardial effusion with no hemodynamic compromise, and arteriovenous fistula.[3] The simultaneous occurrence of PE and PDE is rare. [4,5,6]

Here we present a case of PE and PDE after EPS and RFCA of the slow pathway in a patient with recurrent SVT due to atrioventricular nodal reentry tachycardia (AVNRT). To our knowledge, such a case of PE and PDE has not been reported after SVT ablation.

Case Presentation

Our patient was a 25-year-old woman with a history of recurrent SVTs for several years presenting with intermittent palpitations. She had 3-5 episodes of palpitations every year. She had a documented narrow QRS tachycardia at 200 beats per minute (bpm) with no visible P waves that terminated with IV adenosine. Her past medical history was negative. Management options, including medical therapy versus EPS with RFCA with the exploration of the risks and benefits of each approach were discussed with the patient, and she decided to proceed with EPS and RFCA.Her physical exam was normal.

Her labs, including complete blood count (CBC), renal profile, hepatic profile, and Prothrombin Time (PT)/ Partial Thromboplastin Time (PTT), were normal. Hepatitis B and C and Human immune deficiency virus (HIV) 1 and 2 antibody screening were negative. The baseline electrocardiogram (ECG) was normal. Echocardiogram was normal with no visible patent foramen ovale (PFO) or evidence for an atrial septal defect.

The EPS procedure was performed with three venous accesses via the right femoral vein utilizing one 7, and two 6 French, introducer sheaths. Three catheters were placed in the right ventricular apex (RVa), coronary sinus, and His bundle positions. The sheaths were connected to heparinized normal saline flush. Her baseline intervals were normal, and SVT was easily inducible with programmed electrical stimulation. The SVT was consistent with a typical (slow-fast) (AVNRT). Slow pathway ablation was performed successfully. The procedure was then completed, and the catheters and sheaths were removed from the patient's body after a careful aspiration of all sheaths. The total duration of the procedure was 70 minutes. The patient was transferred to the cardiac holding unit (CHU) in stable condition with an order for bed rest for four hours Seven hours later, the patient became dizzy, and her level of consciousness deteriorated. On physical examination, she was conscious and oriented but lethargic. Her BP was 66/40 mmHg,Temperature 36.7 C, and SpO2 97 to 100% on room air. The cardiovascular and neurological exams were normal. Apart from sinus tachycardia at 109 bpm, her ECG was

Key Words
Pulmonary embloism, Pardoxical emblism, Electrphysiology study.

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normal. Portable chest X-ray showed no significant abnormalities.

A pocket-sized ultrasound device (Vscan) study was immediately conducted to rule out pericardial effusion and tamponade. However, it revealed a mass in the right atrium (RA) and dilated RV. An urgent bedside echocardiogram revealed a large mass (16x17mm) likely thrombus in the RA crossing a PFO to the left atrium (LA) with filamentous thrombus and crossing the mitral valve. It was suggestive of PE with mild dilation of RV and elevated RV systolic pressure at 40-45 mmHg. The RA and LA were normal in size. The inferior vena cava was dilated and not collapsible. [Figure 1] The patient was transferred to the coronary care unit, and high dose heparin was initiated along with IV fluid resuscitation. The patient responded well to IV fluids with normalization of her BP. A whole body computed tomography (CT) scan was performed. The CT brain was clear, but the CT-PE study revealed a massive bilateral acute PE. [Figure 2A] Besides, there was a partially visualized filling defect within the right renal artery branch, associated with multiple bilateral renal wedge-shaped hypodensities, compatible with multiple renal infarctions and very indicative of embolic showering. [Figure 2B] However, the kidney function remained normal. Lower limb ultrasound was performed, and it showed a non-obstructive thrombus in the left popliteal vein. [Figure 3] Blood samples were sent for thrombophilia work up and autoimmune studies.

On the following day, repeated echocardiography revealed that the thrombus in the LA was large and highly mobile. It was felt that the safest approach would be to remove the LA thrombus surgically, so the patient was transferred to the operating room after signing informed consent. However, the pre-operative transesophageal echocardiogram (TEE) about 6 hours from the last transthoracic echocardiogram revealed the disappearance of the RA and LA thrombus. There were no clots within the RV, the main PA or the proximal right and lefts PAs. With these findings, the procedure was aborted, and the patient was returned to her bed in a stable condition. She was therefore started on oral anticoagulation. The patient was

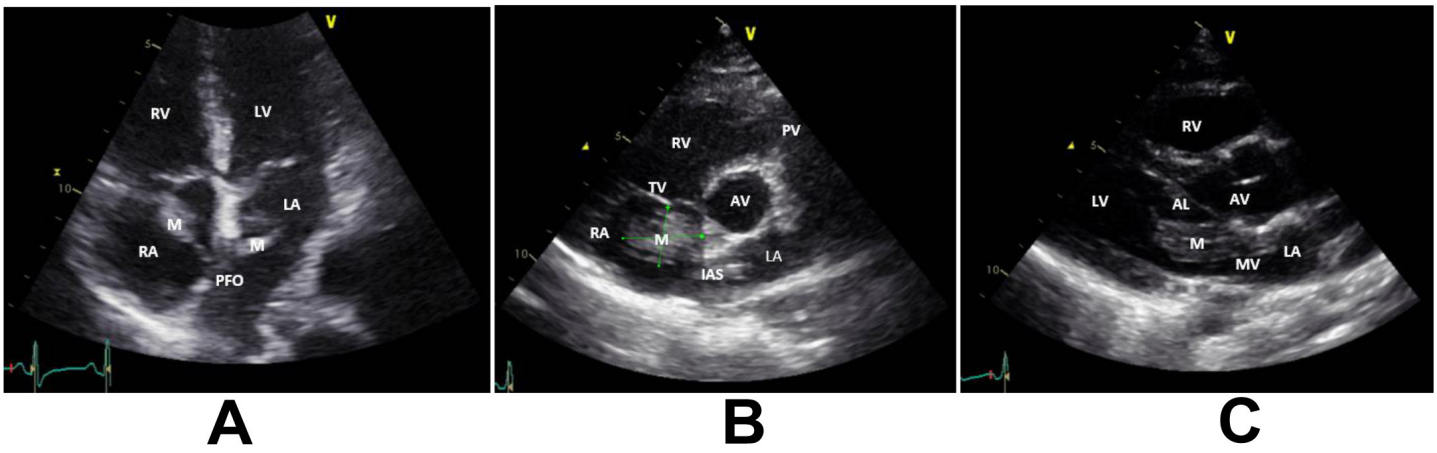

Figure 1: Echocardiogram (2D): A. Apical four-chamber view (A4C) showing right atrial mass crossing patent foramen ovale to the left atrium. B. Short axis view (SAX) at aortic valve level showing the right atrial mass measuring 16x17 mm. C. Parasternal long axis view (PLA) showing the mass protruding through the mitral valve.

AL; anterior leaflet of the mitral valve, AV; aortic valve, LA; left atrium, LV; left ventricle, M; mass, MV; mitral valve, RV; right ventricle.

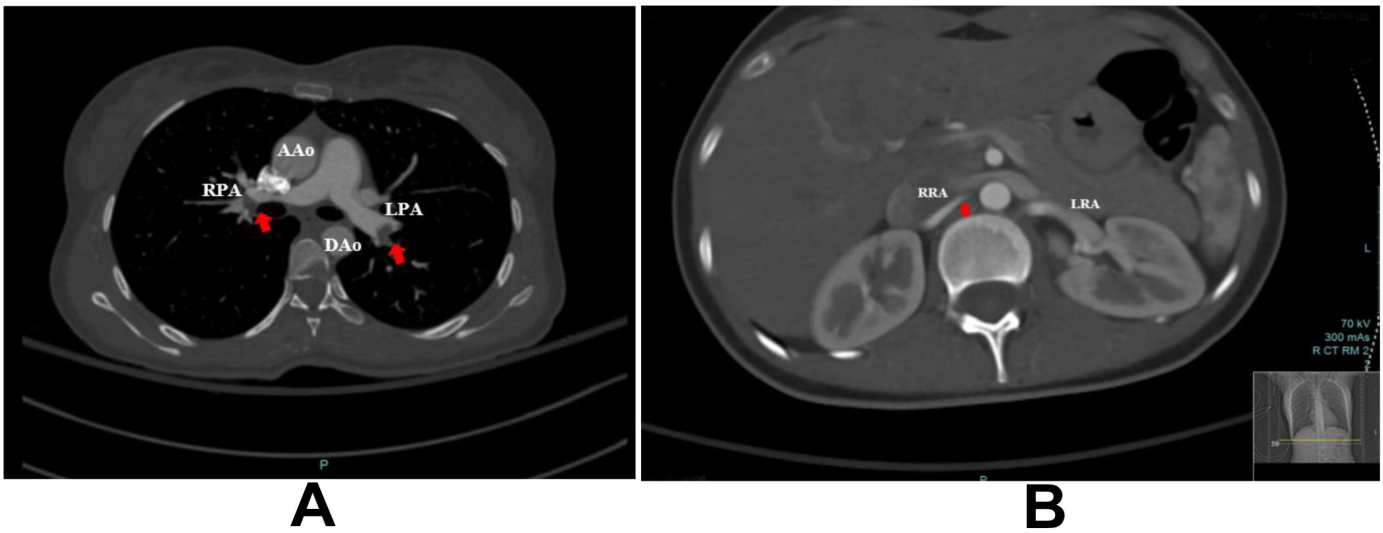

Figure 2: A. Computed tomography (CT)scan, PE study with axial cut showing distal filling defects in right and left pulmonary arteries(red arrows) RPA and LPA. B. Right renal artery with partial occlusion likely thrombus.

AAo; ascending aorta, DAo; descending aorta, LPA; left pulmonary artery, RPA; right pulmonary artery, LRA; left renal artery, RRA; right renal artery.

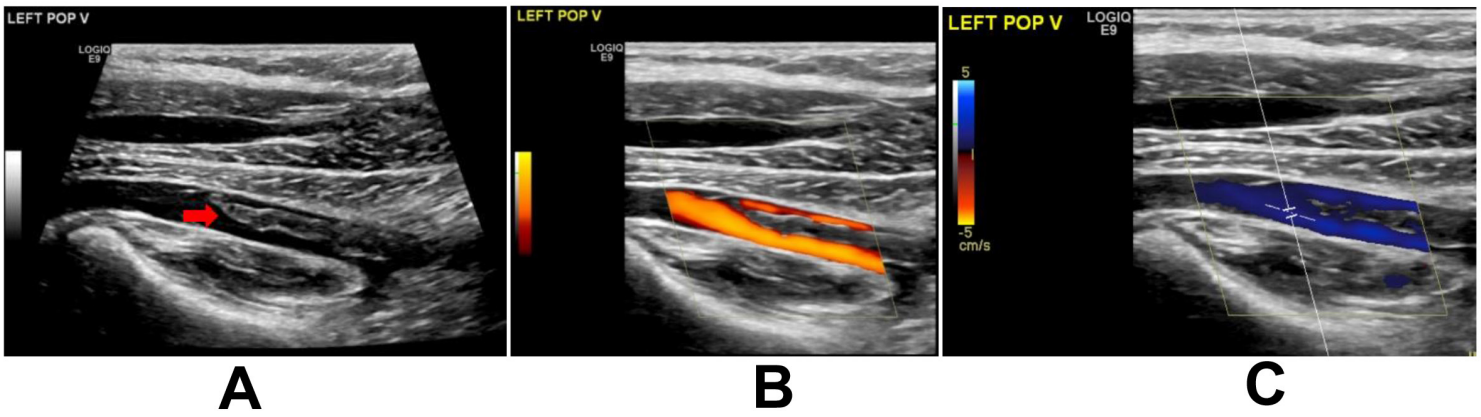

Figure 3: Ultrasound venous Doppler Scan of the left lower limb showing acute nonobstructive thrombus in the left popliteal vein (red arrow).

hemodynamically stable and discharged home a few days later.

The thrombophilia workup showed that her functional Protein C level was low at 0.5 IU/mL (normal 0.7-1.3 IU/mL), as was her Factor V activity which was 0.53 IU/mL (normal 0.6-1.5 IU/mL). Her functional protein S level was within the normal range. Genetic analysis was carried out and showed that the patient was heterozygous for C677T polymorphism.

Follow up echocardiogram a few months later showed normal LV and RV size and function and normal right-sided pressure.

The patient was maintained on oral anticoagulation with follow up in thromboembolic service. She was asymptomatic at 12 months follow up.

Discussion

This case demonstrated a rare complication of EPS and RFCA with simultaneous PE and PDE.

Predisposing factors for thromboembolic events such as deep venous thrombosis (DVT) in patients undergoing EPS include placement of the venous sheath(s) leading to vascular endothelial injury and stasis.[7] The placement of multiple femoral venous sheaths could be a contributing factor. In one study, the placement of multiple femoral venous sheaths was associated with a high incidence of non-occlusive DVT (19.2%) detected through duplex ultrasonography on the next day following the procedure. However, none of these patients experienced symptomatic PE.[8] Another study reported a significant increase in the incidence of femoral vein thrombosis following the use of multiple femoral venous sheaths without administering heparin in patients who underwent EPS (62.5%); however, fixed prophylactic dose with body weight independent low molecular weight heparin significantly decreased the risk of femoral thrombosis in these patients (18%).[9] Similar to the previous study, none of the patients showed clinical features of PE.[9]. The catheters manipulation in blood vessels and cardiac chambers is another risk factor with activation of the coagulation cascade.[7] A thrombus may develop inside the sheath(s) or on the surface of the catheter(s) and attach to the vessel walls, valves or cardiac chambers, and then embolize. Besides, post-procedure compression of the puncture site(s), subsequently leading to venous stasis and an accentuated thrombogenic state.[7] Bed rest with immobilization post-procedure is another contributing factor.

PE is a relatively rare but potentially fatal complication of EPS. The overall incidence of PE with reviewing five studies, including 14,205 patients, underwent EPS was 0.12%.[10] Although the incidence of PE post EPS is low, it carries a mortality rate of greater than 15% during the first three months after diagnosis.[11] The risk of systemic embolism and PDE post EPS and RFCA is less established. PE after routine right cardiac catheterization is likely underestimated. [12] In one study with a small sample size of 57 patients, 12% of the patients had new perfusion defects consistent with PE, which were detected by ventilation-perfusion lung scans just one day after right-heart catheterization.[12] This finding suggests that PE may be more common than previously anticipated.

The PDE occurs due to an intracardiac defect with a right to left shunt. The most common intracardiac defect associated with PDE is the patent foramen ovale (PFO) defect with a venous embolus that crosses the PFO to the systemic circulation. [3-6] Patients with PFO are usually asymptomatic. However, if RA pressure increases, a right to left shunt occurs with risk for PDE. Our patient had elevated right heart pressure following the acute PE and resulted in the PDE. The Brain arteries are the most frequent localization of PDE.[6] However, embolization may happen in any other systemic (not systematic) arteries.

On the full thrombophilia workup, our patient was discovered to have a heterozygous C677T polymorphism, which is an additional risk factor. The C667T genetic mutation is the most common methylenetetrahydrofolate reductase (MTHFR) mutation variant. It is correlated with reduced enzyme activity, which in turn leads to elevated levels of homocysteine. High levels of homocysteine showed an increased risk for atherosclerosis, which may result in a heart attack and/or stroke, and DVT. [13] This polymorphism may be present either in a homozygous or heterozygous state. In the heterozygous, there is reduced enzyme function to about 65% of normal, and in homozygous there is only 30% of normal enzyme function. [13] This mutation is extremely common in certain ethnic and geographic populations. [13] In Saudi population, the presence of the C677T heterozygous and homozygous variants are 25.25% and 2.25% respectively. [14] The association of C677T polymorphism with the development of Venous thromboembolism (VTE) is

not universally accepted. [13] A recent meta-analysis supported the association of MTHFR C677T polymorphism with VTE risk. [15] Our patient was also found to have a low level of Factor V and Protein C. A low level of Protein C was shown to be an independent risk factor for VTE in multiple studies, and it predisposes patients to recurrent VTEs.[16] The patient did not have a factor V Leiden or G20210A prothrombin gene mutation.

With the exclusion of atrial flutter, routine anticoagulation therapy is not routinely recommended before, during, and after a right-heart procedure unless other risk factors for systemic embolism are present. [7] However, There is a need for further evidence-based guidelines concerning anticoagulation and prevention of VTE during and after routine EPS procedures. Risk stratification and early intervention for such cases, along with DVT prophylaxis when indicated, may decrease the incidence of VTE and its complications.

Conflicts of interest

The authors declare no conflict of interest related to this manuscript.

Conclusions

DVT is not uncommon after EPS, and subsequent PE and/or PDE although rare is a serious complication with possibly dramatic consequences. Venous stasis, vascular endothelial injury with activation of the coagulation cascade resulting from multiple venous sheaths, and prolonged hemostatic mechanisms may all contribute to the formation of DVT. PE should be suspected with prompt diagnosis and management in patients who develop acute respiratory distress after a right-heart ablation procedure. There is a need for updating evidence-based guidelines on antithrombotic therapy in the setting of EPS procedures.

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Prolonged Ventricular Dyssynchrony Due to Atrial Fibrillation and Pre-Excitation Syndrome Induced Cardiomyopathy

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Abstract

Various degree of ventricular activation by accessory pathway (AP) and normal conduction system in a patient with pre-excited atrial fibrillation (AF) may lead to ventricle dyssynchrony and cardiomyopathy.

Introduction

Left ventricular (LV) dysfunction due to accessory pathways (AP) is rare. Recognizing pre-excitation as a cause for LV dysfunction is important as it is reversible. Recovery of cardiac function after radiofrequency ablation occurs over a variable period of time. Previous study suggest septal or paraseptal accessory pathway has been documented in patients with overt ventricular pre-excitation who developed LV dysfunction.[1] We report a patient with pre-excited AF from left lateral AP and severe LV dysfunction who underwent ablation of accessory pathway and showed significant improvement of LV function thereafter.

Case Report

A 76 years old male with recurrent palpitation and shortness of breath for 1 year was referred for ablation. The patient was diagnosed with Wolff-Parkinson-White syndrome (WPW) in 2016 [Figure 1]and QRS duration showed less than 130 ms, indicated lesser degree of pre-excitation. There is no history of angina or myocardial infarction.ECG on admission showed pre-excited AF [Figure 2] Transthoracal echocardiography (TTE) on admission showed dilation of all chambers, reduced LV ejection fraction (LVEF 29%) with global hypokinesis, compared to previous TTE (in 2016) that showed normal cardiac chamber size and function (LVEF > 50% and normokinetic).

Two quadripolar catheters were inserted into RV and His position. A Duo-decapolar catheter was inserted along right atrial crista to distal coronary sinus (CS). Baseline rhythm showed pre-excited AF. Sinus rhythm was achieved after electrical cardioversion. During sinus rhythm, AV fusion was seen in distal CS (D1-2/left lateral) [Figure 3]. Right ventricular pacing showed eccentric VA conduction with earliest retrograde atrial activation via the left lateral AP. Ablation procedure on left lateral AP was done by transeptal approach. There was VA dissociate during RV pacing after AP ablation. Ablation procedure on left lateral AP was done by transeptal approach. VA's dissociate during RV pacing were seen after AP ablation.

The patient was discharged on amiodarone 200 mg daily for rhythm control. There were no symptoms of heart failure and palpitations after three months of follow up. Serial ECGs during follow up showed sinus rhythm with no sign of an AP. After 3 months of follow up, TTE showed significant improvement of LV systolic function (LVEF 65%) and no evidence of hypokinesis.

Discussion

This patient had prior episodes of recurrent palpitations especially in the last one year. We assumed that intermittent pre-excited AF frequently occur during that time. Previous studies suggests that LV dyssynchrony may be more pronounced in patients with septal and paraseptal AP.[1] To the best of our knowledge, this is the first case of left lateral AP induced LV dyssynchrony leading to cardiomyopathy.

Cardiomyopathy in this case might occur in several mechanism. First, different various degree of ventricular activation by both AP and His-purkinje system lead to ventricle dyssynchrony [Figure 3]. Second, tachyarrhythmia (pre-existing paroxsysmal AF) itself may play an important role for worsening cardiomyopathy.[2,3] Third, even in sinus rhythm with pre-excited, LV dyssynchrony may occur.[4,5] Thus, the combination of them may lead to cardiomyopathy.

In a retrospective way, this case prove that elimination of pre-excitation in AF can result in mechanical resynchronization which lead to reverse remodeling and improvement in LV synchrony. Preventing tachyarrhythmia by maintaining sinus rhythm and slowing down the ventricular rate also may play important role for LV reversed remodelling.

Key Words

Ventricular Dyssynchrony, Reversed remodelling, Pre-excited AF.

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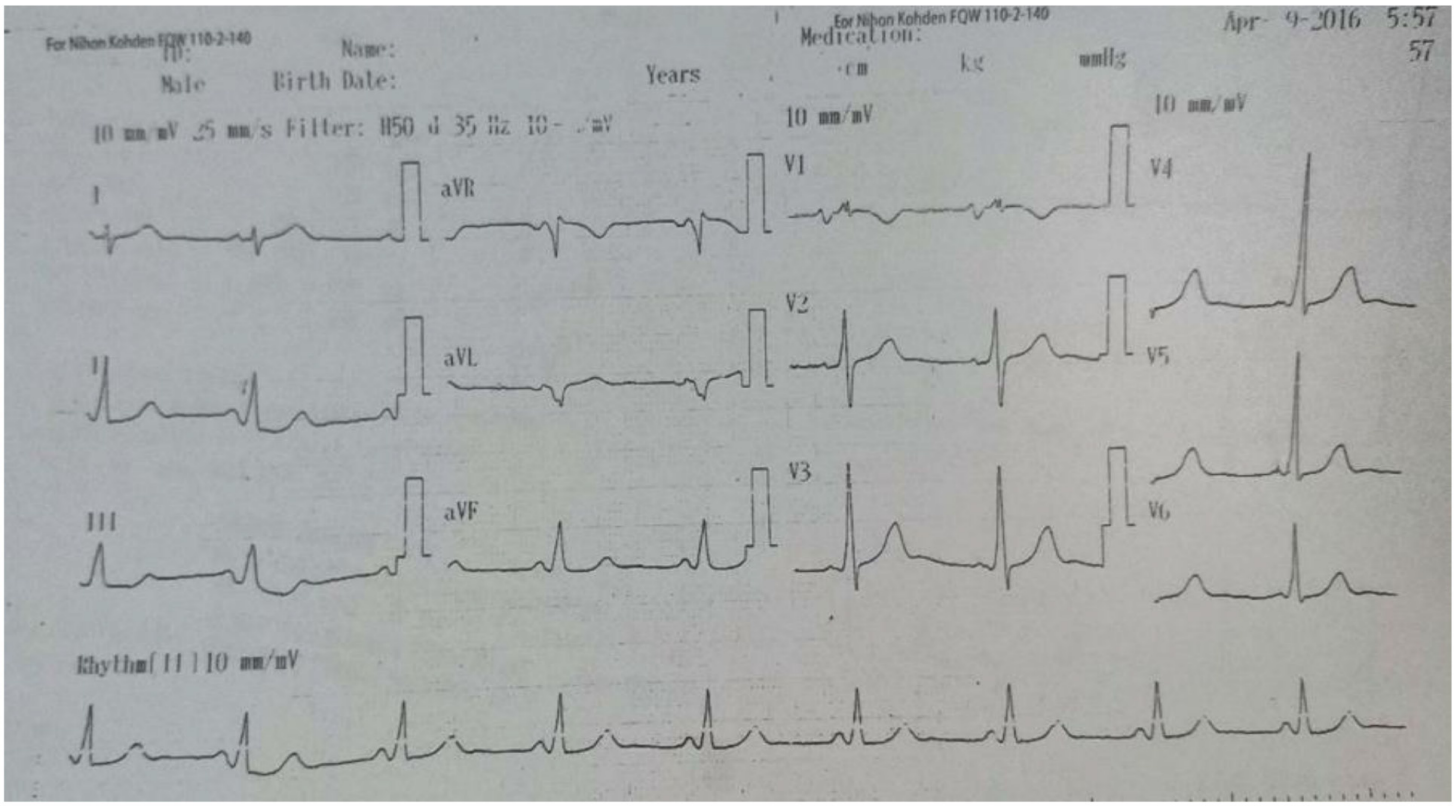

Figure 1: Baseline ECG in 2016 showed sinus rhythm with preexcited. The QRS duration is less than 130 ms. Indicated of the lesser degree of preexcitation.

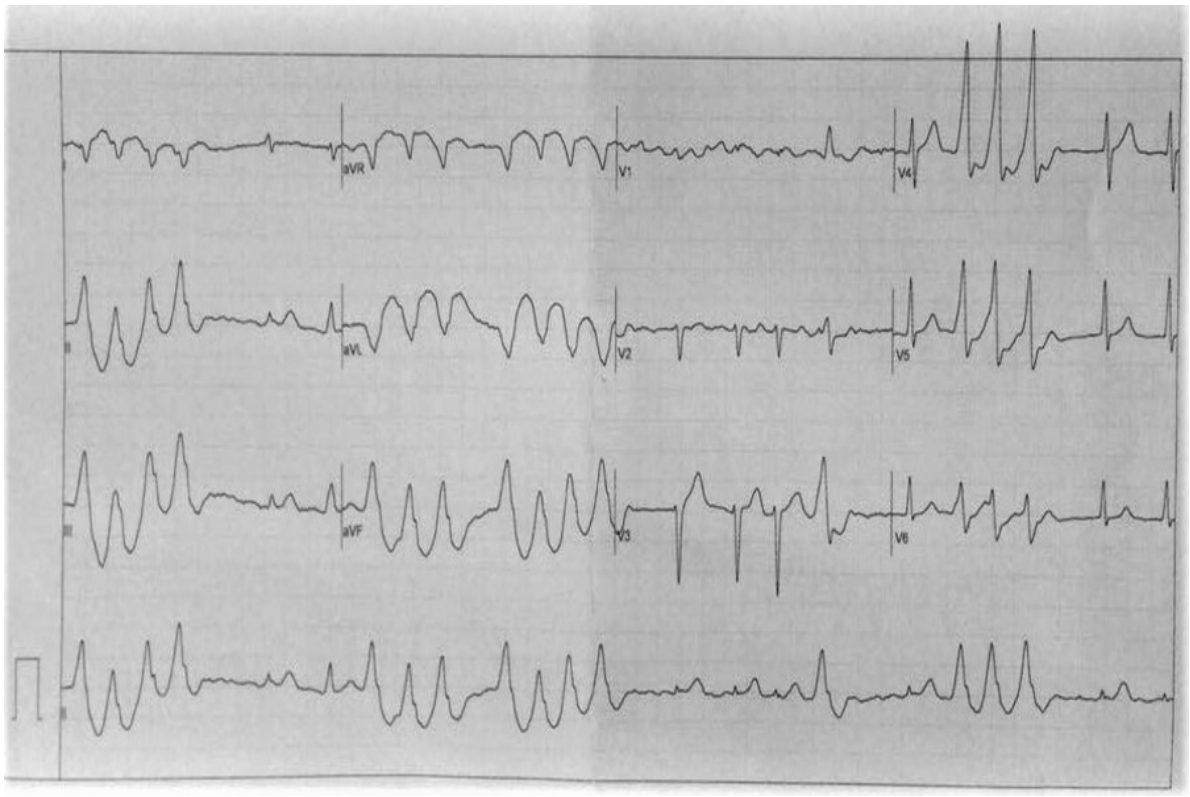

Figure 2: 12 lead ECG during admission. ECG showed pre-excited AF with various degree of preexcitation. The shortest R-R interval showed up to 200 ms and the widest QRS was about 150 ms.

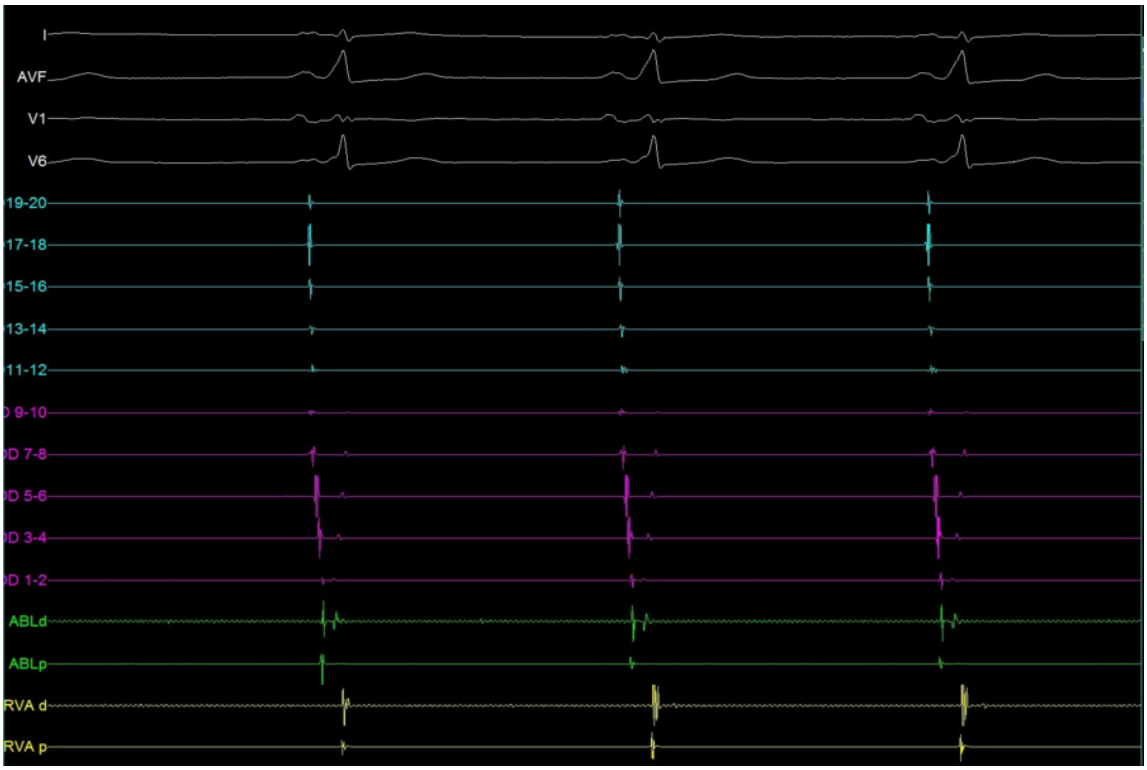

Figure 3: D1-2 was duo-decapolar which inserted along low crista right atrial to distal CS. Electrogram during sinus rhythm showed AV fusion on distal CS (D1-2). Ablation (ABL) catheter was positioned near D1-2

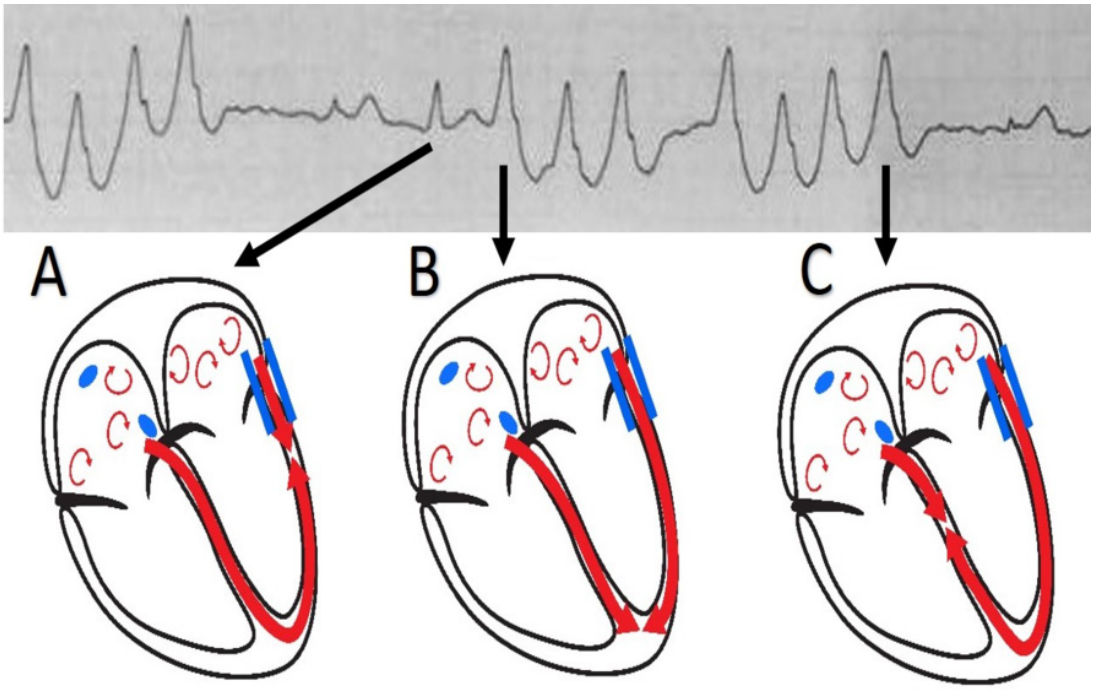

Figure 4: Illustration of mechanical dyssynchrony due to varying degrees of ventricular activation by the AP and normal conduction system. (A) The narrowest QRS duration showed ventricle activation mostly was done by impulse from normal conduction system, (B) The "modest" QRS duration showed ventricle activation was done by impulse from AP and normal conduction system equally, (C)The widest QRS duration with maximal preexcitation, with the majority of ventricular activation over the AP

There are several limitations of this paper. First, we lack of data of how long the patient remained in sinus rhythm (with or without pre-excited) in the last 1 year. But we believed that the symptomatic recurrent palpitation in the last 1 year indicated how much the pre-excited AF occur. Furthermore, 'silent' pre-excited AF may occur and underrecognized by the patient. Second, we did not perform AF ablation. Based on previous studies, the mechanism of AF is related to AP and almost AF burden will resolve spontaneously after AP ablation.[6,7] However, the recurrence rate of atrial fibrillation following successful ablation in patients with paroxysmal atrial fibrillation prior to ablation shows an age-related increase (high reccurence rate in patients older than 50 years of age).[8] Therefore, we decided to give amiodarone as a rhythm control for this patient. The duration of amiodarone to maintain sinus rhythm in such a case remains to be determined. Third, LV dysfunction due to ischemia could not be entirely excluded, because we did not performed coronary angiography (CAG). Our reasons were : (1) there is no indication of CAG for this patient considered no symptoms of chest pain or angina, (2) reverse remodeling and rapid improvement of LV function after catheter ablation also prove that low EF in this patient is due to LV dyssynchrony (reversible cause). Thus, made the cause of LV dysfunction due the ischemia "less likely". Fourth, this is a single case report. Therefore, this findings need to be confirmed by serial case or larger studies.

Acknowledgement

None

Disclosure

The authors declare no conflicts of interest.

Conclusion

Prolonged LV dyssynchrony due to pre-excited AF will lead to reversible cardiomyopathy. Elimination of AP by ablation and maintaining of sinus rhythm may play important role in improving LV synchrony and function.

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Sleep Duration and Risk of Atrial Fibrillation: a Systematic Review

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Abstract

Background: Little is known about a possible association between sleep duration and the incidence of atrial fibrillation (AF), in healthy people. In this systematic review, we conducted a literature search to examine possible association between sleep duration and the incidence of AF.

Methods: Scientific databases (PubMed, Web of Knowledge and Embase) were searched using relevant Medical Subject Headings and keywords, to retrieve studies written in English and published until November 2017. Only population-based observational studies were included. Since sleep duration categories were not consistent, it was feasible to run a meta-analysis.

Results: The average follow-up of the patient population was 1,633.1±1,232.9 (median: 1,438.0) days. Patients who underwent 2-4 and ≥5 DCCVs had mSix eligible studies were included. Long sleep duration (≥ 8 hours) was found to be associated with an increased risk of AF (adjusted hazard ratio (aHR) = 1.13; 95% CI: 1.00-1.27 and aHR= 1.5, 95% CI: 1.07-2.10) in two studies. One study reported that sleep duration less than 6 hours was associated with an increased risk of AF (aHR= 1.58, 95% CI: 1.18 -2.13) compared to sleeping for 6-7 hours. In two studies, mean sleep duration was lower in AF groups compared to the non-AF group. Insomnia was associated with an increased risk of AF in another study (aHR= 1.33, 95% CI: 1.25-1.41).

Conclusions: Unhealthy sleep duration, defined as either less than 6 hours or more than 8 hours, may be associated with an increased risk of AF.

Introduction

Sleep duration and pattern show differences in developed countries due to longer work time, more availability, higher rate of shift-work, induced excessive daytime sleepiness and tiredness [1]. Several studies introduced both short and long sleep duration as risk factors for diseases like metabolic syndrome [2,3], diabetes [4], cerebrovascular accidents [5,6], obesity [7], hypertension [8], myocardial infarction [9-11], and dyslipidemia [12]. Also, effects of sleep duration on progression or suppression of different diseases were shown.[13-15][16,17].

Atrial fibrillation can induce or exacerbate heart failure, myocardial infarction, thromboembolism, cerebral infarction [18] and chronic renal failure [19], which all negatively affect the quality of life and increase the duration of hospital stay [20,21]. More than 1% of adults develop AF, and the prevalence of AF increases with age [22]. Also, over 2 million people in the United States suffer from AF. The cost of continuous examinations and increased rates of hospitalization of AF patients amounted to 459 million Euro in 2000 [20,21,23,24]. Predictions suggest that the world will face a 2.5-fold increase in the prevalence of AF by the year 2050 [25]. Considering the importance of AF and its socioeconomic burden, it is necessary to identify the risk factors which crucially contribute to this condition. Many studies demonstrated associations between some predisposing factors like gender, age, hypertension, diabetes, smoking, heart's valve defects, myocardial infarction, heart failure and sleep-disordered breathing, and the incidence of AF [20,21,23,24]. between sleep duration and the incidence of AF, there is considerable controversy with respect to the result of the related studies.search the literature to evaluate observational studies in the field and assess the possible association between sleep duration and the incidence of AF in order to obtain a quantitative estimate of the risk.

Key Words

Sleep, Atrial fibrillation, Systematic review.

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Methods

Search strategy

Scientific databases including PubMed, EMBASE, and Web of Sciences were searched up to November 2017 using the terms ("sleep" OR "insomnia") AND ("atrial fibrillation" OR "auricular

fibrillation"). All sets included Medical Subject Heading (MeSH) and free-text terms, and papers that were written in English were evaluated. Search strategy is demonstrated in [Figure 1] No limits were applied during the search. Also, relevant publications cited in the studies were checked to increase the sensitivity of the search.

Inclusion criteria

"Inclusion criteria" for the studies that are discussed in this review article were as follows: 1) all English observational studies done in human and written in English; 2) studies which included people with AF and investigated the relation between AF incidence and sleep duration; 3) study participants aging >18 years old; 4) studies in which AF was confirmed by electrocardiography (ECG); and 5) studies in which sleep duration was measured by sleep questionnaire

Duplicate publications, editorials, and letters were excluded. The titles of the identified studies were assessed by two reviewers (AB and NE). If the reviewers had inconsistent ideas about an article, it was re-evaluated by a third party. We also avoided selecting duplicate or overlapping data by analyzing author names and hospitals in which patients were followed up. Quality assessment was done using Joanna Briggs Institute (JBI) critical appraisal tool that is available at http://joannabriggs.org/research/critical-appraisal-tools.html [26].

Data Extraction

critical Data extraction was done by NE; then, the data were entered in Microsoft Excel 2013 and Microsoft Corp, Redmon, Washington, USA and subsequently compared with the original data by NM and AB to assure the accuracy of the extraction process. The extracted data for each study included the following information: first author name, year of publication, country, sample size, age of study population, study design and setting, AF diagnosis method, sleep assessment method, and study results. We contacted the authors who did not report data to obtain detailed information about their study, but received no response. Eligible studies are qualitatively summarized in [Table 1]

Results

After finding 3003 articles in PubMed, Web of Sciences, EMBASE, we excluded duplicated and irrelevant records and finally reviewed six papers to assess eligibility for selection ([Figure 1]).In these six eligible studies ([Table 1]), a total of 186,323 individuals were recruited.

Study characteristics

Among the six studies included in this systematic review, two studies were conducted in China, and one in the USA, Turkey, Taiwan, and Japan each.[13,31,32] and four studies used ECG to evaluate AF [15,32-34]. [13,15,31,32] while other studies used Athens Insomnia Scale (AIS-8) [32], ICD-9-CM code 780.52 [33], and Pittsburgh Sleep Quality Index (PSQI) [34].

Sleep duration per day was classified into three categories (≤6, 7 and ≥8 hours) in two studies [13,15] and four categories (<6, 6-7, 8 and ≥9 hours) in one study [31]. Mean and standard deviation of sleep duration per day were reported by two studies [13,32]; also, one study reported the frequency of insomnia [32].

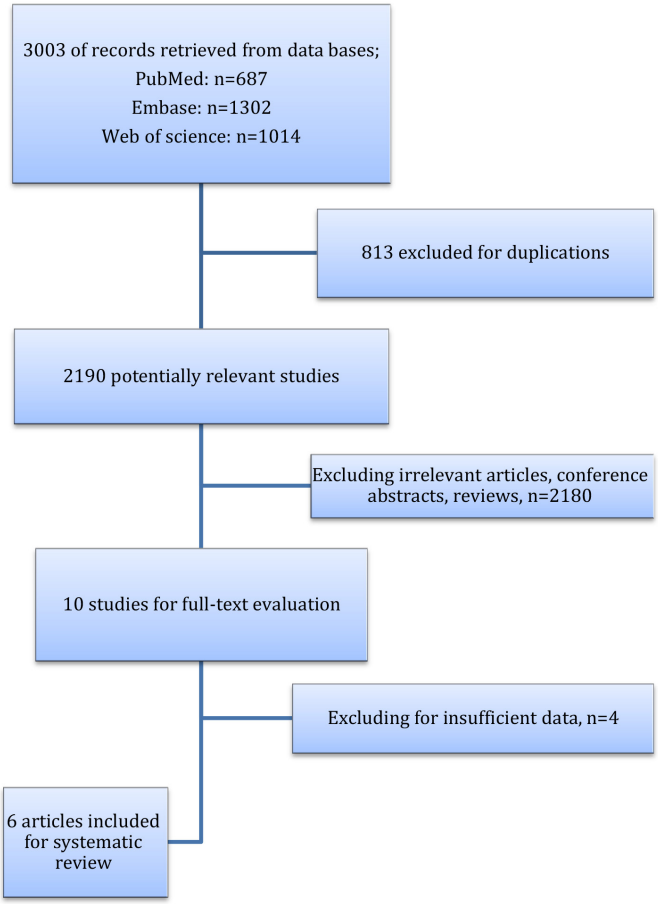

Figure 1: **Flow diagram of the study.**

Two population-based cohort studies reported that sleep duration of ≥8 hours was associated with an increased risk of AF. Also, in one study, this association was of borderline significance as adjusted hazard ratios (aHR) for AF were 1.06; 95% CI: 0.92-1.22 for sleep duration of ≤6 and 1.13; 95%CI: 1.00-1.27 for sleep duration of ≥8 hours compared to 7-hour sleeping. Another study reported aHR= 1.07, 95% CI:0.75-1.53 and aHR= 1.5, 95% CI: 1.07-2.10 for sleep duration of ≤6 and ≥8, respectively compared to 8 hours of sleeping per day [13,15].

In four studies, shorter sleep durations were associated with an increased risk of AF. Also, in a study conducted in Japan, an aHR= 1.58, 95% CI: 1.18 -2.13 was found for sleeping durations of less than 6 hours and increased risk of AF compared to sleeping durations of 6-7 hours per day [31]. In a population-based study conducted in China, patients with AF had shorter sleeping durations compared to those without AF (6.7± 1.3 hours vs. 7.2± 1.2 hours; P < 0.05) [32]. In another population-based cohort study conducted in Taiwan, patients with insomnia were at a higher risk of AF (aHR= 1.33, 95% CI: 1.25-1.41) as compared to patients without insomnia [33].

Sleep duration in a Turkish population-based cohort was lower in patients with AF than the individuals without AF (PSQ score: 1.4±1.1 in subjects without AF vs. 2.00±1.1 in patients with AF,

Table 1: Qualitative summary of studies.

Study details: First author, publication date, country	Sample size, sample size in AF and non-AF (n)	Study Age	Study type, setting	AF diagnosis	Sleep assessment	Study result
Han, 2017, China	8371 AF = 50 Non-AF= 8321	42.4±13.1	cross-sectional study population-based	self-reported history or the standard 12-lead ECG one of the following criteria was present: (1) irregular RR intervals, (2) absence of repeating P waves, and (3) irregular atrial activity.	The Athens Insomnia Scale (AIS-8)	OR: 1.92 for insomnia (95% CI:1.00-3.70, P = 0.05) OR: 1.92 for insomnia in those age <40 years (OR: 6.52, 95% CI: 1.64-25.83, P = 0.01), those age ≥60 years (OR: 2.29, 95% CI: 0.95-5.55, P = 0.07).
Kayrak, 2013, Turkey	1053 AF: 153 Non AF:150	303 patients (mean age: 63 ± 12 years) who had nonvalvular AF and 150 age- and gender-matched control subjects (mean age: 61 ± 14 years)	cohort study hospital-based	Electrocardiography (ECG)	using the Pittsburgh Sleep Quality Index (PSQI).11	Adjusted OR: 3.34 (95%CI:1.99-5.61)in poor sleep (PSQI >5) patients adjusted for: age, sex, body mass index, hypertension, diabetes, heart rate
Khawaja, 2013, USA	18,755 AF:1,468 Non AF: 17,287	mean:68 ±8.6	Prospective cohort study population-based US male physicians(PHS)	Incident AF was ascertained through yearly follow-up questionnaires.	For self-reported sleep duration. duration: ≤6, 7, and ≥8 hours. categories of sleep duration.	adjusted hazard ratios (95% CI) for AF were 1.06 (0.92–1.22) in sleep<=6 h, 1.0 (sleep =7h), and 1.13 (1.00–1.27) in sleep >=8 adjusted for: age, sex, exercise frequency, body mass index, alcohol consumption, smoking, hypertension, diabetes, dyslipidemia, sleep apnea, snoring, coronary heart disease, congestive heart failure subgroup analysis: in sleep apnea patients: 2.26 (1.26-4.05) in sleep<=6 h, 1.0 (sleep =7h), and 1.34 (0.73-2.46) in sleep >=8
Kokubo, 2014, Japan	6,780 AF:244 Non AF: 6536	30 to 84 years old	Prospective cohort study population-based (Suita study)	Incident AF including: AF was present on/ AF was indicated as a present illness by either annual questionnaire responses or medical records.	Sleep duration was classified into 4 categories: <6, 6 and 7, 8, and ≥9 hours levels.	Compared with 6 and 7 hours sleep duration, the adjusted HRs (95% CIs) of incident AF were 1.58 (1.18-2.13) for who slept less than 6 hours. adjusted for: age, sex, body mass index, alcohol consumption, smoking, hypertension, diabetes, dyslipidemia
Lee, 2017, Taiwan	64,421 cases with insomnia and 128,842 control AF: 1,674 (2.6%) cases in patients with insomnia 2,925 (2.3%) in non-insomnia group Non AF: 62,747 cases in patients with insomnia 125,9170 in non-insomnia group	18-40 : Insomnia(14,402), Non-insomnia(28,804) | 41-65: Insomnia(32,621), Non-insomnia(65,242) | ≥65: Insomnia(17,398), Non-insomnia(34,796)	retrospective National Cohort Study population-based	Incident Atrial fibrillation (ICD-9-CM codes 427.31) is defined as the diagnosis of atrial fibrillation in an outpatient department and admission.	patients with a diagnosis of insomnia 3 times [based on (ICD-9-CM) code 780.52] within one year	HR = 1.33, 95% CI: 1.25-1.41 in patients with insomnia Matched cohort on age, sex, index date, comorbidity
Qiaofeng Song, 2017, China	n=87,693 AF:322 Non AF: 87,371	50.54 (18-98)	prospective cohort study population-based	Incident Atrial fibrillation diagnosis was made on a standard 12-lead electrocardiogram and via self-reported history	self-reported responses to the question, were categorized into three groups: short (≤6 hours), average (7 hours), and long (≥8 hours).	adjusted hazard ratios (95% CI) for AF were 1.07 (0.75-1.53) in sleep<=6 h, 1.0 (sleep =7h), and 1.5 (1.07-2.10) in sleep >=8 adjusted for: age, sex, education, body mass index, alcohol consumption, physical activity, smoking, hypertension, diabetes, dyslipidemia, sleep apnea, snoring, myocardial infarction, uric acid, and high sensitivity C-reactive protein.

p<0.001) [34]. In a sub-group of patients with sleep apnea, the risk of AF was higher in patients who slept for ≤ 6 hours compared to those with 7-hour sleep duration (aHR= 2.26, 95% CI: 1.26-4.05) [13].

Discussion

To the best of our knowledge, this study is the first systematic review assessing possible association between sleep duration and AF. We found that both short and long durations of sleep were associated with AF, with shorter durations being associated with a higher risk. Four studies out of the six identified studies, reported that shorter sleeping duration was associated with increased risk of AF, while two studies reported that longer sleeping duration was associated with increased AF risk. In the subgroups, patients with sleep apnea showed a similar association while patients without sleep apnea did not exhibit such an association.

The link between sleep duration and AF is still unclear. Sleep deprivation was associated with alterations in ECG parameters including signs of AF. Moreover, sleep deprivation was associated with P-wave dispersion, QT dispersion and P-wave duration, which are also predictors of AF [35,36]. Some experimental studies showed that short duration of sleep, as defined by short-term forced sleep deprivation, negatively affected endocrinological, immunological and metabolic systems [37,38]. Sleep deprivation in healthy adults was shown to be associated with left atrial early diastolic strain rate reduction which is also known as "left atrium functional impairment"

[39]. Furthermore, insomnia is regarded as a risk factor that increases the probability of the development of cardiovascular diseases through autonomic dysregulation and induction of inflammation pathways [40,41].

In the MESA (Multi-Ethnic Study of Atherosclerosis) Sleep Study, longer duration of slow wave sleep (SWS) was associated with lower odds of AF before and after adjustment for apnea-hypopnea index (AHI) [42]. The association between SWS time and AF emphasizes the importance of the sleep duration in sleep health. SWS is defined as the status with the highest parasympathetic activity [43]. Sleep was associated with high parasympathetic and low sympathetic activities, which might, in turn, be associated with AF occurrence [44].

In this systematic review, both short and long sleep durations were associated with a higher risk of AF in different studies, suggesting a U-shaped association between sleep duration and AF. Nonetheless, residual confounders such as depression or anxiety disorders, which are associated with cardiovascular risk, may play an important role in this relationship [45]. Moreover, differences among the subjects of the study populations in terms of shorter or longer sleep durations, might be due to a predisposing depression [46-49]. The U-shape associations between sleep duration and cardiovascular disease (CVD), CVD risk factors and all-cause mortality were reported earlier [50,51].

It was proposed that longer sleep duration which is regarded as a deviation from normal physiological aging, may put such individuals at higher risk of premature death [52].

The studies included in this review used different categories for sleep duration; therefore, it was not possible to perform a meta-analysis based on the categories reported in the studies. Thus, we decided to report sleep durations as short and long sleep categories as well as insomnia and non-insomnia based on studies that were included. Also, since "categories" were reported and discussed instead of exact duration of sleep, it was not possible to draw a conclusion with a cut off for public health.

Acknowledgements

Authors acknowledge the help and support provided by Clinical Research Unit, Mashhad University of Medical Sciences, Mashhad, Iran.

Declarations of interest

Authors have no conflict of interest to declare.

Conclusions

Unhealthy sleep duration defined as sleeping for less than 6 hours or more than 8 hours per day, is associated with an increased risk of AF. Further studies are warranted to ascertain the potential association between sleep duration and AF risk as well as the optimal sleep duration that is associated with the least risk of AF.

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Left Atrial Appendage Epicardial Clip (AtriClip): Essentials and Post-Procedure Management

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Abstract

Left atrial appendage exclusion is a viable alternative to anticoagulation for stroke risk reduction in atrial fibrillation patients. In this article we address the essentials and post-procedural management of left atrial appendage exclusion using the AtriClip. Ischemic strokes that are related to atrial fibrillation (AF) are the most devastating and the most disabling ischemic strokes due to larger emboli compared to carotid disease. Anticoagulation (AC) is the standard approach for stroke risk reduction in AF patients. Unfortunately, near 10 percent percent of AF patients who would benefit from AC (CHA2DS2-VASc score of 2 or more) have absolute contraindications for AC. A higher percentage may have relative contraindications. Moreover, among the patients who can be on AC, only sixty percent are able to maintain a therapeutic international normalized ratio (INR). This has traditionally left almost half of AF patients at a significant stroke risk without protection. The advent of newer non-vitamin K anticoagulants (NOACs) has slightly improved the problem given their improved intracranial bleeding profile, the inherent and still significant risk of bleeding from anticoagulation persists.

Introduction

Ischemic strokes that are related to atrial fibrillation (AF) are the most devastating and the most disabling ischemic strokes due to larger emboli compared to carotid disease.[1,2] Anticoagulation (AC) is the standard approach for stroke risk reduction in AF patients. Unfortunately, near 10 percent percent of AF patients who would benefit from AC (CHA2DS2-VASc score of 2 or more) have absolute contraindications for AC.[3,4] A higher percentage may have relative contraindications. Moreover, among the patients who can be on AC, only sixty percent are able to maintain a therapeutic international normalized ratio (INR).[5] This has traditionally left almost half of AF patients at a significant stroke risk without protection. The advent of newer non-vitamin K anticoagulants (NOACs) has slightly improved the problem given their improved intracranial bleeding profile, the inherent and still significant risk of bleeding from anticoagulation persists.[6]

A growing interest in the left atrial appendage (LAA) has been driven by the observation that ninety percent of thrombi in non-valvular AF and sixty percent of those in valvular AF develop in the LAA.[7] Left atrial appendage exclusion however has been inconsistent in terms of techniques, rates of complete exclusion, and thus adoption.[10] This led to redundant evidence regarding whether the concept of left atrial appendage occlusion offers any reduction in stroke risk for AF patients. In the past decade, the interest in the LAA exponentially increased and a larger body of evidence has evolved in association with newer LAA occlusion devices. The validity of the concept of LAA occlusion in AF-related stroke risk reduction has been best demonstrated by the PROTECT AF trial's 45 months follow up outcomes.[11] For the first time in a well powered study they demonstrated that LAA occlusion is non-inferior to anticoagulation in stroke risk reduction.

Feasibility of a number of devices as well as their efficacy in achieving reliable complete LAA occlusion has been demonstrated.[11-16] Devices designed to exclude the LAA from the circulation are either applied from the outside (epicardial devices) or reside inside the appendage (endocardial devices). The most widely used endocardial device is the Watchman device, which is a percutaneously delivered polyester fabric on a nitinol frame ([Figure 1B]). The Lariat device utilizes a combined percutaneous and epicardial approach to deliver a lasso around the appendage guided by an intraluminal magnet tip ([Figure 1A]). The Atriclip is made of a two polyester-covered parallel tubes with nitinol springs ([Figure 1C]). Generally, endocardial devices are in contact with blood stream, and for that reason, the recommendation is to resume anticoagulation for 2 months after endocardial devices are implanted, making this a less attractive option for patients with absolute contraindications for AC. Also, endocardial devices do not sit as well within LAAs with abnormal morphologies; a situation better addressed by epicardial devices. Our preference is to use the Atriclip epicardial clip. In our experience, this device is easy to use and allows adjusting position of the clip after deployment as needed. Also, the Atriclip was not associated with pericarditis and/or thrombosis, which makes it in our opinion safer that the reported outcomes with the Lariat system.[17-19] These reports however are not large enough to draw definitive conclusions.

Key Words

Atrial fibrillation, Left atrial appendage, Stroke.

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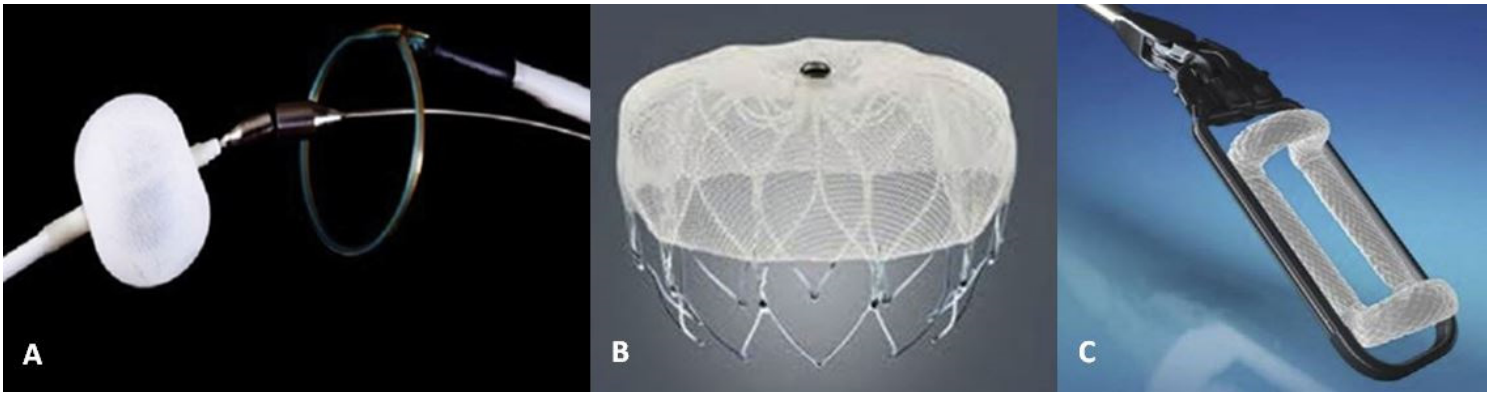

Figure 1: A: the Lariat system. B: the Watchman device. C: the Atriclip

In this article, we outline our experience using the Atriclip and our recommendations for its use and management after the procedure. Although no societal guidelines exist to date, our recommendations are in agreement with other reports from high-volume centers publishing their experiences with the Atriclip.

The AtriClip

This LAA occlusion device is made of two parallel titanium tubes with elastic nitinol springs covered by knit braided polyester. The delivery allows for application on a beating heart, as well as allows redeployment in case of initial suboptimal placement. It has shown excellent results regarding feasibility and near 100 percent occlusion rates documented by CT scan and TEE, leading to its approval by the CE and the FDA.[12,13]

Indications and Application

Closure of the LAA is indicated for any patient with atrial fibrillation (paroxysmal or chronic) undergoing a cardiac surgery or an ablation procedure. For patients not undergoing cardiac surgery, LAA exclusion is indicated if anticoagulation is not tolerated, not preferred by patient or failing to achieve adequate protection. In this case, absolute contraindications to AC or abnormal LAA morphology both favor the Atriclip over a percutaneous endocardial device. For patients undergoing an ablation, isolated thorascopic LAAE is part of the procedure, and our preference is the use of the Atriclip in this situation. Our algorithm for application of the Atriclip in patients not undergoing cardiac surgery is outlined in [Figure 2].

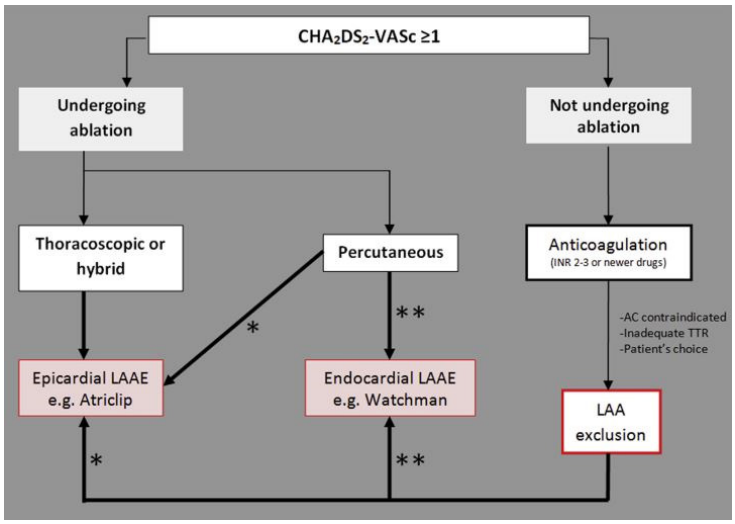

Figure 2: Our algorithm for patients with atrial fibrillation not undergoing cardiac surgery.

*Preferred, with contraindications to anticoagulation or unfavorable left atrial appendage morphology. **Preferred with nonsurgical candidates and those with previous cardiac or left thoracic surgery. CHA2DS2-VASc, congestive heart failure, hypertension, age >75 and diabetes Adapted with permission from Bedeir K, Holmes DR, Cox JL, Ramlawi B. Left atrial appendage exclusion: An alternative to anticoagulation in non-valvular atrial fibrillation. The Journal of Thoracic and Cardiovascular Surgery 2017;153:1097mellitus, previous history of stroke or transientischemic attack, vascular disease, age 65-74 years, and female sex category; AC, anticoagulation, TTR, time in therapeutic range, LAA, left atrial appendage; LAAE, left atrial appendage exclusion. -105.

The AtriClip is applied epicardially with no foreign body contact to bloodstream. The clip is applied to the base of the appendage, and the process is not affected by atypical LAA morphologies. It can be applied with concomitant cardiac operations as well as in isolated thoracoscopic procedures. With either, intra-operative transesophageal echocardiography (TEE) is necessary to ensure absence of a LAA thrombus prior to application, as well as to confirm the absence of residual flow or a significant stump after clip application. In cases with concomitant cardiac surgery, our preference is to apply the clip after initiation of cardiopulmonary bypass but before cardioplegic arrest. In the isolated thoracoscopic procedures, the appendage is approached via the left chest while using a double lumen endotracheal tube. The patient is supine with a bump under the left hemithorax and with the left arm positioned above the head. This position allows for groin access and makes conversion to a sternotomy accessible, if needed.[20]

Post-Procedural Concerns and Management

Whether done thoracoscopically or with concomitant cardiac procedure, occlusion of the LAA using the AtriClip is a fairly simple procedure with a low morbidity profile, provided that the patient can tolerate single lung ventilation. Post-procedure management should address the infrequent adverse events as well as decisions regarding anticoagulation and routine follow up imaging. The prevalence of post-procedural adverse events is primarily driven from single center experience reports, and their respective management is based on experts' opinion from centers of large AtriClip experiences. Adverse events include pericardial effusions with or without pericarditis, tachyarrhythmias and respiratory dysfunction mostly related to atelectasis.

Table 1: Anticipated post-procedural adverse events.

Adverse event	Etiology	Management
Pericardial effusion	- Volume overload, partly related to sudden decrease in ANP	- Prevention: 1) empiric 7 day couse of furosemide, 2) delayed removal of chest tubes after open surgery
	- Pericarditis (rare after Atriclip)	- Treatment if occurs (~1%): 1) Course of oral steroids with quick taper, 2) dieresis, 3) if symptomatic or hemodynamic impact, drainage.
Tachyarrythmias	- Non specific to Atriclip, although volume overload due to decrease ANP may be related	- Avoid volume overload - Standard treatment of RVR with beta blockade, amiodarone and DCCV if needed.
Respiratory dysfunction	- Usually with isolated thoracoscopic LAAE in patients with borderline FEV1.	-Judicious pain control, minimize narcotics as able. - Dieresis
	-Usually related to atelectasis	- Early ambulation, chest physical therapy.

ANP: Atrial natriuretic peptide, RVR: rapid ventricular response, DCCV: direct current cardioversion, LAAE: left atrial appendage exclusion, FEV1: forced expiratory volume/1second

Adverse Events

Pericardial effusions, can occur after Atriclip application. Although initial European and US reports of feasibility and safety reported no pericardial effusions in one hundred and four patients, subsequent experiences however did reveal an occurrence of pericardial effusions in approximately one percent of patients, that is rarely of clinical consequences.[12,13] Other epicardial devices reported a pericardial effusion rate of ten to fifteen percent.[18,19]
Accumulation of fluid in the pericardial sac is difficult to predict, and is usually related to volume overload, pericarditis, or both. While volume overload is universal in on-pump concomitant cardiac surgery, it is less so with isolated thoracoscopic AtriClip application with judicious peri-operative fluid management. Theoretically however, effective exclusion of the LAA may accentuate volume overload by sudden withdrawal of serum atrial natriuretic peptide (ANP) levels, which is primarily secreted from the atrial appendages. Beside volume overload, pericarditis may be another cause of pericardial effusions, although less common. In canine models, the AtriClip has been shown to be completely inert and to produce minimal to no reaction to the tissues in contact.[21] Despite that, post pericardiotomy pericarditis can still occur after AtriClip application, with unclear direct relationship to the clip itself.

Regardless of the etiology, we recommend initial prevention using a short course of empiric diuresis. Our practice is to administer forty mg of oral furosemide daily for the first seven postoperative days. For clip application with concomitant cardiac surgery, we commonly keep the mediastinal drains in for an extra 24 hours beyond our usual practice. In approximately one percent of patients, effusions may develop despite the preventive measures taken. In this case, a short course of oral methylprednisolone with a quick taper is recommended. Most cases resolve with a short course of steroids and diuresis and produce no clinical symptoms. In the very rare incidence of a significantly large effusion with symptoms or echocardiographic evidence of impaired right sided filling, a pericardial window should be done.

Atrial tachyarrhythmias are common after cardiac surgery, and the specific role of the AtriClip is difficult to delineate. In our experience, this has not been an additional problem in patients with an AtriClip added to their concomitant cardiac operation. Rapid ventricular response in these patients may be attributed to a number of non-clip related postoperative factors including myocardial excitability, systemic inflammatory response as well as volume and electrolyte abnormalities. All these factors tend to normalize in the early post-operative period. Our approach to managing tachyarrhythmias with rapid ventricular response is standard. We use amiodarone for rate control and possible cardioversion, and with potential electrical cardioversion if clinically indicated.

Respiratory dysfunction manifested by hypxia following thoracoscopic AtriClip application is usually related to atelectasis after single lung ventilation and is addressed in the standard approach. Adequate pain control without respiratory suppression is crucial, together with early ambulation, respiratory toilet, physical therapy and avoidance of volume overload. Common adverse events are summarized in [Table 1]. Other post-operative events are usually non-clip specific and are managed in their respective standard fashion with no specific managements related to the clip.

Decisions after the procedure

Decisions regarding anticoagulation and imaging (postoperative and routine follow up) should be made and are usually tailored to patient and procedural characteristics. Regarding anticoagulation the decision is often straight forward, given that a contraindication to anticoagulation is commonly the reason why these patients were referred for LAA exclusion. For patients without contraindications to anticoagulation, the decision is less straight forward. The Zurich group published their three and half year follow up for 36 patients receiving the AtriClip.[22] The mean CHA2DS2-VASc score was 3.7 and only three patients were continued on anticoagulation. There was one transient ischemic attack (TIA) during the follow up period of 1284 patient-days and there were no strokes observed. The same group reports a reduction in stroke rate in 291 patients with a mean CHA2DS2-VASc score was 3.1, who received the AtriClip with concomitant surgery. Patients that did not receive anticoagulation after LAA exclusion had a stroke incidence of 0.5 per 100 patient years (compared to an expected stroke rate of four strokes per 100 patient years). Also, the 45 months follow-up data from the PROTECT AF trial demonstrate the efficacy of LAA exclusion in preventing strokes in patients not on anticoagulation.[11] Based on the above evidence, there is an expert consensus that anticoagulation is not needed after AtriClip application. Aspirin is usually started post-operative day one and continues indefinitely.

Routine imaging post-operatively or during follow up is not cost effective. Ailawadi et al[1] imaged sixty one patients undergoing LAA AtriClip application at three months post-operative using computerized tomography angiography (CTA), or TEE when contrast agents were contraindicated. All patients with confirmed intra-operative complete LAA occlusion had no flow at follow up. Out of three patients that had incomplete LAA exclusion seen intra-operatively, two patients had no flow into the LAA at three months, and only one patient had persistent flow. Emmert et al[7] performed a CTA on thirty two patients at one, two and three years follow up.

All patients had a completely occluded LAA, with no residual flow or stump more than one centimeter. There were no left atrial thrombi noted. Kurfirst et al[23] followed up 101 patients undergoing AtriClip application (the majority through a thoracoscopic approach) for a mean of eighteen months. Patients underwent either a CTA or a TEE and all the patients showed stable clips without residual flow or significant stump, and no left atrial thrombus. Based on the above evidence, we do not obtain follow up imaging when intra-operative TEE confirms satisfactory occlusion of the LAA at its base.

Disclosure

Dr Ramlawi is a consultant for Sorin, Medtronic, and Atricure

No sources of funding for this work

Conclusion

Exclusion of the LAA is a concept with growing evidence and increasing adoption. The AtriClip is the most commonly used epicardial device with one hundred thousand units sold worldwide before May 2017. Application process is simple, short and safe with minimal adverse events related to the device itself. Potential adverse events are minor and with rare clinical consequences. The evidence is sufficient to justify no routing follow up imaging if intraoperative placement is satisfactory. Evidence regarding anticoagulation management postoperative is less robust and extrapolated from data utilizing other LAA exclusion devices. Further well-powered long-term evidence is needed to confidently guide anticoagulation management in patients receiving the AtriClip but have no contraindications to anticoagulation.

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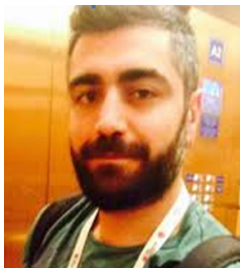

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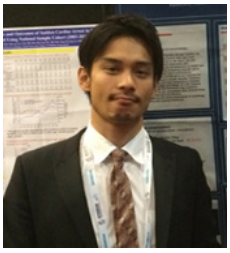
Emeritus Professor of Cardiology, Aristotle University, Thessaloniki Greece, Director of Cardiac Catheterization Laboratory, AHEPA Hospital (1983-2006), Director of Department of Cardiology, AHEPA Hospital (1996-2006).



Dr. Kyoichiro Yazaki, MD

Affiliation: Ogikubo Hospital, Department of Cardiology,Cardiovascular Center, Tokyo, Japan.
Clinical research of electrophysiology, catheter ablation, and Device therapy are of my interests

Dr. Ashraf Alqaqa, MD, FACC

Dr. Farhad Farokhi received his medical degree from the Kansas City University of Medicine & Biosciences. He finished his internal medicine residency at the Grandview Hospital in Dayton, OH. He currently holds board certification in Cardiovascular Disease and Clinical Cardiac Electrophysiology from the American Osteopathic Board of Internal Medicine, Internal Medicine from the American Osteopathic Board of Internal Medicine, and Echocardiography from the American Society of Echocardiography. Dr. Farokhi's clinical interests include Atrial Fibrillation, Catheter Ablation, Ventricular Arrhythmia, and Left Atrial Appendage Closure (LARIAT).

Dr. Hickey

Dr. Hickey is an Associate Professor of Nursing at Columbia University Medical Center and holds a joint appointment in the Division of Cardiology (electrophysiology) as both a family and adult nurse practitioner. Her interdisciplinary research, clinical practice and scholarship is focused in the areas of cardiac genetics, the clinical care of those with chronic cardiac conditions and arrhythmias, and the prevention of sudden cardiac death. Her current grant awards include a R01 from the National Institute of Nursing Research (iHEART) focusing on arrhythmia telehealth monitoring in those with atrial fibrillation, her newly awarded (multiple-PI) P30 award with Dr. Suzanne Bakken is focusing on improving symptom self-management for underserved populations with or at risk for chronic health conditions.

Dr. Andres Enriquez, MD

Dr. Enriquez received his medical degree from the Universidad de Concepcion, in Chile. He specialized in Internal Medicine, Cardiology and Cardiac Electrophysiology at Pontificia Universidad Catolica de Chile in Santiago.

Between 2013 and 2015 he moved to Canada to continue his electrophysiology training at Queen's University, Kingston, Ontario.

He currently resides in Philadelphia with her wife Karen and is a second-year fellow in the Advanced Clinical Electrophysiology program at the Hospital of the University of Pennsylvania, under the mentorship of Dr. Francis Marchlinski.

Dr. Enriquez interests include electrocardiology, clinical electorphysiology catheter ablation and cardiac devices.

Dr. Ryan Dean White. MD

Dr. Ryan Dean White, MD, medical degree from the University of Missouri and currently training in internal medicine at Indiana University School of Medicine in Indianapolis, Indiana.