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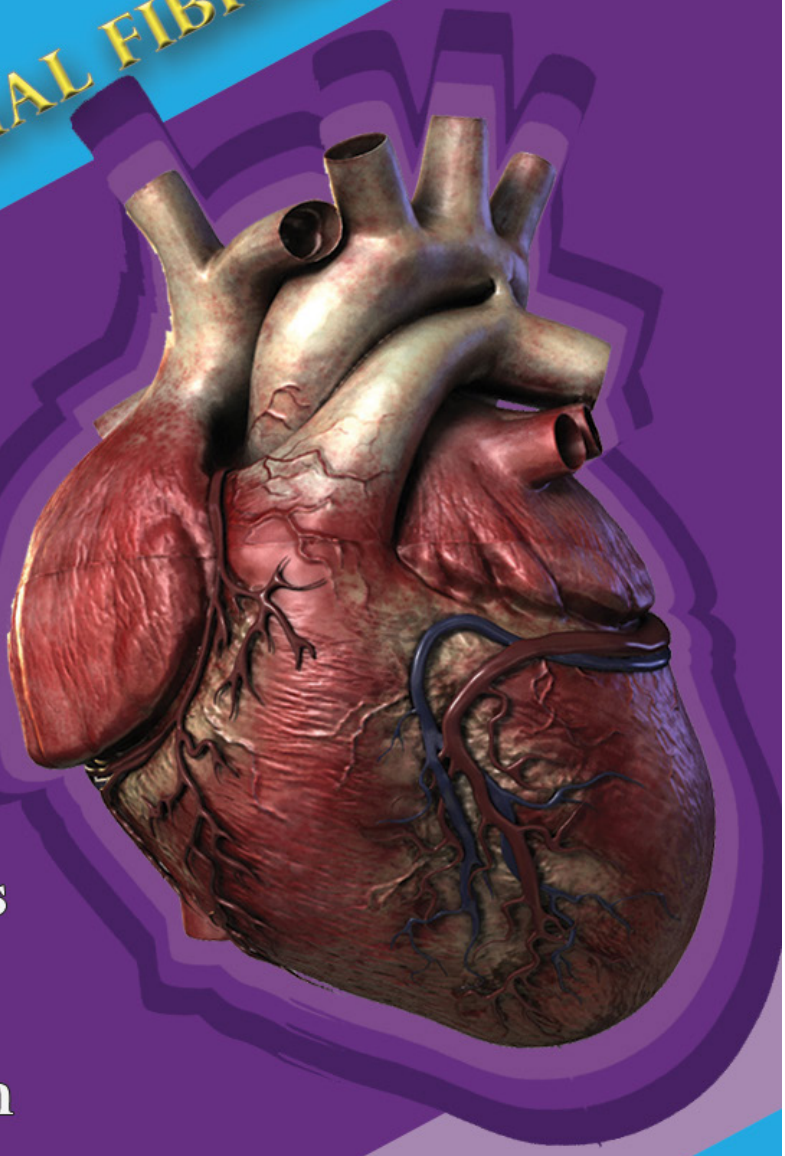

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Dr. Pugazhendhi Vijayaraman,
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Contents

Oct-Nov 2016
Volume 9, Issue 3

JAFIB® Journal of Atrial Fibrillation

CASE REPORT:

FEATURED REVIEW:

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Editorial

Journal of Atrial Fibrillation

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Happy Holidays!!!

Dear Colleagues

Welcome to the Journal of Atrial Fibrillation. Hope you had a great last quarter. We are sure ever one is busy with wrapping up the clinical year and preparing for the Holidays. As you are aware the journal has been approved for PUBMED listing a few months ago. The technical team has been working hard to get all the previous issues to be available online very soon here. Each and every one of the papers from the past will be part of the online PUBMED listing.

Several important scientific meetings have happened this quarter. Congratulations to Dr. Young Hoon Kim and his colleagues from the far east on organizing a terrific annual Asia Pacific Heart Rhythm Society (APHRS) meeting in Seoul, Korea in October. There were a wide array of topics in electrophysiology that covered by the best presenters around the world. While Dr. Vivek Reddy and colleagues finished their annual VT symposium in New York City. It is incredible to see the significant advances we have made in the VT space over the last decade. This upcoming weekend, the annual Atrial Fibrillation & Ventricular Tachycardia Symposium in Chicago will provide another unique learning experience to the fellows and EP colleagues from around the country.

In this issue of the Journal we have several important original articles and interesting case reports for your perusal. It covers a wide array of topics from the use of edoxaban in cardiac surgery patients to vacuum suction of clots on the pacemaker leads during lead extractions. Schaerf etal published their early experience in AngioVac suction of the thrombus or vegetation attached to the leads. This looks like a new approach to preventing massive embolization of unwanted materials into the pulmonary circulation. Sucu and colleagues from Turkey showed that coronary slow flow can indeed cause significant repolarization abnormalities which in turn could be associated with ventricular arrhythmias and sudden cardiac death syndromes. There are several nice review articles including the one by Aizawa on Brugada Syndrome.

On behalf of the entire team from the Journal we wish you happy Holidays. Stay warm and safe.

Sincerely

Dhanunjaya (DJ)Lakkireddy
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Internet Survey: Health Screening in Sports

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Abstract

While cardiovascular screening protocols exist, they have been focused on teenaged and college aged athletes versus adult athletes. To assess community awareness of health screening as related to adult athletes, we have created an internet questionnaire (QN). The survey was posted through social media (e.g. Facebook, Reddit, Flotrack and Active), for 11 months, that queried sports history, medical history, and symptoms while playing sports. A total of 3,750 respondents (R) answered the questionnaire, 2,776 male and 974 female. Age range: 18-83 yrs, avg: 33.7±11.22 yrs, median: 31 yrs. Seventy four per cent of R (2,775/3,750) reported having at least one of the following symptoms while playing sports: dizziness, blacking/passing out, racing heartbeat, or chest pain, and 13.5% (505/3,750) of R reported two or more. 62.3% (1,730/2,775) did not recall having symptoms. This underreporting was a result of "no one asking" 49.5% (857/1,730); "not answering after being asked" 28.2% (488/1,730), and "not telling the truth" 22.2% (384/1,730). Of interest, 97.1% (3,642/3,750) want a screening QN; 95.8% (3,592/3,750) want pre-screening by an MD. Prior to sports, only 22.9% (857/3,750) were required to answer a QN vs 38.0% (1,424/3,750) had a physical exam (PE); 14.9% (560/3,750) of individuals had both PE and QN. We conclude that adult participants in sports commonly experience symptoms but do not report them. Nearly all respondents favor participating in a screening questionnaire that would assess for cardiovascular problems.

Introduction

Screening protocols have been used to identify cardiovascular disorders in adult participants of sporting events, but these protocols are not uniformly administered in the various sports competitions such as marathons, triathlons, cycling races or endurance events. Atrial fibrillation (AF) is the most common cardiac arrhythmia.[1]

This internet survey aims to reach those adults who participate in any athletic activity. We would like to elicit responses about symptoms of cardiovascular disease among adult athletes.

While atrial fibrillation is the most common cardiac arrhythmia, the incidence of AF in adult athletes and its associated risk factors are not well studied.[2] In the general population, AF is approximately 0.5% in men less than age 40, and increases to 8% in men over age 80 years. Cardiac and non cardiac conditions such as age, structural heart disease, diabetes, hypertension and hyperthyroidism have been implicated as risk factors in the development of AF. In patients younger than 60 years, routine evaluation has revealed no specific risk factors.[2]

One study showed that atrial fibrillation caused long-lasting palpitations in young elite athletes.[3] Those with atrial fibrillation at a younger age had lower rates of mild hypertension compared to those who were not engaged in sports activity.

Studies have indicated the elevated risk of atrial fibrillation exists in adult athletes who participate in an intense exercise regimen such as marathons or more than 5-7 exercise sessions per week.[3] Thus, recreational athletes may have an enhanced risk of developing cardiovascular problems via weekend sports competitions. This group of athletes have not been well studied.

Electrophysiological testing has been used as a method to identify risk of atrial fibrillation for athletes.[4] The American Heart Association (AHA) recommends preparticipation screenings for athletes prior to athletic engagement. The AHA suggests that incorporating screening methods would identify risk for cardiovascular consequences, such as sudden cardiac death, nonfatal myocardial infarction, stroke, angina, acute coronary syndromes or heart failure.[5]

The purpose of our study was to assess the awareness of cardiac symptoms and symptom reporting in recreational and amateur sports participants via an internet survey. We chose the internet for its anonymity, its demographics and the possibility of reaching a large

Key Words:
Sudden Cardiac Death, Social Media, Internet Survey, Athletes, High School Athletes, Recreational Athletes, Health Awareness, Health Screening.

Disclosures:
None.

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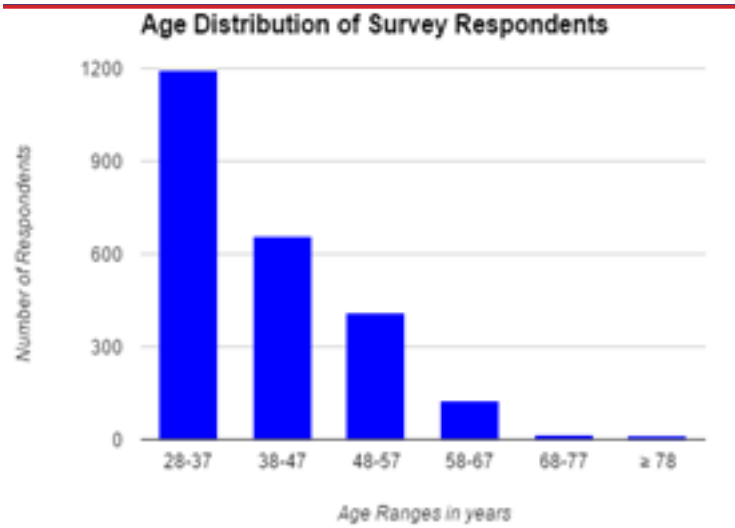

Figure 1: Age distribution of respondents to the survey

number of respondents. It may be important to identify the presence of cardiac conditions and arrhythmias in adult athletes through screening prior to athletic participation. Therefore, our aim was to evaluate the existence of cardiovascular symptoms in the general population through a social media survey.

Material and Methods

A 17-question survey was designed on Google Survey and distributed on various social media outlets and sports forums, such as Facebook, Reddit, Flotrak, and Active. Questions were designed to evaluate demographic factors, athletic history, and risk factors for

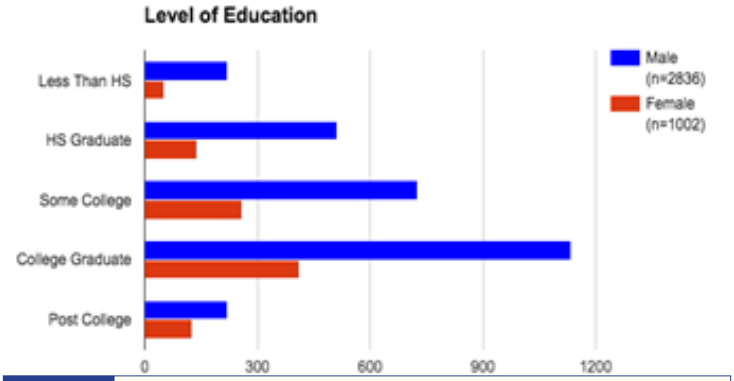

Figure 2: Highest level of education

cardiovascular disease (Table 1). The survey was reposted on these forums every day over the course of four months from October 24, 2014 to February 2015. Participants were required to be at least 18 years old, and informed consent was necessary in order to proceed with the survey.

Results

A total of 3,839 respondents answered the questionnaire, 2,837 male and 1002 female. 43.9% (1685/3839) of the population was under the age of 30. Respondents ranged from ages 18 to 83 years old (mean: 33.7±11.22 yrs), (Fig 1). The majority of respondents had college and post-college education (Fig 2). For country of origin/ethnicity: United States, United Kingdom, India and Europe.

With respect to the level of athletic participation (Qn 5), the majority played in high school and college, (Fig 3). Most played sports for 2-5 years (Qn 6), (Fig 4). Most participated in years of 2001-2010 (Qn 7). Thus, most of the respondents participated in sports during the last decade (Fig 5).

Question 8 asks if the respondents had the following symptoms while participating in sports (Fig 6,7): 72.2% of the respondents (2,775/3,839) reported having at least one of the following symptoms while playing sports: dizziness, blacking/passing out, racing heartbeat, or chest pain, and 13.2% (505/3,839) of respondents reported two or more symptoms.

Question 10 asks "Did you ever have symptoms while playing sports and not tell anyone? "Yes"responses totaled 1730; "No" responses totalled 1052. " Not applicable" totalled 726 responses.

Yet of symptomatic respondents who answered this question (n=1730) and of the 2775 who had one of symptoms in Qn 8 (n=2775): 62.3% (1,730/2,775) did not report them. This underreporting noted in the answers of question 10 was a result of "no one asking" 49.5%

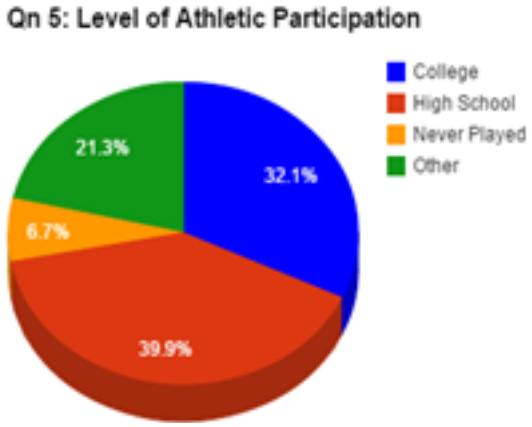

Figure 3: Level of most recent sports participation and competition

(857/1,730); "not answering after being asked" 28.2% (488/1,730), and "not telling the truth" 22.2% (384/1,730), (Fig 8).

For question 11: "Were you required to have a physical examination when you participated in sports," the majority of the respondents were not screened at all (n=2139) (Fig 9). 246 respondents never played sports but answered this Internet Survey. Of note, 469 respondents were screened by their own doctor, 384 respondents were screened by the team doctor, 365 respondents were screened by the coach, 247 respondents were screened by the team athletic trainer (Fig 10).

Regarding question 13:"Have you ever been told that you have

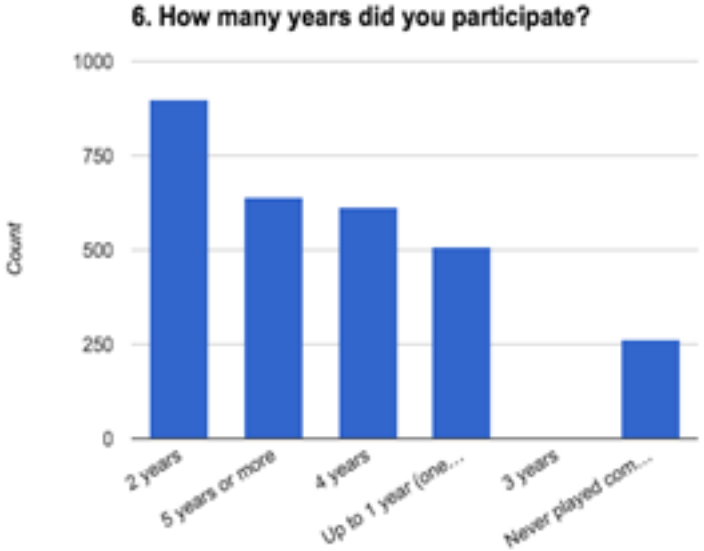

Figure 4: Number of years participating in a sport

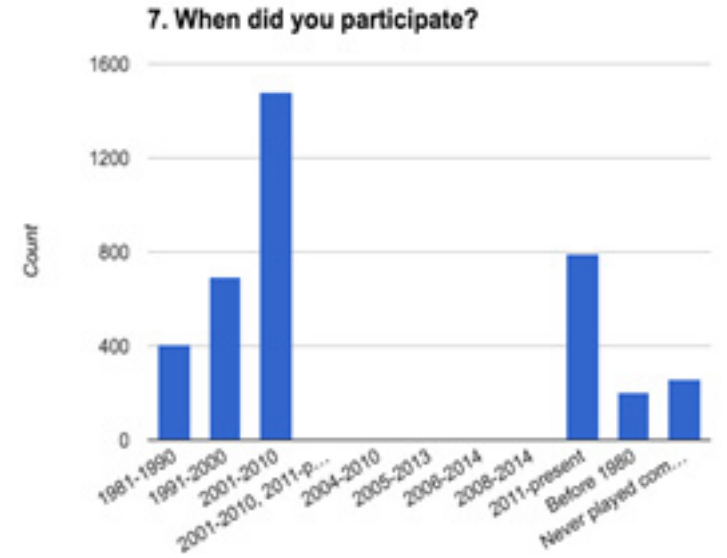

Figure 5: Sports participation by decade

an irregular heartbeat, a heart murmur, a heart condition, or a combination of the above?" The majority were never told of these conditions (Fig 11).

Question 14 deals with screening questionnaires: "Prior to sports participation, were you required to fill out a health screening questionnaire? 39.8% (1453/3839) were required to have a physical exam; 22.9% (880/3839)were required to complete a health screening questionnaire; 14.9% (573/3839) were required to have completed both screening questionnaire and physical exam.

Figure 6: Reported symptoms experienced by respondents while playing sports

For question 15: "Should health questionnaires be used before athletic competitions:" 95.0% (3,642/3,839) prefer screening questionnaires prior to sports participation. For question 16: "Should physical exam by a medical be required before athletic competition?" 94%% (3,592/3,839) would like pre-screening by an medical doctor. The responses to the last two questions suggests that there is strong public interest regarding preparticipation screening and examination for athletes (Fig 12).

Discussion

In our study population, the majority of individuals who experienced symptoms did not report them. While patient reliability is to be considered in these screening questionnaires, two-thirds of symptomatic respondents did not report their symptoms, and half did not report because "no one asked." These individuals with symptoms may be experiencing denial of the importance of these symptoms. The survey findings may demonstrate that individuals may not want to discontinue athletic participation despite having experienced symptoms. A known diagnosis may hinder an individual's enjoyment of sports as a hobby or recreational sports activities. A longitudinal study investigating arrhythmias in Olympic and World champion athletes found that temporary discontinuation of athletic activity could potentially eliminate atrial fibrillation.[4]

Intense exercise is linked to cardiovascular changes that may contribute to the development of AF.[3,6,7] Intense sports involvement contributes to vagal tone and increased risk of atrial fibrillation. Competitive athletes show left atrial enlargement due to left ventricular cavity enlargement.[6] Another study demonstrated that

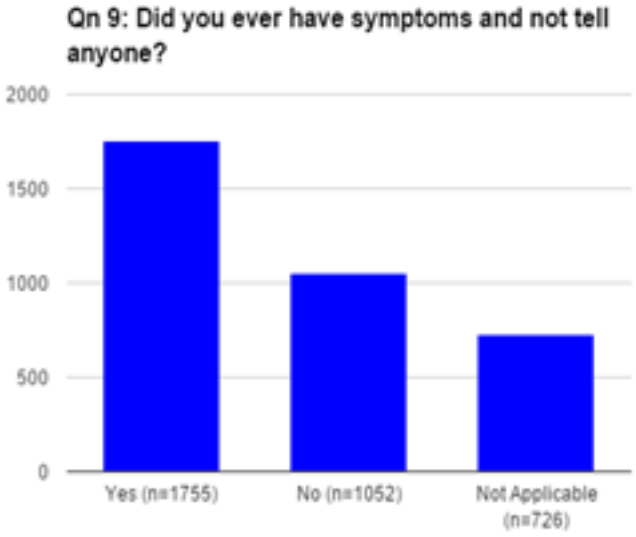

Figure 7: Reporting the presence of symptoms

those who participated in frequent exercise had greater ventricular mass, as well as larger atrial and ventricular dimensions.[7] These studies support that intense exercise enhances the risk of AF.[3,6,7]

For individuals over age 50 and participate in rigorous activity, the risk of developing AF decreases. People who exercised five to seven times per week increased their AF risk by 20%, by 53% if they jogged, compared to individuals who were sedentary. Recreational athletes

Figure 8: Combined data from Qn 9, 10 suggests that public response was not truth-based and/or their athletic organizers/staff never asked the appropriate questions when the respondents were asked about their symptoms

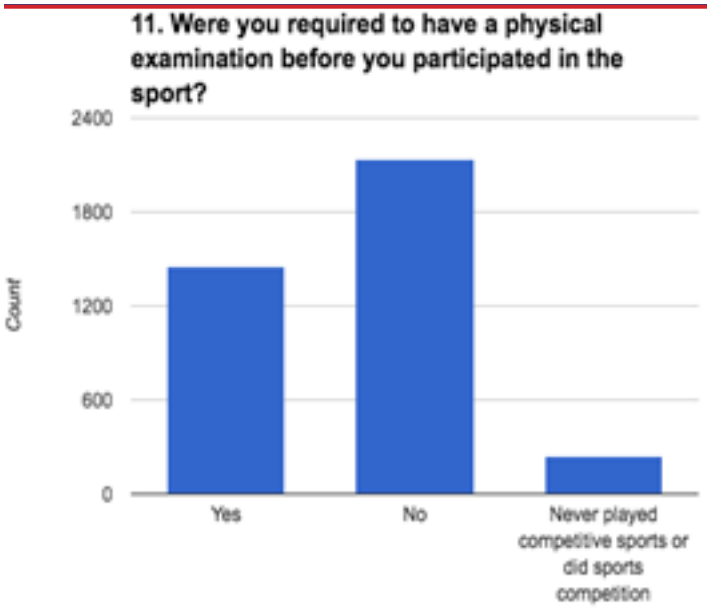

Figure 9: Physical examination requirement prior to sports participation

have differing levels of training and stressors on their cardiovascular systems. The type of exercise has an impact on risk of developing AF.[3] Engagement in dynamic exercise leads to enhanced dimensions of heart cavities, whereas static exercise results in hypertrophy.[7] This suggests that adult athletes are at risk for developing AF and all adults who participate in regular sports competitions might benefit from cardiovascular screenings according to the AHA guidelines.

Limitations in our study are that this is an internet based study and the responses are skewed towards younger adults, male preponderance. Thus, it may be difficult to generalize about the entire adult athletic community which would include college athletes, professional athletes, occasional athletes, adult sports league participants, and adult competitors who are non-professional athletes and older/senior athletes Not all of these adult athletes would be found in the internet blog and forum sites where we posted the questionnaire. Due to the demographics of the forums where the survey was distributed, the study population may have been particularly interested in sports and health. This group's enthusiasm for preparticipation screening and physical exams may be a reflection of the self-selected group of people who like to participate in sports and athletic blogs. Respondents also needed a computer and access to internet to complete the survey, suggesting a higher education and socioeconomic status.

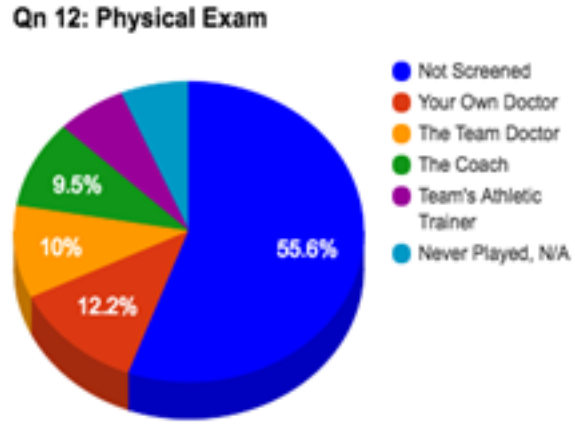

Figure 10: Whether or not the individual was screened by physical exam. If screened, who did the screening

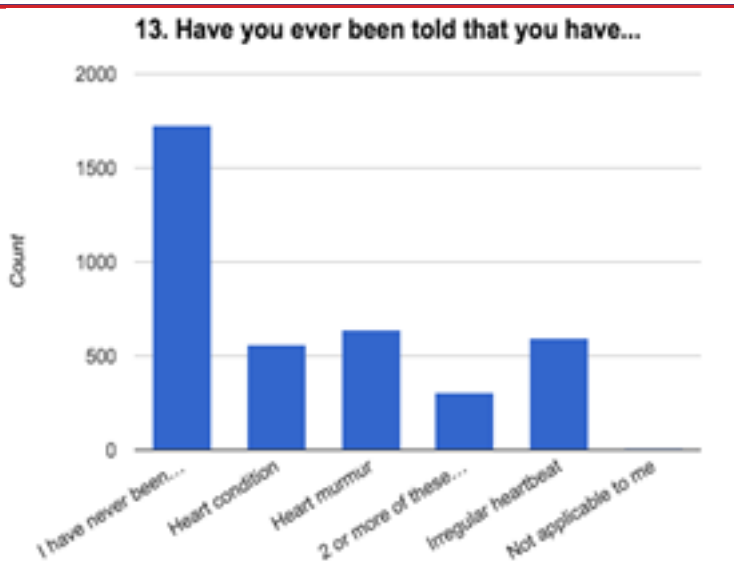

Figure 11: Reporting of symptoms

While this survey was skewed towards the young and educated demographic with access to the internet, these findings could guide us towards further discussion about health screening in sports among cardiologists and primary care physicians. In our study we identified a high proportion of reported symptoms, including racing heartbeat, unconsciousness, dizziness, and chest pain. A majority of those who exhibited cardiac-like symptoms, more than half, did not report them to their MDs, RNs, coaches or trainers because "no one asked." The results from our study suggest that patients could benefit from being informed on the impact of frequent exercise on cardiovascular disease.

Conclusions

In our study, the respondents reported the presence of cardiac symptoms related to and separate from athletic participation. Despite the screening standards provided by the American Heart Association, pre-screening is not performed consistently for high school and recreational athletes. The responses from our Internet survey show that more public education is needed since there are no formal screening protocols that are uniformly applied to high school and recreational athletes. There is almost unanimous desire among the respondents for screening and physical examinations prior to athletic events. As a first step, advocating for greater awareness of the American Heart Association guidelines among all physicians would help in the effort of public education for Sudden Cardiac Death.

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Safety of The Direct Oral Anticoagulant Edoxaban for Atrial Fibrillation After Cardiac Surgery: Pilot Study

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Abstract

Direct oral anticoagulants have recently been recommended for non-valvular atrial fibrillation, but have rarely been studied in the field of cardiac surgery. We prospectively investigated the safety of edoxaban, a novel oral anticoagulant, for use in cardiac surgery patients with postoperative atrial fibrillation (POAF), which is the most common complication of cardiac surgery and can lead to stroke.

The subjects were adult cardiac surgery patients with POAF who received oral edoxaban for 2 months in an open-label pilot study. The primary endpoint was cerebrovascular/bleeding events up to 2 months, while the secondary endpoints were hemoglobin, prothrombin time, and activated partial thromboplastin time.

There were no cerebrovascular or bleeding events during edoxaban treatment and the test drug was not discontinued by any patient. There was no macroscopic hematuria and hemoglobin did not decrease, being significantly higher than the baseline level after 2 months. The prothrombin time was significantly prolonged from 1 week to 2 months and the activated partial thromboplastin time was significantly prolonged from 1 day to 2 months. Echocardiography detected pericardial effusion in 1 patient, but hemoglobin did not decrease and the effusion improved with diuretic therapy.

In conclusion, despite the limited sample size of this pilot study, it was demonstrated that edoxaban does not induce bleeding in patients with POAF after cardiac surgery, suggesting that it is safe to perform a large-scale efficacy study of edoxaban as anticoagulant therapy for POAF.

Introduction

Direct oral anticoagulants (DOAC) have recently been recommended for patients with non-valvular atrial fibrillation by cardiovascular guidelines.[8,9] Large-scale studies have demonstrated comparable or better efficacy of DOAC for preventing stroke with significantly less intracranial bleeding compared to conventional warfarin therapy, indicating that these agents display favorable safety and efficacy.[4,6,7,10] However, DOAC have rarely been investigated in the cardiac surgery field.

Postoperative atrial fibrillation (POAF) is the most common complication of cardiac surgery and occurs in 16-85% of patients. Many studies of pharmacological treatment to prevent POAF or restore sinus rhythm have been conducted and we have also investigated this issue.[11,12,14,15] The most important consequence of POAF is stroke, which significantly affects the prognosis. At our hospital, a total of 761 patients underwent isolated coronary artery bypass grafting (CABG), among whom POAF occurred in 24% and stroke was observed in 1.4%. All of our patients who developed postoperative stroke had POAF. Hence, it is important to start anticoagulant therapy in the early phase of POAF.[13] At our hospital, anticoagulant therapy with heparin and warfarin is initiated as soon as possible after the onset of POAF, but 1.4% of patients still developed stroke. Therefore, a more effective anticoagulant therapy would be desirable.

Since bleeding is an issue after cardiac surgery, we conducted a prospective pilot study to investigate the safety of initiating DOAC therapy immediately after the onset of POAF.

Key Words:
Edoxaban, Novel Oral Anticoagulant, Postoperative Atrial Fibrillation, Direct Oral Anticoagulation.

Disclosures:
Akira Sezai has received lecture fees from Daiichi Sankyo Company. The other authors have no conflicts of interest associated with this study.

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Methods

Study Protocol

The subjects were adult patients who developed POAF following cardiac surgery (Table 1). POAF was defined as AF that occurred after surgery and did not improve for more than 12 hours despite pharmacotherapy.

Exclusion criteria were as follows:

1. Patients with artificial heart valve(s) or rheumatic mitral stenosis because NOAC are indicated for non-valvular atrial fibrillation.

Table 1: Patients characteristics

Number	15
Age (y.o)	72.7±7.6 (58~84)
Gender (male:female)	10:5
Body weight (kg)	
>60kg	6
≤60kg	9
Main disease	
Ischemic heart disease	5
Valve disease	3
Aortic disease	7
Surgical procedure	
Isolated CABG	5
MAP	2
MAP+TAP+Maze	1
Total arch replacement	4
Ascending aorta replacement	1
Total arch replacement+CABG	2
Risk factors	
Diabetes mellitus	1
Hypertension	12
Hyperlipidemia	6
Smoking	9
Obesity	1
Cerebrovascular disease	1
Chronic heart failure	6
Chronic kidney disease (CRCL<60mL/min)	9
CRCL (mL/min)	
50<CRCL	7
15≤CRCL≤50	8
$CHADS_2$	1.9±0.8 (1~3)
CHA_2DS_2-VAS	3.6±1.5 (1~6)

CABG: coronary artery bypass grafting, MAP: mitral valve annuloplasty, TAP: tricuspid valve annuloplasty, CRCL: Creatinine clearance

2. Blood loss from the surgical drain ≥10 mL/hour.
3. Unconscious patients.
4. Inability to take oral medication.
5. Infectious endocarditis.
6. Creatinine clearance (CRCL) <15 mL/min.
7. Hepatic disease accompanied by abnormal coagulation.
8. A history of bleeding events such as gastrointestinal bleeding.
9. Patients who were unsuitable for other reasons as judged by the attending physician.

Patients were assigned to oral treatment with edoxaban (Dai-chi Sankyo Co., Ltd., Tokyo, Japan) at a dose of 60 mg/day for a body weight > 60 kg or 30 mg/day for a body weight ≤60 kg. If the CRCL at baseline was ≤50 mL/min, the dose was also reduced to 30 mg/day. Treatment was continued for 2 months.

This pilot study to investigate efficacy was conducted in an open-label manner. This study was approved by the Institutional Review Board of Nihon University Itabashi Hospital, the details of the study were explained to the subjects, and informed consent was obtained from each patient. The study was registered with the University Hospital Medical Information Network (study ID: UMIN000021138).

Endpoints: The primary endpoints were cerebrovascular events (stroke, cerebral hemorrhage, etc.) and bleeding events (major: significant bleeding events, minor: clinically significant event albeit not major by Month 2 of the study.

The secondary endpoints were as follows: hemoglobin, prothrombin time (PT), and activated partial thromboplastin time (APTT) at baseline, Day 1, Week 1, and Months 1 and 2; urinary occult blood at baseline, Week 2, and Months 1 and 2; and the presence or absence of pericardial effusion on echocardiography in Week 1. Criteria for discontinuation of treatment included the onset of bleeding events and allergy to the study medication.

Statistical Analysis

Results were expressed as the mean ± standard error. For time-course analysis, repeated measures analysis of variance (ANOVA) was used with Fisher's protected least squares difference test. In all analyses, $p<0.05$ was considered statistically significant.

Results

None of the patients died after surgery or experienced complications. POAF was detected at an average of 4.8±2.8 days (2-10 days) postoperatively. Sinus rhythm was restored in all patients by discharge.

Edoxaban was administered at a dose of 30 mg and 60 mg to 13 patients and 2 patients, respectively (Table 2). Treatment was initiated in the intensive care unit for 6 patients and on the ward for 9 patients. The surgical drain was still in place when treatment was initiated in 11 patients, but there was no increase of bleeding from the drain and it was removed on the next day or up to 2 days later. As antiplatelet therapy, aspirin was used in 9 patients and aspirin + prasugrel was given to 1 patient.

Primary Endpoints: None of the patients experienced cerebrovascular events or major or minor bleeding events by Month 2. In addition, none of the patients discontinued treatment with edoxaban.

Secondary Endpoints: Hemoglobin (Figure 1): Baseline hemoglobin was 11.4±1.4 g/dL. It did not decline after initiation of treatment and instead was significantly higher by Month 2 compared with baseline ($p=0.03$).

PT and APTT (Figure 2): PT was normal at baseline (12.7±0.8 seconds) and remained within the normal range after starting treatment. Although there was no significant difference of PT between Day 1 and baseline ($p=0.805$), it was significantly prolonged during the period from Week1 to Month 2 (Week 1: $p=0.007$, Month 1: $p=0.016$, Month 2: $p=0.011$). APTT was normal at baseline (30.4±2.4 seconds), but it was significantly prolonged from Day1 to Month 2 versus baseline (Day 1: $p=0.025$, Week 1: $p=0.001$, 1M: $p=0.012$, Month 2: $p=0.021$).

Urinary occult blood: At baseline, occult blood was 2+ in 1 patient and in 1+ in 3 patients. After the start of treatment, occult blood became negative in those patients. Among the 11 patients who had negative occult blood at baseline, 2 patients became 2+ after starting treatment. However, there was no decrease of hemoglobin and macroscopic hematuria was not observed, so treatment could be continued.

Table 2: Dose of edoxaban and the number of patients

Number	Body weight>60kg	Body weight≤60kg
CRCL>50 mL/min	2 (60mg)	5 (30mg)
15 mL/min ≤CRCL≤50 mL/min	4 (30mg)	4 (30mg)

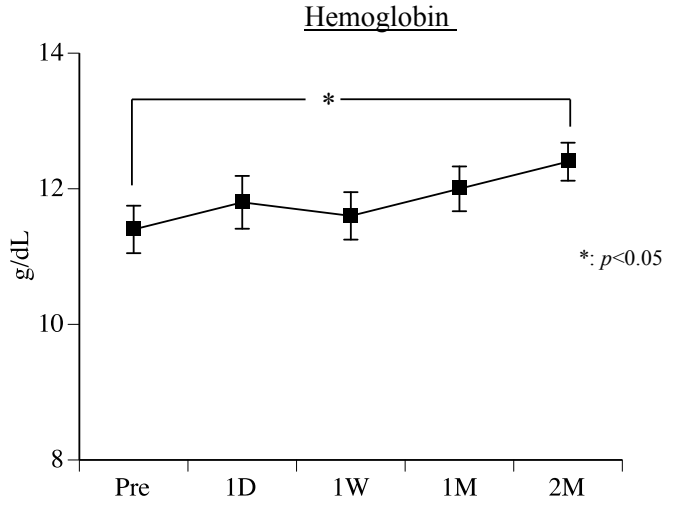
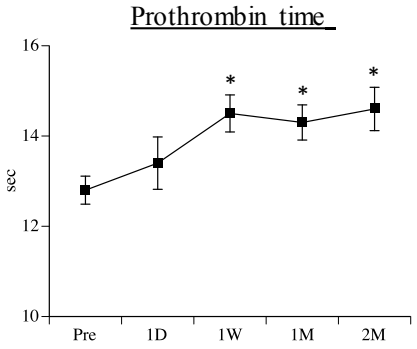


Figure 1: Change of hemoglobin

Pericardial effusion: A pericardial effusion was detected by echocardiography in 1 patient. However, it was only 8 to 11 mm and cardiac function was not affected. Moreover, there was no decrease of hemoglobin and it was considered that the possibility of bleeding was low. Treatment with a diuretic was performed and improvement was observed in Month 2.

Discussion

This pilot study demonstrated that anticoagulant therapy with edoxaban for POAF following cardiac surgery was not associated with bleeding. The most important consideration when investigating anticoagulant therapy is safety, and these findings suggested that an efficacy study of DOAC therapy after cardiac surgery could be safely initiated. It has been reported that dabigatran and rivaroxaban prolong APTT and PT, respectively, while edoxaban prolongs both



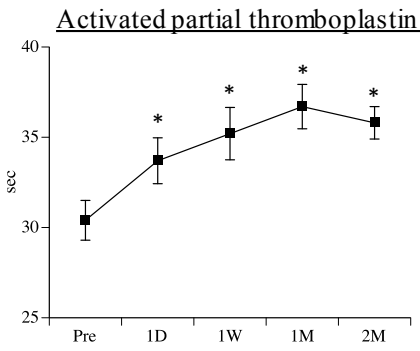


Figure 2: Changes of the prothrombin time (PT) and the activated partial thromboplastin time (APTT)

parameters. These parameters are considered to be related to the blood drug concentration and may be employed as efficacy markers. However, use of different reagents for measurement may result in variation of PT and APTT, and there are also no clear-cut criteria for clinically significant elevation of each parameter.[1] In this study, PT and APTT were prolonged during treatment with edoxaban, but excessive prolongation was not observed in any of the subjects even though they were treated during the acute postoperative period when the coagulation-fibrinolytic system is altered by the effects of surgery.

Anticoagulant therapy based on warfarin is recommended for POAF following cardiac surgery, irrespective of whether heparin bridging is performed.[5] However, it takes several days before warfarin reaches the therapeutic range. According to the results of a meta-analysis and several large-scale studies, heparin bridging is associated with a 3- to 5-fold higher incidence of bleeding compared to non-use of heparin bridging.[16,17] While anticoagulant therapy with DOAC has recently been recommended for the management of non-valvular atrial fibrillation,[8,9] there is little information available about the use of DOAC following cardiac surgery. The 2014 ESC/EACTS Guideline states that 4 weeks of treatment with heparin or DOAC is recommended for POAF that persists for 48 hours or longer, although there is no clinical evidence.[5] However, the 2014 Guideline uses the 2012 Guideline as a reference, but there is no description of DOAC therapy for POAF following heart surgery in the earlier guideline.[3] The only clinical study that we could find about DOAC therapy for POAF following cardiac surgery was a retrospective investigation performed by Anderson et al. in patients who developed POAF following isolated CABG. Warfarin (with low molecular weight heparin bridging in 27 patients) was used to treat 45 patients while DOAC (apixaban in 21 patients, dabigatran in 1 patient, and rivaroxaban in 5 patients) was used for 27 patients. There was no stroke in both groups and in hospital bleeding was not different between the two groups. However, there was no delayed major bleeding after discharge in the DOAC group, while it affected 2 patients in the warfarin group. Also, the time to reach the therapeutic range was significantly longer in the warfarin group. While drug costs were significantly higher in the DOAC group, the total anticoagulation cost (including INR tests for 30 days) was significantly higher in the warfarin group. Anderson et al. concluded that DOAC treatment provided more rapid anticoagulation and was cost-effective.[2]

Concerns with warfarin therapy include:

1. A longer time until therapeutic anticoagulation.
2. An increased incidence of bleeding if used concomitantly with heparin.
3. The effect of various foods.

Anticoagulant therapy using DOAC can address these issues related to warfarin. The present study also suggested that the risk of bleeding was not increased even when edoxaban was used in the early postoperative period.

In the future, a larger study will performed to assess the efficacy of edoxaban and identify any potential issues.

Limitations

This was a pilot study and the number of patients enrolled was too small. In addition, comparison versus warfarin was not performed. However, a future large-scale study is planned to address these limitations. In this study, CRCL >95 mL/min was not included into

the exclusion criteria. Evidence has not been obtained for Edoxaban in nonvalvular atrial fibrillation patients with CRCL >95 mL/min. Although patients at CRCL >95 mL/min were not enrolled into this study, we would like to decide if we continue to exclude CRCL >95 mL/min or include it. The duration of treatment with edoxaban was 2 months in this study. All patients achieved sinus rhythm at discharge. We will continue to study if 2 months treatment period was appropriate or 1 month is sufficient or not.

Conclusions

This pilot study demonstrated that use of edoxaban for anticoagulant therapy in patients with POAF after cardiac surgery was not likely to be associated with postoperative bleeding complications. Because the important safety concern for a large-scale study has been addressed, we are now planning an efficacy study of DOAC therapy for patients with POAF after cardiac surgery.

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Percutaneous Vacuum-Assisted Thrombectomy Device Used for Removal of Large Vegetations on Infected Pacemaker and Defibrillator Leads as an Adjunct to Lead Extraction

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Abstract

This case series reports our early experience with a minimally invasive percutaneous method of safely removing large vegetations during lead extraction in septic cardiac implantable electronic devices (CIED). Debate exists concerning the management of vegetations involving these devices. Lead extraction is mandated for infections, but vegetations may embolize, causing complications. Surgical debridement is recommended; alternatives include cardiopulmonary bypass, minimally invasive thoracotomy, or transatrial approaches. The AngioVac device allows percutaneous right heart bypass and suction removal of vegetations under echocardiographic and fluoroscopic guidance. This case series describes our first 20 patients, all critically ill with persistent sepsis and vegetations despite long-term antibiotics. This series includes patients who would not have been eligible for alternative procedures due to contraindications and highlights the potential role of this new technology.

Introduction

Implantation of CIED, including implantable cardioverter defibrillators (ICDs), has increased in recent years due to results of large clinical trials and a corresponding expansion of indications for use. Historically, infection rates have been reported as ranging from 0.8% to 19.9% of patients.[1] Mortality rates for infected CIEDs vary in the published literature, with highest rates occurring among patients treated with antibiotic alone (31% to 66%) and as low as 13% to 33% with antibiotics and lead removal.[2] In an 8 year review exploring increased utilization of these devices and resulting infections published in 2006, Voight and colleagues found a there was a 49% rise in the number of new cardiac rhythm management (CRM) devices over the study period. In the same period, the number of hospitalizations with CRM device infection increased 3.1-fold, the increase in infections has not been proportional to the increase in device utilization.[3] The authors also found a CRM device infection conferred a significantly increased risk of in-hospital death (odds ratio [OR] 2.41, $p < 0.001$).

The Heart Rhythm Society consensus guidelines recommend these patients receive antibiotic therapy and removal of the infected hardware including generators and electrodes.[4] Historically, patients with device-related infection and vegetations over 1 cm have often been referred for surgical thoracotomy for removal of the CRM system due to the risk of septic embolization.[5] But many patients presenting with these larger vegetations may not eligible for an invasive procedure due to a myriad of factors including comorbidities, advanced age, debilitative previous surgeries; they may refuse the procedure.

This case series presents our early experience with a minimally invasive, percutaneous method facilitating removal of large vegetations (2-6 cm) during lead extraction in CIED patients with sepsis and vegetative endocarditis despite adequate antibiotic therapy.

Key Words:
Lead Extraction, Percutaneous Thrombectomy, Vegetation.

Disclosures:
None.

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Material and Methods

Device Background and Technique

The AngioVac cannula is a 22Fr stainless steel coil-reinforced venous drainage cannula designed to facilitate the removal of undesirable intravascular material via a balloon-actuated funnel-shaped tip (see Figure 1). It is indicated for the removal of fresh or soft thrombi or emboli from vessels including, but not limited to, the superior and inferior vena cavae, iliofemoral veins, and right atrium. The removal of vegetations, and by extension the size limitations of vegetation which may be targeted for removal, is not specifically mentioned in the labeling. Two central venous access points are obtained, using any combination of internal jugular (IJ) and femoral veins. The AngioVac cannula is inserted through a 26Fr sheath and advanced over a 0.035" stiff guidewire using fluoroscopic guidance; in

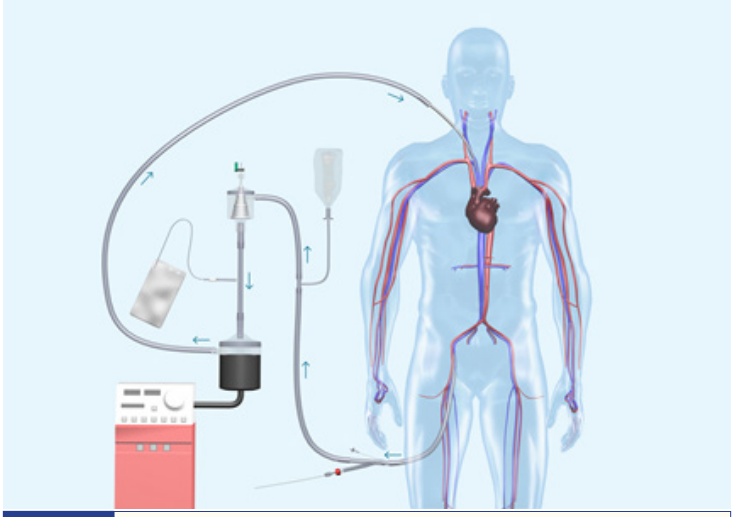

Figure 1: The AngioVac System Used with permission from AngioDynamics Inc

cases involving the right atrium, transesophageal electrocardiography (TEE) and/or intracardiac ultrasound is utilized (see Figure 2).

Before engaging the material, flow through the cannula and circuit is initiated and optimized to a rate of 3 to 5 l/min or just prior to vascular collapse. Undesirable material is engaged by the tip of the cannula, and the shed blood is circulated through the extracorporeal circuit. Undesirable material is captured in an inline filter (See Figure 3). The shed, filtered blood is then reinfused to the patient via a 16F or greater reinfusion cannula.

In most cases, the cannula is advanced to the material for direct removal of the material from the CIED leads. Once the vegetation is removed or debulked, the AngioVac cannula is used to follow the lead out of the right atrium and placed at the superior vena cava/right atrium (SVC/RA) junction during removal of the lead to help protect against any remaining material present on the ICD leads from embolizing to the lungs. Our purpose is to examine the effectiveness of the AngioVac in the removal of large vegetations on infected pacemaker and defibrillator leads.

We perform our AngioVac procedure under general anesthesia with endotracheal intubation. Two large bore intravenous cannulae, an arterial line, and foley catheter are placed. A transesophageal echocardiogram (TEE) probe is placed and the patient is prepped from chin to knees. We secure venous access from both femoral veins,

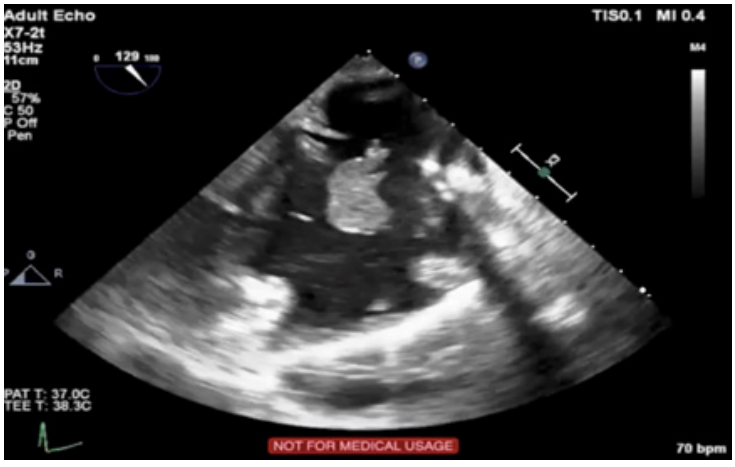

Figure 2: Pre-procedure TEE showing vegetation on ventricular lead; blood culture positive for S. Aureus despite 6 weeks of antibiotic therapy

Table 1: Patient Selection

Case	Age	Device(s)	Veg Size (cm)	Length of Stay (days)	Organism
1	82	Biventricular ICD	5	3	Staphylococcus epidermidis
2	92	DC Pacer	6	3	Methicillin-sensitive Staphylococcus aureus
3	78	DC Pacer	3	7	Streptococcus bovis
4	87	Biventricular ICD	5	8	MRSA
5	79	DC Pacer	3	3	Staphylococcus epidermidis
6	71	DC Pacer and 4 Leads	5	3	Staphylococcus epidermidis
7	89	DC ICD	2	2	Staphylococcus capitis
8	59	DC ICD	3	3	Methicillin-sensitive Staphylococcus aureus
9	82	Biventricular ICD	3	3	Enterococcus
10	77	Subcutaneous ICD	2	4	MRSA
11	86	Biventricular ICD	4	4	MRSA
12	82	DC Pacer	3	3	MRSA
13	48	DC Pacer	5	3	Strep
14	65	DC ICD	4	9	Pseudomonas Staphylococcus epidermidis
15	69	DC ICD	5	6	Coagulase-negative staphylococci
16	74	DC Pacer	2	2	Methicillin-sensitive Staphylococcus aureus
17	76	Biventricular ICD	2	2	Staphylococcus hominis
18	82	Biventricular ICD with 2 DF Leads	3	4	Streptococcus bovis
19	68	DC ICD with 2 DF Leads	3.5	3	Coagulase-negative staphylococci
20	73	Biventricular ICD	4	4	Staphylococcus epidermidis

and often have a guidewire placed in the right internal jugular vein.

Once the guidewires are in place, the patient is systemically heparinized and activated clotting time (ACT) is measured. We then place the Angiovac cannula into the right atrium under fluoroscopic guidance and TEE, and attain right heart bypass. Once right heart bypass is established, the extraction procedure is performed using either laser, mechanical, or traction alone, and vegetations are viewed under TEE. In our experience, the majority of the vegetations are moved when one or more culprit leads are freed by the extraction tools. When the procedure is completed, the heparin is reversed, and the cannulae are removed. Surgical debridement of the extraction

Figure 3: Large Vegetations visible in inline filter

sites is then completed.

Results

All 20 patients survived the procedure and resolved their infections (Table 1: Patient Selection). The ACT values measured during the procedure all were within the range of 300-40 seconds. Two intraprocedural complications occurred. In Patient No. 4, an injury to an iliac vein occurred and was repaired with a stent. In another Patient No. 14, a pseudoaneurysm of a previous mycotic femoral aneurysm required resection and vein repair. With several exceptions, length of stay for patients was the same as our usual post-operative length of stay for infected patients. Our usual protocol is to discharge only after a definitive organism has been identified from the operative cultures. Patient No. 3 stayed an additional 3 days to have an unrelated procedure. Patient 4 was a Jehovah's Witness; the patient had preoperative and postoperative hemoglobin levels of 9 and 3 mg/dl, contributing to an extended length of stay. Patient No. 15 presented with septic pulmonary emboli and required observation for antibiotics not covered by his insurance carrier for outpatient delivery. With the exception of Patient No. 15, none of the patients had positive postoperative blood cultures. Patient information was not gathered after hospital stay as part of a follow-up.

No clinical or ultrasound evidence of vegetative emboli was seen post-procedure. In our opinion, persistent endocarditis and presence of vegetations (despite adequate antibiotic therapy) with greater than or equal to 2 cm, is an indication for this procedure. This is supported by similar findings where the utilization of the AngioVac assisted with the successful removal of larger, bulky vegetations.[6,7] The procedure requires a team made up of surgeons (cardiothoracic and/or vascular) with specialty in cardiology, anesthesia, infectious disease, and perfusion.

Conclusions

Lead extraction in infected patients with vegetations has become a routine and safe procedure, done in many centers. We have found that even in relatively small sized vegetation cases, some patients have postoperative fevers and septic episodes which may be related to embolization of vegetation fragments, and may cause severe morbidity and death. We have found that the size of the vegetations is often underestimated by the preoperative transesophageal echocardiogram. Patients with documented vegetations who have positive blood cultures and persistent 2 to 3 cm or greater vegetations may benefit from a less invasive mechanical removal of their vegetations.

This single center case series describes our initial experience with a new minimally invasive approach to removal of right heart masses. It has replaced our previous method of sternotomy and cardiopulmonary bypass, which we felt would have been contraindicated in many of our patients in this series. A limitation of this study is the lack of follow-up data; further studies are necessary to reproduce the safe outcomes we have been fortunate to have obtained, but also to determine if this equipment might have more use than simply for 2 cm or larger vegetations. Furthermore, future studies examining the risks associated with breaking up larger vegetations before AngioVac utilization would shed more light on device efficacy.

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E/Ea For The Prediction of Left Atrial Appendage Thrombi in Patients with Atrial Fibrillation and Severe Mitral Stenosis

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Abstract

Atrial fibrillation (AF), left atrial appendage thrombi (LAAT) and subsequent embolic stroke are the most frequent complications of mitral stenosis .E/Ea is used traditionally for the assessment of left atrium pressure, and besides AF and dilated LA size which promotes stasis of blood in LA, high LA pressure also play a role to clot formation in LA .The receiver operator characteristics (ROC) curve point-coordinates identified an E:e' value of ≥ 36.5to have 57.14% sensitivity and 90.91% specificity for LAAT;We find this ratio relatively specific for prediction of LAAT, independent of MVA and LA volume, however it needs to be externally validated.

Introduction

It is possible that impaired diastolic function also plays a role to form a clot in LAA,[1] however enlargement of the left atrium secondary to severe mitral stenosis, longer duration of symptoms, presence of spontaneous echo contrast and advanced age lead to left atrial stasis and increased risk of clot formation. Prior reports suggest that in patients with severe mitral stenosis, besides atrial fibrillation, depressed LAA function and small mitral valve area had a higher risk of LAAT formation. In this investigation, we sought to determine whether E:e' is predictive of LAAT formation in patients with severe MS and AF.

Methods

In this descriptive study, 30 patients with severe MS, who referred to our echo lab for percutaneous mitral valvuloplasty or mitral valve surgery, were included. We excluded patients with mitral regurgitation or aortic regurgitation greater than 2+ in severity and LVEF <50%. Two board-certified (NBE) echocardiologist, who were blinded to the TTE and clinical data, reviewed all TEE images to determine the presence or absence of LAAT [LAAT(+)group A and LAAT(–) group B].The Doppler measurements were obtained by averaging data from 5 consecutive beats. The left ventricular systolic and diastolic volumes and LVEF were measured using the biplane Simpson's method. A 1-mm to 3-mm sample volume is placed between the mitral leaflet tips during diastole to record E velocity .To measure Ea, the sample volume is placed in the ventricular myocardium immediately adjacent to the mitral annulus. All patients underwent transthoracic and transoesophageal echocardiography and the results were recorded and analyzed. A two-tailed P value ≤0.05 was considered statistically significant in all analyses. PASW-18 software (SPSS, Inc. - Chicago, IL) was used for all data analyses with the exception of the comparisons between ROC curves for which STATA-11 (College Station, TX) was used.

Results

Nine patients (30%) were male. Median age was 44.8 ±12.3 years. 8 patients (26.6%) had a clot in the LAA and the remainder had no clot. The average mitral valve Wilkins score was 8.3 ±1.9 in group A and 7.9 ±1.5 in group B; the difference was not significant (p = 0.431).

The mean E:e' among LAAT(+) patients was significantly higher than those who were LAAT(–) [38.08±24.45 vs. 25.17±14.76, respectively; P = 0.01]. The receiver operator characteristics (ROC) curve point-coordinates identified an E:e' value of ≥ 36.5to have 57.14% sensitivity and 90.91% specificity for LAAT; The size of the left atrium was 74.67±13.17cc in the LAAT (+) group and 89.1±45.72cc in the LAAT(–); the difference was not significant (p =0.458).

Mitral valve area in group A was 0.47±0.12 vs 0.67±0.23cm^2 in group B. which is not statistically significant (P=0.5).

Discussion

E/Ea is used traditionally for the assessment of left atrium pressure, and besides AF and dilated LA size which promotes stasis of blood in LA, high LA pressure also play a role to clot formation in LA because of diminished atrial emptying, leading to more atrial blood

Key Words:
Left Atrial Appendage Thrombi, Atrial Fibrillation, Mitral Stenosis.

Disclosures:
None.

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stasis and thrombus formation. We find this ratio relatively specific for prediction of LAAT, independent of MVA and LA volume, however it needs to be externally validated. Our investigation confirms previous findings by Iwakura et al.[2] demonstrated that E:e' is associated with LAAT independent of other echocardiographic parameters . Small sample size constitutes a limitation in our study.

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Novel Ventricular Repolarization Indices in Patients with Coronary Slow Flow

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Abstract

Background: Coronary slow flow (CSF) phenomenon is described angiographically as delayed progression of the injected contrast agents through the coronary arteries. Aim of this study was to analyze ventricular repolarization in CSF patients by using Tpeak-Tend interval, Tpeak-Tend/QT ratio, Tpeak-Tend/QTc ratio and other repolarization parameters since these parameters are used as predictors for ventricular arrhythmogenesis.

Materials and Methods: We have retrospectively analyzed diagnostic coronary angiography results of 160 patients between 2010 and 2014. Patients were divided into two groups according to coronary flow results. CSF group consisted of 33 female, 82 male patients with mean age 51,9±11,5 years. Control group included patients with normal coronary flow; 13 female, 32 male with mean age 50,8±11,7 years. In all patients, ventricular repolarization parameters as well as other associated electrocardiographic intervals were measured on the twelve-lead surface electrocardiogram.

Results: The ventricular repolarization parameters: QTmax interval, QTmin interval, QTc, QTI, QTcI, JTmax interval, JTmin interval, JTdispersion and JTIndex were not significantly different between the groups. However followings parameters differed significantly between patients and controls; QRS (92,8±11,5 msn versus 78,3±16,713,40 msn, respectively; p=0.001), T wave (89±20,2 msn vs. 73,3±13,3 msn respectively, p=0.001), QT dispersion (26,8±17,5 msn vs. 13,5±20,4 msn respectively, p=0.002), JTcorrected (331,6±39,8%; vs. 350,1±39,7% respectively; p=0.01). Furthermore; Tpeak-Tend duration (89±20,2 msn vs. 73,3±13,9 msn respectively; p=0.001), T wave (204±34,9 msn vs. 189,2±24,8 msn respectively; p=0.003), Tpeak-Tend/QT ratio (0,22±0,05 msn vs. 0,19±0,03 msn respectively, p=0.001) were significantly higher in patients compared to controls. Tpeak-Tend/QTc ratio was also significantly higher in the CSF group compared to the controls. (0,21±0,05 msn vs. 0,17±0,03 msn respectively, p =0.001).

Conclusion: Ventricular repolarization parameters are prolonged in patients with CSF.

Introduction

The coronary slow flow (CSF) is an important coronary angiographic entity characterised by delayed progression of the injected contrast agents through the coronary arteries. It is a frequent finding, typically observed in patients with acute coronary syndromes. Myocardial repolarization can be evaluated with QT interval (QT), corrected QT interval (QTc), QT dispersion (QTd), and transmural dispersion of repolarization. The Tpeak-Tend interval, which is the interval between the peak and the end of the T wave on twelve-lead electrocardiogram (ECG), could be used as an index of transmural dispersion of repolarization.[1] Saya et al. reported a case with CSF and increased QTc dispersion which was associated with ventricular tachycardia.[2] Tpeak-Tend interval, which is the interval between the peak and the end of T wave on electrocardiogram (ECG), is accepted as an index of transmural dispersion of ventricular repolarization.[3] JT dispersion (JTd), corrected JT (JTc), corrected JT index (JTcI), Tpeak-Tend/QT ratio, Tpeak-Tend/QTc ratio are also used as an electrocardiographic index of ventricular arrhythmogenesis.[1] In this study, we assessed ventricular repolarization patterns in order to reveal any possible arrhythmogenic substrate in patients with CSF.

Key Words:

Electrocardiography, Coronary Slow Flow, Ventricular Arrhythmia.

Disclosures:
None.

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Methods

Study Population

One hundred-sixty patients who were admitted to the cardiology outpatient clinics with complaints of chest pain between January 2010 and December 2014, aged between 18 and 70 years, and who underwent coronary angiography for diagnostic purposes were included in the study. The patients were divided into two groups according to coronary flow characteristics. One hundred fifteen patients with CSF (33 female, 82 male patients; mean age 51,9±11,5 years) and 45 patients with normal coronary flow (13 female, 32 male; mean age 50,8±11,7 years) were included in the study. The exclusion

Table 1: Characteristics of the Study Population

Patients (n=115)	Control(n=45)	P(value)	%
Sex(Female/Male)	33/82	13/32	0,563
Age(years)	51,9±11,5	50,8±11,7	0,571

Values are presented as mean±SD.p<0.05

criteria were arterial hypertension, left ventricular wall anomalies, ejection fraction (EF) below 50%, primary cardiomyopathy, valvular heart disease, rhythm other than sinus on the ECG, bundle branch block and atrioventricular block, thyroid dysfunction, renal failure, and a history of drug abuse.

Electrocardiography

We used a standard twelve-lead surface ECG tracing at 25 mm/s paper speed and 10 mm/mV amplitude. Measurements were taken manually by two independent investigators. If possible, parameters were determined in all 12 leads and mean results were calculated from three consecutive cardiac cycles. RR interval distance between two consecutive R waves, PR interval distance from the beginning of the P wave to the beginning of the Q wave, T wave duration and amplitude was measured. If the T-wave amplitude was <1.5 mm in a particular lead, that lead was excluded from analysis. The QT interval was measured from the onset of the QRS interval to the end of the T-wave in all leads where the end of the T-wave could be clearly defined.[4] All of the QT intervals in each lead were analysed, and the highest values of three consecutive intervals were used for the analysis. The QT interval was corrected for heart rate using the Bazett formula.[5] The dispersion of the corrected QT interval (QTcd) was defined as the difference between the maximum and the minimum of the corrected QT intervals measured in any of the leads. QTc=measured QT interval(s)=√RRinterval. The QT interval index (QTI) was measured by the following formula: QTI% =(QT/656) x(HR+100).[4,6]

The JT interval was measured in each of the 12 leads in three consecutive intervals in milliseconds, from the J point to the terminal inscription of the T wave. The U wave was not taken into consideration. When U wave was present, the JT interval was measured to the nadir of the curve between the T and U waves. The corrected JT (JTc) interval calculated by subtracting the QRS duration from the QTc interval in leads II, and V5. The dispersion of the corrected JT interval (JTcd) was defined as the difference between the maximum and the minimum of the measured corrected JT intervals in ms in any of the measured D2 and V5 leads. The JT interval index (JTI) was calculated by the following formula: JTI =(JT/518)x(HR+100).[4,6]

Table 2: Electrocardiographic Measurements of the Between Groups

	Patients(n=115)	Control(-)(n=45)	P(value)
RR(msn)	838,7±158,1	794,0±155,2	0,022
Heart Rate(beat/min)	71,8±15,5	78,3±15,4	0,020
QRS(msn)	92,8±11,5	78,3±16,7	0,001
T wave duration (msn)	204,0±34,9	189,2±24,8	0,003
Tpeak-Tend (msn)	89,0±20,2	73,3±13,9	0,001
QTmax(msn)	392,2±36,9	381,3±35,8	0,091
QTmin(msn)	365,2±37,8	365,5±36,5	0,959
QTc(msn)	424,5±38,1	428,4±39,5	0,564
QTd(msn)	26,8±17,5	15,5±20,4	0,002
QTI(%)	102,2±8,6	103,1±8,7	0,544
QTcI (%)	111,6±18,6	116,8±17,6	0,092
JTmax(msn)	296,4±40,2	292,6±41,9	0,566
JTmin(msn)	273,7±39,3	281,2±41,1	0,299
JTd(msn)	25,2±15,9	18,7±46,5	0,369
JTc(msn)	331,6±39,8	350,1±39,7	0,010
JTI(%)	97,8±11,9	99,9±11,5	0,293
JTcI(%)	98,7±10,3	105,1±10,7	0,001
Tpeak-Tend/QT(msn)	0,22±0,05	0,19±0,03	0,001
Tpeak-Tend/QTc(msn)	0,21±0,05	0,17±0,03	0,001

QTd: QT interval dispersion, QTI: QT interval index, QTc: Corrected QT interval, QTcI: QTc interval index, JTd: JT interval dispersion, JTc: Corrected JT, JTcI: Corrected JT interval index. NS:not significant. Values are presented as mean±SD:p<0.05

The Tpeak–Tend is the interval from the summit of the T-wave to the end of the QT interval. Tpeak-Tend and QT intervals were measured in leads D2 and V5. If V5 was not suitable, leads V4 and V6 in that order were measured.[1,7]

Tpeak-Tend/QT interval as well as Tpeak-Tend/QTc interval ratios (Tpeak-Tend interval divided by a QTc) were also calculated as indexes of repolarization. The Tpeak-Tend/QT ratio was calculated as the ratio of Tpeak-Tend in that lead to the corresponding QT interval.[8] All ECG measurements were performed by two independent cardiologists, who were blinded to patient information. When measurements were not identical, the mean of the values was calculated.

Coronary Angiography

Coronary angiography is the only tool for the diagnosis and evaluation of CSF. All patients had been referred to diagnostic coronary angiography for evaluation of exertional chest pain suggestive of angina pectoris or positive treadmill testing. The diagnostic coronary angiography was performed via transfemoral approach with the Judkins technique. Coronary flow rates of all subjects were documented by Thrombolysis in Myocardial Infarction (TIMI) frame count. TIMI frame count method is a simple, reproducible, objective, and quantitative index of coronary flow velocity.[9] Initial frame count is defined as the frame in which concentrated dye occupies the full width of the proximal coronary artery lumen, touching both borders of the lumen, and forward motion down the artery. Distal end was defined as the distal bifurcation for the left anterior descending artery (LAD), the distal bifurcation of the segment with the longest total distance for the circumflex artery (Cx), and the first branch of the posterolateral artery for the right coronary artery (RCA).[9] For objective quantification of the coronary flow, two independent observers, blinded to the clinical data of the study subjects, assessed the coronary flow in coronary arteries using TIMI frame count method.

Statistical Analysis

The SPSS software package (Version 15.0 for Windows, Inc.,Chicago, IL, USA) was used for statistical analysis. Data are expressed as mean values+standard deviation. Categorical data were analysed by the Pearson x^2 test. The mean differences between the study groups were evaluated by calculating Student's t-test. Categorical data were expressed as count and percentages. Multivariate logistic regression was used to identify the independent predictors of CSF. P-value <0.05 was considered significant. A P-value of, 0.05 was considered to be statistically significant.

Results

Demographic and clinical characteristics of the SCF patients and control group are presented in Table 1. The mean age was 51,9±11,5

years in the SCF patients and 50,8±11,7 years in the control group (p>0.05). There were 33 female and 82 male patients in the SCF group, and 33 male and 12 female in the control group (p<0,05). The average heart rate for the CSF group and the control group was 71,8±15,5 and 78,3±15,4 beats/min, respectively (p=0,02). P wave amplitude, PR interval and QT interval were not significantly different between the groups but T wave duration and QRS complex duration were significantly longer in CSF group compared to controls (Table 2). Furthermore; Tpeak-Tend interval was significantly prolonged in the CSF group compared to control group (89,0±20,2 msn vs. 73,3±13,9 msn respectively; p<0.001). Tpeak-Tend/QT ratio was significantly higher in the CSF group compared to the control group (0,22±0,05 vs. 0,19±0,03 msn respectively; p<0.001). Tpeak-Tend/QTc ratio was also significantly higher in the CSF group compared to the control group (0,21±0,05 vs. 0,17±0,03 msn respectively; p<0.001). JTc (331,6±39,8% vs. 350,1±39,7%; p=0.010) and JTcI (98,7±10,3 vs. 105,1±10,7%; p=0,001) was significantly higher in the CSF group compared to the control group. The difference in JTd between the groups did not reach statistical significance (25,2±18,7 vs. 18,7±46,5 msn; p=0,369).

Discussion

We investigated the ventricular repolarization parameters in patients with CSF and in healthy controls with normal coronary flow pattern. The clinical series and individual case reports have shown that CSF may be associated with typical angina, infarction, ischemia, and even sudden cardiac death.[2,10,11]

In a recent study, CSF was found to be associated with microvolt T-wave alternans positivity.[12] The QT and QTc dispersion and associated parameters are measures of cardiac electrical heterogeneity.[12] They may be of prognostic value in CSF patients. In our study, we revealed that the mean values of the QT dispersion were longer, and the JTc and corrected JT interval index were longer than QTcI. Zhou et al reported that in normal conduction, the JT interval may reflect the closest action potential durations in the basal portion of the heart and the corrected QT interval has no distinct electrophysiological meaning at the cellular level.[14] They stated that the JT rather than QT interval is the proper measure of the repolarization duration and that the JT parameter should be used as a single parameter, without QRS duration, which is also compatible with our findings. Rautaharju et al showed that JT adjustment obtained as QTc - QRS retained a strong residual correlation with ventricular rate.[15] Prolonged transmural dispersion of repolarization (TDR) is associated with inducibility as well as spontaneous development of VT in higher risk patients. TDR may be a useful index for predicting ventricular tachyarrhythmias.[16] Antzelevich reported an association between ventricular arrhythmogenesis and Tpeak-Tend prolongation.[17] In our study, we observed that the mean values of the Tpeak-Tend interval was longer in CSF patients. Yan et.al. demonstrated that dispersion in repolarization may arise from differences in the action potential durations between cells situated in different myocardial layers.[18] They showed that the M cells are characterized by prolonged repolarization compared with the epicardial or endocardial layer cells. The peak of the T wave in a transmural ECG was found to reflect the termination of action potentials from the epicardial layer. In addition, the T wave offset was found to represent the termination of repolarization in the M cells. The Tpeak –Tend/QT ratio is a new index of ventricular repolarization that remains constant despite dynamic changes in heart rate. The Tpeak–Tend/QT ratio is considered as a more sensitive index of arrhythmogenesis compared to Tpeak–Tend interval as it provides an estimate of dispersion of repolarization relative to total duration of repolarization.[19] This ratio varies from 0.15 to 0.25 in adults. The Tpeak –Tend interval was measured in precordial leads that are considered to reflect the transmural axis of the left ventricle, and therefore to provide an index of transmural dispersion of repolarization1. Prolonged transmural dispersion of ventricular repolarization is associated with inducibility as well as spontaneous development of VT in higher risk patients. Tpeak–Tend interval has been evaluated in congenital long QT syndrome (LQTS) patients, short QT syndrome, Brugada syndrome, hypertrophic cardiomyopathy and myocardial infarction.[19,20] An increased Tpeak–Tend interval has been associated with the development of ventricular tachyarrhythmias and thus may be considered as a non-invasive marker of arrhythmogenesis. Transmural dispersion of ventricular repolarization may be a useful parameter for predicting ventricular tachyarrhythmias.[16] Increased QT dispersion of repolarization is known to be an important factor in the development of ventricular arrhythmias.[21]

QTc dispersion, indicating increased risk for ventricular arrhythmias and cardiovascular mortality, was found to be significantly higher in patients with slow coronary artery flow.[22]

The QTc dispersion of more then 60 msec has been correlated with increased risk for sudden cardiac death in the elderly.[21] In our study, we found that patients with CSF had increased QTd compared to subjects with normal coronary artery flow.

Recently published studies reported that Tpeak-Tend interval and Tpe/QT ratio were increased in CSF patients.[23,24] The number of patients in both studies was too small and the results showed a single institution records. We have shown that T wave duration Tpeak-Tend interval, Tpe/QT ratio and Tpe/QTc ratio were increased in patients with CSF in a much bigger patient population.

Amasyali et.al. reported a young man with aborted sudden cardiac death. His coronary angiography revealed slow coronary flow phenomenon as a possible cause of this condition.[11] In Tatlı E. opinion, CSF is not purely an incidental angiographic finding; on the contrary, it may lead to angina pectoris and true myocardial ischemia.[25]

Conclusions

In conclusion, Our results show that SF is associated with prolonged T wave duration, Tpeak-Tend interval and increased Tpeak-Tend/QT and Tpeak-Tend/QTc ratio. The findings of our study support a possible association between CSF and ventricular arrhythmias, which needs to be studied further.

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Cryoballoon versus Radiofrequency Ablation for Atrial Fibrillation: A Meta-analysis of 16 Clinical Trials

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Abstract

Introduction: We aimed to study the procedural characteristics, efficacy and safety of cryoballoon ablation (CBA) versus radiofrequency ablation (RFA) for catheter ablation of paroxysmal atrial fibrillation (AF).

Methods: A systematic literature search was performed using PubMed, EMBASE, Web of Science, and Cochrane Central Register of Controlled Trials to clinical trials comparing CBA and RFA for AF. Outcomes were evaluated for efficacy, procedure characteristics and safety. For each study, odd ratio (OR) and 95% confidence intervals (CIs) were calculated for endpoints for both approaches.

Results: We analyzed a total of 9,957 participants (3,369 in the CBA and 6,588 in RFA group) enrolled in 16 clinical trials. No significant difference was observed between CBA and RFA with regards to freedom from atrial arrhythmia at 12-months, recurrent atrial arrhythmias or repeat catheter ablation. CBA group had a significantly higher transient phrenic nerve injury (OR 14.19, 95% CI: 6.92-29.10; p<0.001) and persistent phrenic nerve injury (OR 4.62, 95% CI: 1.97-10.81; p<0.001); and a significantly lower pericardial effusion/cardiac tamponade (OR 0.43, 95% CI: 0.26-0.72; p=0.001), and groin site complications (OR 0.60, 95% CI: 0.38-0.93; p=0.02). No significant difference was observed in overall complications, stroke/thromboembolic events, major bleeding, and minor bleeding.

Conclusion: CBA was non-inferior to RFA for catheter ablation of paroxysmal AF. RF ablation was associated with a higher groin complications and pericardial effusion/cardiac tamponade, whereas CBA was associated with higher rates of transient and persistent phrenic nerve injury.

Introduction

Approximately 2.7 to 6.1 million patients suffer from atrial fibrillation (AF) in USA.[1] The incidence rate has been estimated to be approximately 0.4%, which continues to grow with aging population, improvement in medical therapies and longer survival with heart disease.[2] Since Haïssaguerre's seminal observation identifying pulmonary veins as triggers for AF, there has been a dramatic increase in the number of patients undergoing catheter-based pulmonary vein isolation over the past 15 years.[3] In 2012, the Heart Rhythm Society/ European Heart Rhythm Association/ European Cardiac Arrhythmia Society issued a Class I recommendation for catheter ablation in patients with antiarrhythmic refractory symptomatic paroxysmal AF and class IIa recommendation in patients with symptomatic AF prior to initiating antiarrhythmic therapy.[4] Despite scientific advancements in mapping and catheters for radiofrequency (RF) ablation, data from multicenter registries have shown that only about 75% of patients with paroxysmal AF achieve durable maintenance of sinus rhythm.[3] These observations have catalyzed the development of alternative techniques and energy sources for catheter ablation with the aim of simplifying the procedure and improving outcomes. The conventional RF ablation using irrigated catheter has also evolved from its point-by-point approach to circumferential approach and now includes contact-sensing and phased duty-cycled RFA technology. A recent network meta-analysis by Kabunga et al explored the 3 most commonly used AF ablation strategies to compare outcomes of RFA using conventional irrigated catheter, phased duty-cycled RFA, and cryoballoon ablation (CBA). However, since their report, 7 additional prospective and randomized trials have been added to the literature comparing RFA and CBA. We aimed to compare the efficacy, procedural characteristics and complications of both the approaches and provide with the most updated evidence on this topic.

Methods

Key Words:
Catheter Ablation, Cryoballoon, Radiofrequency, Atrial Fibrillation.

Disclosures:
None.

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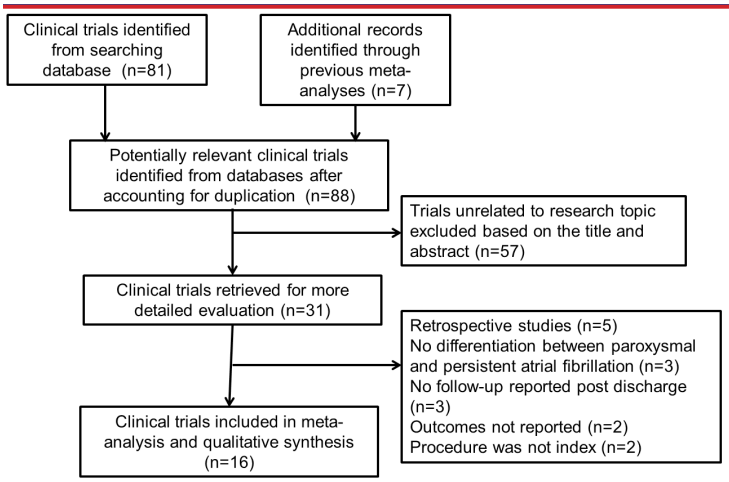


Figure 1: **Process of study selection for randomized and prospective trials (PRISMA Statement)**

The present review was performed according to Cochrane Collaboration and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statements.

Search Strategy

We performed electronic searches on PubMed, The Cochrane Library, EMBASE, EBSCO, Web of Science and CINAHL databases from the inception through April 14, 2016 to identify trials comparing RFA and CBA in patients with paroxysmal AF. We combined the terms ("radiofrequency") AND ("cryoballoon" OR "cryoablation") AND ("atrial fibrillation") as keywords or medical subject heading terms. All references of the retrieved articles were reviewed for further identification of potentially relevant studies. The identified studies were systematically assessed using the inclusion and exclusion criteria described below.

Eligibility Criteria

The eligibility criteria for our systematic review and meta-analysis included

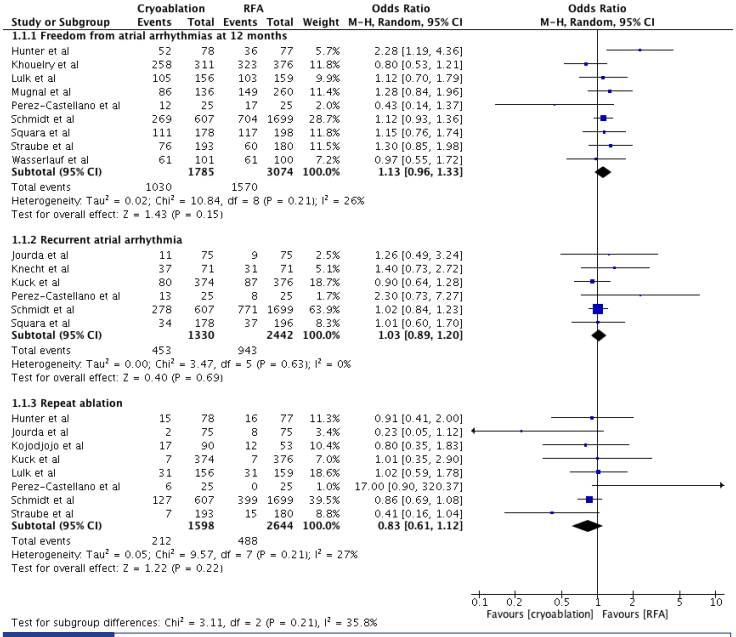


Figure 2: **Forest plot demonstrating primary efficacy outcomes in patients with atrial fibrillation undergoing cryoablation versus radiofrequency ablation**

1. Human subjects undergoing catheter ablation for paroxysmal AF using conventional RFA, CBA, or phase-duty cycled RFA.

2. Reported clinical outcomes, procedure time and complications.

3. Literature published in English.

4. Either randomized controlled trials (RCTs) or prospective cohort studies. Studies that did not have randomized or matched cohorts were excluded. Retrospective studies, abstracts, case reports, conference presentations, editorials, reviews, and expert opinions were excluded. We used the longest available follow-up data from individual studies for our analysis. All the data was extracted and jadad score calculated independently by 2 reviewers (JG and RC). Discrepancies between the two reviewers were resolved by discussion and consensus. Final results were reviewed by senior investigator (AN) (Figure 1).

Outcomes

The primary efficacy outcome in our study was "freedom from any atrial arrhythmia at 12 months", "recurrent atrial arrhythmias", and "need for repeat ablation". Studies reporting only acute procedural success rates were excluded from efficacy analysis. Secondary procedural outcomes included "procedural time" and "fluoroscopy time".

The primary safety outcome was the combined endpoint of "all-cause mortality","overall complications","stroke or thromboembolism event", "major bleeding", "minor bleeding", "groin site complications (including arteriovenous fistulae, pseudoaneurysms and hematomas requiring any intervention or prolonged hospital stay)", "transient phrenic nerve injury"(resolved immediate post-procedure),"persistent phrenic nerve injury", "pericardial effusion or cardiac tamponade" (requiring intervention), "atrio-esophageal fistula", and "pulmonary vein stenosis". For analysis, the conventional and duty-phased RFA strategies for ablation were grouped together in the RFA group.

Statistical Analysis

Random effects model was used to estimate the odds ratio (OR) and respective 95% confidence intervals (CI) using Cochrane Collaborative software, RevMan 5.3. Measure of heterogeneity between the studies was assessed using the chi square test and was considered significant if I^2>50%. All p values were 2-sided, and p value of <0.05 was considered significant.

Quality Appraisal And Publication Bias

Assessment of risk of bias for each selected study was performed according to PRISMA 2009 guidelines. Qualitative evaluation of bias using the following key parameters were performed for each

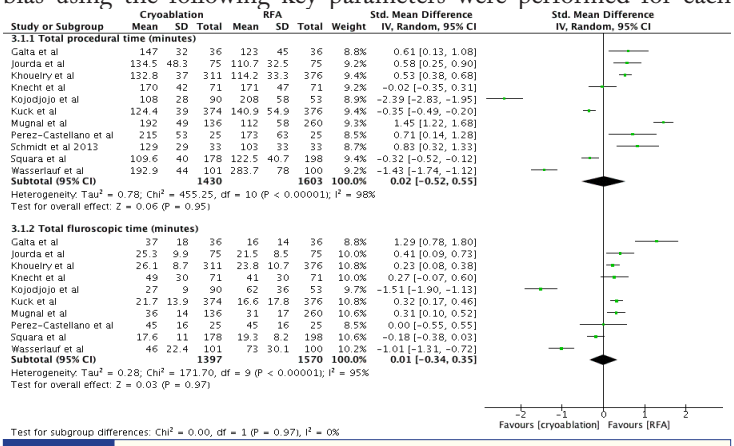


Figure 3: **Forest plot demonstrating procedural outcomes of cryoablation versus radiofrequency ablation**

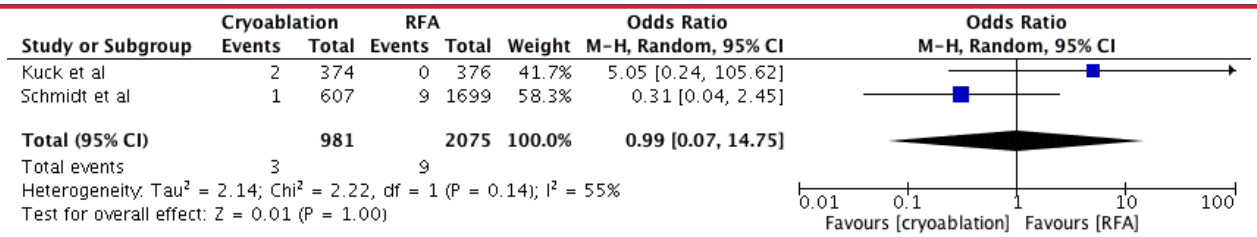


Figure 4: Forest plot demonstrating all-cause mortality in patients with atrial fibrillation undergoing cryoablation versus radiofrequency ablation

study:

1. Clear definition of study population.
2. Clear definition of outcomes and outcome assessment.
3. Independent assessment of outcome parameters.
4. Sufficient duration of follow-up.
5. Selective loss during follow-up.
6. Important confounders and prognostic factors identified.

Evidence of publication bias was investigated visually using funnel plots and analyzed using Egger and Begg methods.

Results

A total of 88 studies were identified after exclusion of duplicate or irrelevant references (Figure 1). After a detailed evaluation of these studies, 16 relevant studies were included, that incorporated a total of 9,957 participants (3,369 in the CBA and 6,588 in RFA group) undergoing catheter ablation for paroxysmal AF. Of these, 5 were RCTs[5-9] and 11 were prospective observational studies.[11-20] The characteristics of these trials, mean follow-up periods and mode of arrhythmia detection are described in Table 1.

Quality Assessment And Publication Bias

Overall, there were clear definitions of the study population, outcomes, and assessment in most component studies, but blinded assessment of outcomes was not reported in all studies resulting in potential bias. Jadad score was calculated for all RCTs with a mean Jadad score of 3 indicating that the studies involved were of high quality (Table 1). No significant publication bias was observed using funnel plots (Egger's test and Begg's test had p values >0.05 for all analyses) (Supplementary appendix Table 1, Supplementary appendix, Figure 1).

Baseline Characteristics

In the participant studies, there were no significant differences between the two groups in terms of age, gender, body mass index, left ventricular ejection fraction (LVEF), hypertension or coronary artery disease. A higher prevalence of diabetes was observed (p<0.05)

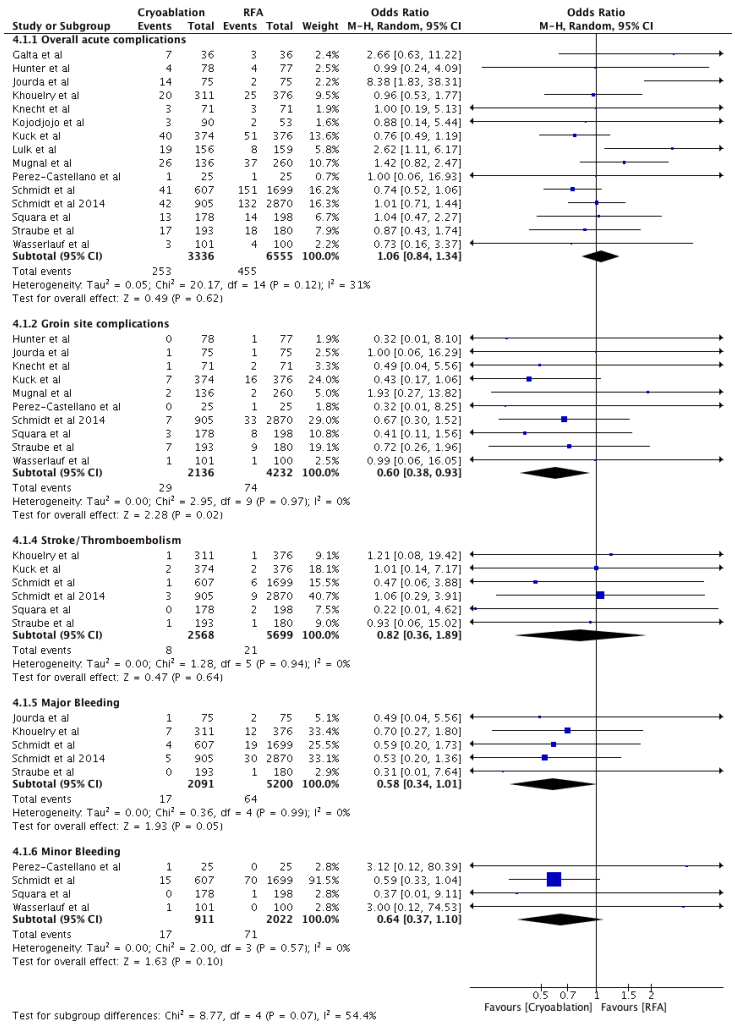


Figure 5A: Forest plot demonstrating safety outcomes - overall acute complications, stroke/thromboembolism, major bleeding, minor bleeding and groin site complications in patients with atrial fibrillation undergoing cryoablation versus radiofrequency ablation

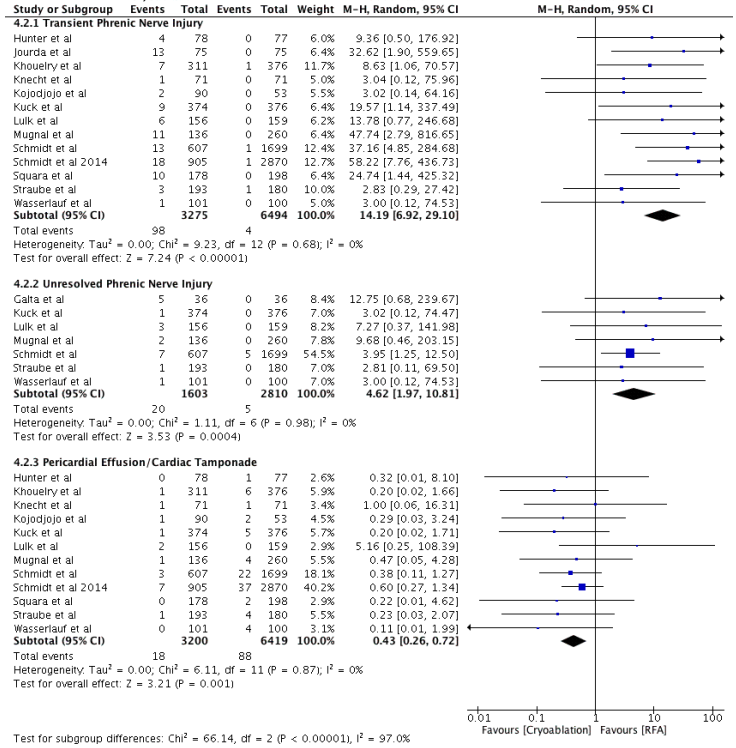
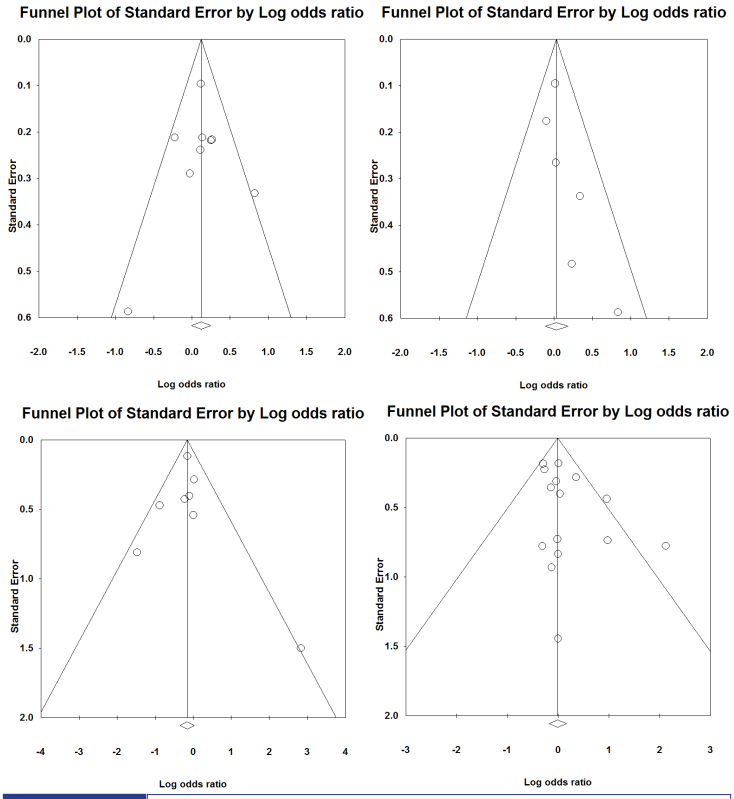


Figure 5B: Forest plot demonstrating safety outcomes - transient and unresolved phrenic nerve injury, and pericardial effusion/tamponade in patients with atrial fibrillation undergoing cryoablation versus radiofrequency ablation

Table 1: Characteristics of the included studies

Name of Study	Year	Type of trial	Cryoballoon characteristics		CBA, n	Radiofrequency characteristics		RFA, n	Follow-up duration (mean, months)	Mode of follow-up for arrhythmia detection	Jadad Score
			Generation	Size		Type of RFA	Approach for ablation				
Kuck et al	2016	RCT	CB-1;CB-2	23 and 28 mm	374	C - IRF	point by point	376	18 months	24h Holter monitor	3
Hunter et al	2015	RCT	CB-1	23 and 28 mm	78	C - IRF	point by point	77	12 months	7 day Holter	3
Luik et al	2015	RCT	CB-1	23 and 28 mm	156	C-IRF	NS	159	12 months	7 day Holter or event recorder	3
Pérez - Castellano et al	2014	RCT	CB-1	23 or 28 mm	25	C-IRF	point by point	25	12 months	Insertable cardiac monitor	3
Schmidt et al	2013	RCT	NS	28 mm	33	C-IRF	NS	33	NS	NS	3
Khoueiry et al	2016	P; OS	CB-1; CB-2	28 mm	311	C-IRF and CS-IRF	Circumferential PVI	376	14 months	24h Holter monitor	NA
Schmidt et al	2016	P; OS	NS	23 and 28 mm	607	C-IRF	NS	1699	12 months	12 lead ECG	NA
Straube et al	2016	P; OS	NS	23 and 28 mm	193	C-IRF and CS-IRF	NS	180	17 months	24h Holter monitor	NA
Squara et al	2015	P; OS	CB-2	23 and 28 mm	178	CF-IRF	Circumferential PVI	198	12 months	24h Holter monitor	NA
Wasserlauf et al	2015	P; OS	CB-1; CB-2	23 and 28 mm	101	C-IRF	NS	100	12 months	24h to 48h Holter monitor	NA
Jourda et al	2015	P; OS	CB-2	NS	75	CF-RFA	NS	75	12 months	24h Holter monitor	NA
Knecht et al	2014	P; OS	CB-1	23 or 28 mm	71	C-IRF	Circumferential PVI	71	28 months	7 day Holter	NA
Mugnai et al	2014	P; OS	CB-1	28 mm	136	C-IRF	Circumferential PVI	260	23 months	24h Holter monitor	NA
Schmidt et al	2014	P; OS	NS	23 or 28 mm	905	C-IRF	NS	2870	NS	NS	NA
Gaita et al	2011	P; OS	CB-1	23 or 28 mm	36	C-IRF	point by point	36	NS	NS	NA
Kojodjojo et al	2010	P; OS	CB-1	28 mm	90	C-IRF	Circumferential PVI	53	14 months	24h Holter monitor	NA

CBA= Cryoballoon ablation; RFA= Radiofrequency ablation; RCT=Randomized Controlled trial; P;OS = Prospective Observational Study; CB-1 = Cryoballoon 1st generation; CB-2= Cryoballoon 2nd generation; NS=Not specified; C-IRF= Conventional Irrigated Radiofrequency catheter; PRF= Duty-cycled phased radiofrequency; CS-IRF=contact sensing-radiofrequency; PVI=Pulmonary Vein Isolation

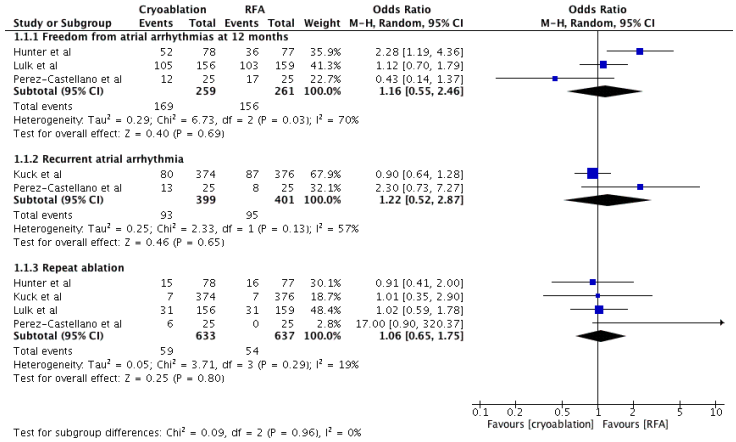


Supplementary Figure 1: Funnel plots evaluating publication bias in all studies: a) Freedom from atrial arrhythmias at 12 months; b) Recurrent atrial arrhythmias; c) Repeat ablation within 12 months since index ablation; d) Overall acute complications

in CBA group whereas left atrial diameter (LAD) and stroke or thromboembolic events were significantly greater in patients with RFA group. No significant heterogeneity was observed for stroke and diabetes. However, a significant heterogeneity was observed in LAD (Table 2). On sub-analysis of LAD only in prospective trials, the standard mean difference was found to be -0.13 (95% CI -0.26 to -0.001; p=0.04) with no significant heterogeneity (I^2=1.05).

Assessment of Efficacy

The clinical outcomes were assessed off anti-arrhythmic therapy in 7 trials,[5-8,14-16] on anti-arrhythmic therapy in 4 trials[10-12,18] and this information was not available for 5 trials.[9,13,17,19,20] No significant difference was observed between CBA and RFA in freedom from



Supplementary Figure 2: Forest plot demonstrating primary efficacy endpoints (randomized controlled trials only) in patients with atrial fibrillation undergoing cryoablation versus radiofrequency ablation

Table 2: Baseline demographics of study population

Baseline Characteristic	CBA	RFA	N	Studies (n)	RR or SWD (95% CI)	Heterogeneity		P for overall effect
						P value	I^2 (%)	
Age, yrs	59.2	60.1	3,138	11	-0.08 (-0.19 to 0.03)	0.01	53.3	0.14
Males, %	70.3%	70.5%	6,411	15	0.99 (0.97 to 1.03)	0.53	0	0.91
BMI	27.0	26.7	2,125	5	0.05 (-0.12 to 0.22)	0.007	71.6	0.58
LVEF, %	60.6%	60.0%	1,687	7	0.04 (-0.12 to 0.21)	0.02	57.8	0.58
LAD, mm	40.4	41.1	5,315	7	-0.18(-0.32 to -0.05)	0.01	61.6	0.008
Stroke/TIA, %	4.9%	7.7%	502	10	0.77 (0.63 to 0.93)	0.61	0	0.008
Hypertension, %	46.8%	48.1%	5,337	16	0.96 (0.90 to 1.03)	0.02	44.9	0.24
Diabetes, %	7.4%	6.5%	718	14	1.17 (1.01 to 1.36)	0.58	0	0.04
CAD, %	11.9%	13.6%	1,219	8	0.93 (0.82 to 1.04)	0.6	0	0.21

CBA=Cryoballoon ablation; RFA=Radiofrequency Ablation; RR=Relative Risk; SWD=Standardized Mean Difference; LVEF= Left Ventricular Ejection Fraction; BMI=Body-mass index; LAD= Left atrial diameter; TIA=Transient Ischemic Attack; CAD=Coronary artery disease

atrial arrhythmia at 12-months follow-up (OR 1.13; 95% confidence interval [CI]: 0.96-1.33), recurrent atrial arrhythmias (OR 1.03; 95% CI 0.89-1.20) or repeat ablation (OR 0.83; 95% CI 0.61-1.12) (Figure 2). No significant heterogeneity was observed.

Assessment of Procedural Duration

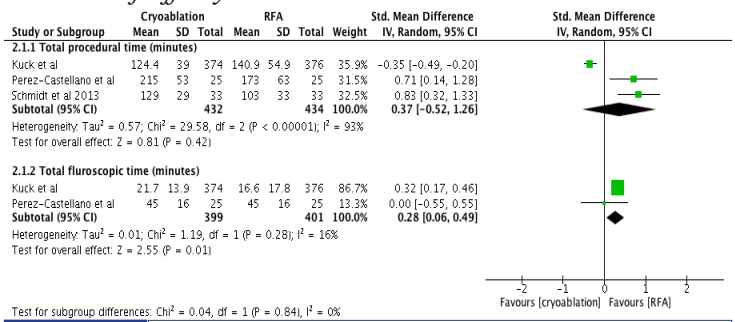
The total procedure time was not significantly different between CBA and RFA groups (Standard mean difference [SMD] 0.02, 95% CI -0.52 to 0.55; I^2=98%). Similarly, the total fluoroscopy time was not significantly different between the two groups (SMD 0.01, 95% CI -0.34 to 0.35; I^2=95%) (Figure 3). Significant heterogeneity was observed in both these measures.

Assessment of Safety and Complications

The all-cause mortality (OR 0.99, 95% CI 0.07-14.75; I^2=55%) for CBA and RFA respectively, Figure 4) and overall complications (7.5% vs. 6.9% for CBA and RFA respectively, (OR 1.06, 95% CI 0.84-1.34; I^2=31%) p=0.62; Figure 5a) were not significantly different. Among individual complications, CBA group had significantly lower groin site complications (1.35% vs. 1.74%, p=0.02; OR 0.60, 95% CI 0.38 - 0.93) and lower hemodynamically significant pericardial effusion/cardiac tamponade (0.56% vs. 1.37%, p=0.001), as compared to RFA respectively, higher rates of transient phrenic nerve injury (3% vs. 0.06%, p<0.001; OR 14.19, 95% CI 6.92-29.10) and persistent phrenic nerve injury (1.24% vs. 0.17%, p<0.001; OR 4.62, 95% CI 1.97-10.81) a for CBA and RFA respectively. No significant difference was observed in stroke/thromboembolic events, major bleeding, and minor bleeding (Figure 5a and b). There were no reports of atrio-esophageal fistula or pulmonary vein stenosis.

Analysis of Data from Randomized Controlled Trials Only

Assessment of Efficacy



Supplementary Figure 3: Forest plot demonstrating procedural outcomes (randomized controlled trials only) in patients with atrial fibrillation undergoing cryoablation versus radiofrequency ablation

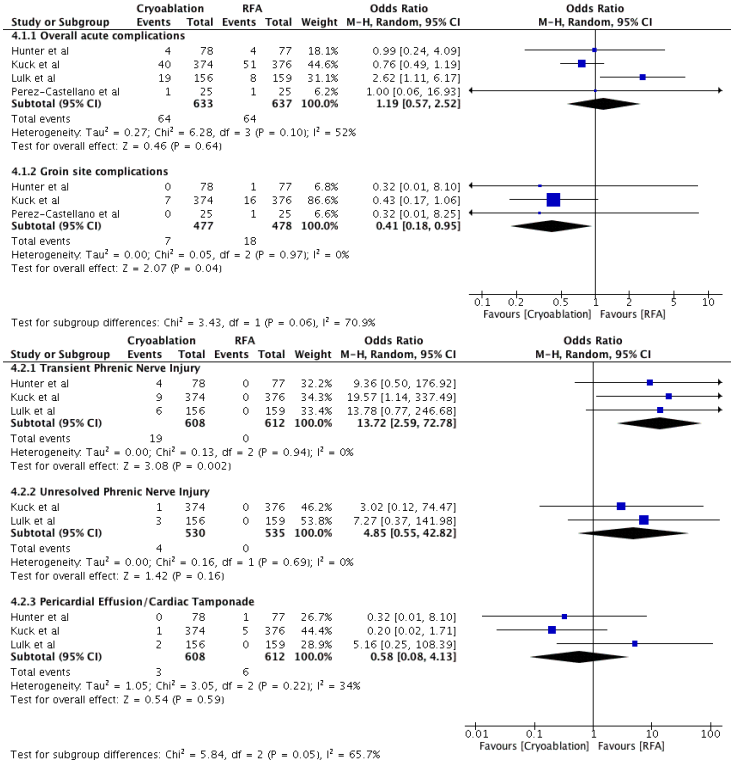
Cryoablation and Radiofrequency ablation had comparable rates of freedom from atrial arrhythmia (OR: 1.16, 95% CI: 0.55-2.46; I^2=70%), recurrent atrial arrhythmias (OR: 1.22, 95% CI: 0.52-2.87; I^2=57%) and need for a repeat ablation (OR: 1.06, 95% CI: 0.65-1.75; I^2=19) (Supplementary appendix, Figure 2).

Assessment of Procedural Duration

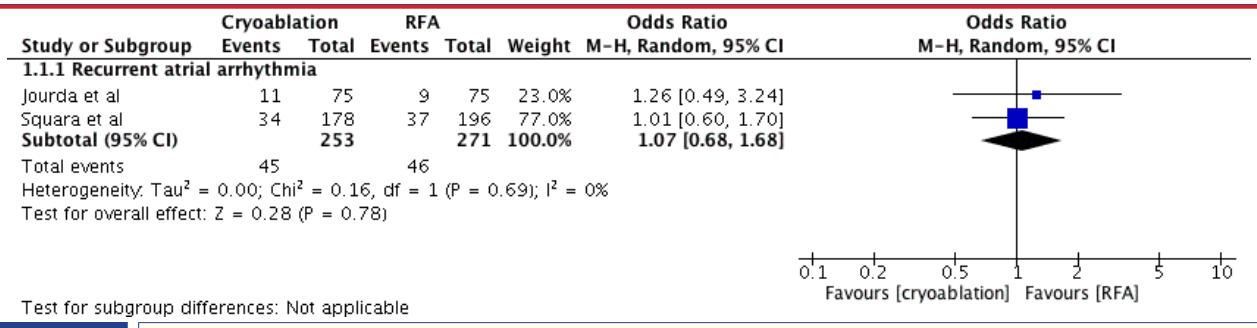
Cryoablation group was associated with increased total fluoroscopy time (Standard mean difference 0.28, 95% CI: 0.06 - 0.49; I^2=16%) and similar total procedural time (Standard mean difference: 0.37; 95% CI: -0.52 – 1.26; I^2=93%) compared to RFA group (Supplementary appendix, Figure 3).

Assessment of Safety and Complications

The overall complications were similar in both the groups (10.11%



Supplementary Figure 4: Forest plot demonstrating safety outcomes (randomized controlled trials only) - overall acute complications, groin site complications, transient and unresolved phrenic nerve injury and pericardial effusion/tamponade in patients with atrial fibrillation undergoing cryoablation versus radiofrequency ablation



Supplementary Figure 5: Forest plot demonstrating primary efficacy endpoints in studies evaluating 2nd generation CBA catheter versus contact-sensing RFA catheter

versus 10.04%; OR: 1.19, 95% CI 0.57-2.52). Among individual complications, CBA group had significantly lower groin site complications (1.46% versus 3.76% for RFA group; OR: 0.41, 95% CI 0.18 – 0.95) and higher rates of transient phrenic nerve injury (3.1% versus 0 events in RFA group; OR 13.72, 95% CI 2.59 – 72.78) compared to RFA group. No significant difference was observed in unresolved phrenic nerve injury and significant pericardial effusion/cardiac tamponade between the two groups (Supplementary appendix, Figure 4).

Analysis of Data from Trials Evaluating 2nd Generation CBA and Contact-Force RFA

In the sub-analysis, evaluating 2nd generation CBA (CBA-2) and RFA using contact force-sensing (CF-RFA) catheters, only 2 trials were included.[13,15] In these trials both groups had comparable rates of recurrent atrial arrhythmias (17.8% versus 17%; OR 1.07, 95% CI 0.68 – 1.68) (appendix, Figure 5).

Cryoablation was associated with similar total procedural time (Standard mean difference: 0.12; 95% CI: -0.76 - 0.99; I^2=95%) and total fluoroscopy time (Standard mean difference: 0.10; 95% CI: -0.47 - 0.68; I^2=89%) as RFA (Supplementary appendix, Figure 6).

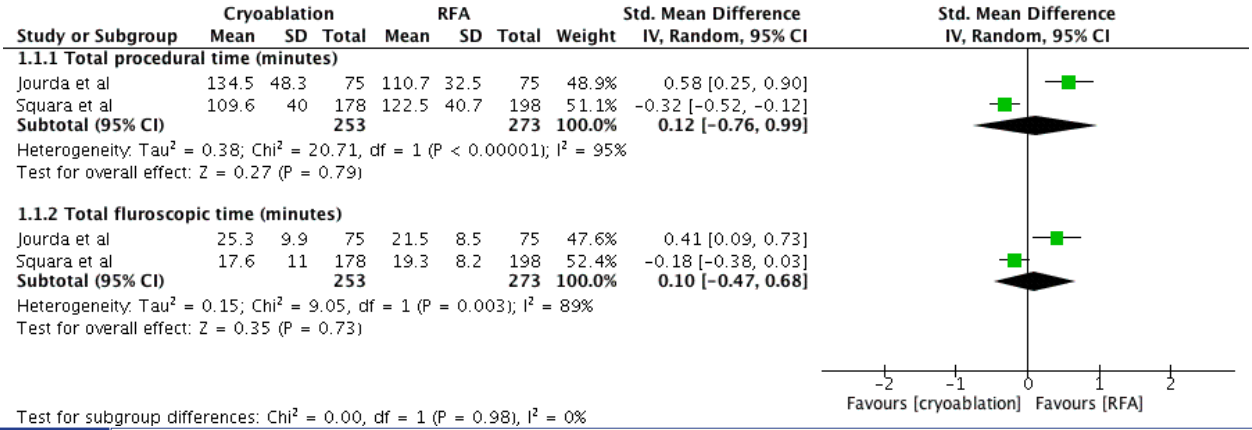
The overall complications were similar in both the groups (10.6% versus 5.8%; OR 2.66, 95% CI 0.33 – 21.23, I^2=83%). CBA group (2nd generation) had higher rates of transient phrenic nerve injury (9% versus 0 events in RFA group; OR 28.04, 95% CI 3.75 – 209.32) as compare to RFA group. No difference was observed in groin site complications (1.6% versus 3.2%; OR 0.48, 95% CI 0.14 – 1.62) between the two groups (Supplementary appendix, Figure 7).

Discussion

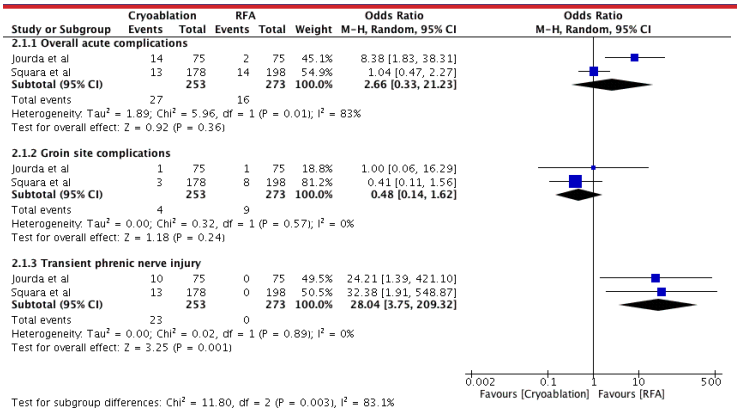
To the best of our knowledge, this is the largest meta-analysis of prospective and RCTs comparing the overall efficacy, safety and procedural characteristics of CBA with RFA in patients with paroxysmal AF. Our analysis suggests that CBA and RFA do not differ in terms of efficacy, procedural times, and overall complications. However, the analysis of individual complications demonstrated increased incidence of transient and persistent phrenic nerve injury and reduced hemodynamically significant pericardial effusion/cardiac tamponade and groin site complications with CBA as compared to RFA. No significant difference was observed in rates of major and minor bleeding and stroke/thromboembolic events. Interestingly there were no reports of atrio-esophageal fistula and pulmonary vein stenosis in both groups.

Freedom from Atrial Arrhythmia

Our study demonstrated no difference between CBA and RFA in rates of freedom from atrial arrhythmias at 12 months follow-up, recurrent atrial arrhythmias and repeat ablations. Traditionally, point-by-point ablation is expected to have gaps in ablation lines and hence more recurrence compared to the "single-shot" approach offered by CBA.[21] Improved outcomes have been reported with RFA since the introduction of contact force-sensing catheter technology.[22] However, this modality was not used consistently in our component studies and pooled together with traditional RFA (Table 1). Hanninen et al have previously reported a higher incidence of recurrent arrhythmia with CBA compared to RFA, especially atrioventricular nodal reentrant tachycardia.[23] There have been two prior meta-analyses on this subject by Xu et al[24] and Kabunga et al.[25] We only included prospective and RCTs in our analysis as opposed to the prior meta-analyses, and incorporated data from 7 additional contemporary trials since the last meta-analysis. Our data did not detect any evidence of superiority in efficacy with either of the two modalities. Even after restricting the analysis to RCTs, no difference in the primary efficacy



Supplementary Figure 6: Forest plot demonstrating procedural outcomes in studies evaluating 2nd generation CBA catheter versus contact-sensing RFA catheter



Supplementary Figure 7: **Forest plot demonstrating safety outcomes – overall acute complications, groin site complications and transient phrenic nerve injury in studies evaluating 2nd generation CBA catheter and contact-sensing RFA catheter**

endpoints was observed between the two groups. Subgroup-analysis comparing the 2nd generation CBA with contact force-sensing RFA also demonstrated no significant difference in the primary efficacy end-points between the two groups (although results should be interpreted with caution in view of only 2 trials).

Procedural Characteristics

Contrary to the findings from prior meta-analyses by Xu et al[24] and Kabunga et al,[25] we found no significant difference in procedural characteristics including total procedural duration and fluoroscopy time. However, this needs to be interpreted with caution as a significant heterogeneity was observed in both these outcomes. The grouping of different techniques of RFA and different generations of CBA catheters could be a possible contributor to the significant heterogeneity observed in the participant studies.

Upon separate analysis of only the RCTs, there was reduced total fluoroscopic times in RFA group as compared to CBA group with no significant heterogeneity. The longer fluoroscopy times may be related to the impact of a learning curve for CBA. A steep learning curve with CBA has been shown in a large single center study even at a later stage in well-experienced center.[26] In the trials comparing only 2nd generation CBA catheters with contact-sense RFA catheters, no difference was observed, although significant heterogeneity persisted. This could possibly be due to local variations in experience and varied preferences in ablation technique.

Secondary Safety Outcomes and Associated Complications

Overall complications rate observed was similar to registry data previously reported by Deshmukh et al[27] and Cappato et al.[3] Although no significant difference in overall complications was observed between the two groups, it is imperative to discuss the pattern of individual complications observed with the two approaches. Higher incidence of groin-site complications were seen with RFA as compared to CBA with the effect persisting in the sub-analysis with RCTs. This can potentially be explained by increased groin injuries, which may be caused by the two-sheath system often used with RFA (a radiofrequency catheter and a separate mapping catheter).[28,29] Unfortunately, the included studies did not mention the number of sheaths used during the procedure to better quantify the role of this effect.

Additionally an increased incidence of hemodynamically significant pericardial effusion/cardiac tamponade was observed in the RFA group. However no difference was observed in the

Supplement Table 1: **Summary of Egger's and Begg's test for publication bias**

CBA versus RFA	Egger's test p-value	Begg's test p-value
Freedom from atrial fibrillation	0.83	1.00
Recurrent atrial arrhythmia	0.12	0.06
Repeat ablation	0.97	0.71
Overall complications	0.09	0.48

P value of <0.05 indicates publication bias

subgroup analysis for RCTs only. A total of 12 trials reported this complication[5-7,10,11,13,14,16-18,20] of which 3 were RCT's.[5-7] Number of transeptal punctures is a major factor contributing to development of cardiac tamponade or significant pericardial effusion.[30] In 6 trials, the use of a single or double transeptal puncture was not specified[5,7,11,13,14,18] a double transeptal puncture approach was performed in 2 trials[16,20] and a single transeptal puncture for CBA and double for RFA was performed in 4 trials.[6,10,12,17] The use of double transeptal puncture approach with RFA could have likely contributed to an increased incidence of cardiac tamponade in this group. However similar results were not observed in the subgroup analysis (RCT's only). This could be potentially due to the use of double transeptal approach in majority patients in both CBA and RFA groups (although this was not specified in the RCTs).

Cryoablation was predominantly complicated by transient and unresolved phrenic nerve injury. One of the potential reasons for this association could be from the forward pressure exerted during CBA with the sheath for achieving a satisfactory circumferential seal around the target pulmonary vein. This motion likely pushes the atrium closer to surrounding structures including the phrenic nerve. Majority of phrenic nerve injuries were transient and spontaneously resolved with progression of approximately 1.3% injuries to persistent phrenic nerve injury at 12 months.[31,32]

Study Limitations

Potential sources of bias in our study include combination of 1st and 2nd generation CBA catheters into one group and different approaches of RFA in a single group (irrigated catheters, contact force-sensing catheters and duty-cycled phased RFA) and inclusion of data from prospective non-randomized trials. Additionally, there was a lack of uniformity in the participant trials in protocol for detection of recurrent AF; specifically, the follow-up periods, mode of arrhythmia detection, inclusion of patients on anti-arrhythmic therapy for assessment of efficacy outcomes. We tried to eliminate some of these biases by performing a sub-analysis of RCTs, which demonstrated results similar to original analysis with both groups showing similar efficacy, procedural characteristics, and complications profile.

Conclusions

Our analysis demonstrates that the two technologies for catheter ablation of AF are equivalent in efficacy, procedural characteristics and overall complications with higher rates of groin site complications and significant pericardial effusion/cardiac tamponade in the RFA group and phrenic nerve injury in the CBA group. Based on these data, we believe that currently, there is insufficient evidence to suggest superiority of one ablation strategy over the other for pulmonary vein isolation. Our study highlights the need for better technologies that would help us achieve a more efficient and durable pulmonary vein isolation.

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Amiodarone-Induced Third Degree Atrioventricular Block and Extreme QT Prolongation Generating Torsade Des Pointes in Paroxysmal Atrial Fibrillation

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Abstract

Amiodarone is still the most potent antiarrhythmic drug in the prevention of life threatening ventricular arrhythmias and demonstrates a very low incidence of torsade de pointes. An unusual case of an 81-year-old woman who developed serious abnormalities of the conduction system of the heart and torsade des pointes during intravenous infusion of amiodarone for the treatment of paroxysmal atrial fibrillation is described. To the best of our knowledge, this is the first case showing an association of intravenous amiodarone-induced third degree atrioventricular block and extreme QT interval prolongation generating torsade des pointes in a patient with paroxysmal atrial fibrillation who required an implantable cardioverter-defibrillator. Currently, amiodarone is still one of the few remaining treatment options for the medical therapeutic management of serious ventricular arrhythmias and to reduce the incidence of atrial fibrillation without increasing mortality or sudden cardiac death rates in heart failure patients like our elderly present patient. Nevertheless, we have to keep in mind that intravenous amiodarone may generate serious abnormalities of the conduction system of the heart and lethal ventricular arrhythmias in certain patients.

Introduction

Lethal ventricular arrhythmias are one of the major causes of death in patients with structural heart disease. Several investigations have demonstrated the usefulness of intravenous amiodarone in the medical treatment of ventricular arrhythmias, and it is now recommended as a first line antiarrhythmic agent for the treatment of ventricular tachycardia (VT).[1-6] In addition, amiodarone plays a major role in the treatment of atrial fibrillation, especially in heart failure with severely impaired left ventricular function, where class-I antiarrhythmic drugs or dronedarone are contraindicated.[3,4]

We describe an unusual case of an 81-year-old woman who developed serious abnormalities of the conduction system and torsade des pointes during intravenous infusion of amiodarone during the treatment of paroxysmal atrial fibrillation. To the best of our knowledge, this is the first case showing an association of intravenous amiodarone-induced third degree atrioventricular block and extreme QT interval prolongation generating torsade des pointes in a patient with paroxysmal atrial fibrillation who required an implantable cardioverter-defibrillator.

Key Words:
Amiodarone, Torsade Des Pointes, Paroxysmal Atrial Fibrillation, Third Degree AV Block, QT Interval Prolongation, Implantable Cardioverter-Defibrillator.

Disclosures:
None.

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Case Report

An 81-year-old woman with arterial hypertension, transient ischemic attack, and paroxysmal atrial fibrillation presented with complaints of progressive dyspnea and inferior limbs edema that began 2 days earlier. She was receiving a daily ambulatory treatment of losartan 50 mg, carvedilol 25mg, atorvastatin 20 mg, amiodarone 200 mg, and acenocumarol. At the time of hospitalization, she was in New York Heart Association (NYHA) functional class III in atrial fibrillation with an irregular heart rate of 142 bpm; her blood pressure was 140/90 mmHg. She had moderate lung congestion, hepathomegaly, and inferior limbs edema was also present. The chest radiograph showed mild cardiomegaly and pulmonary venous congestion. The electrocardiogram (ECG) showed atrial fibrillation with rapid ventricular response, narrow QRS complexes with normal values of QT and QTc intervals (Figure 1). Transthoracic color-flow Doppler echocardiography revealed diffuse hypokinesia of the left ventricle with an ejection fraction of 48%, moderate mitral regurgitation with moderate left atrial enlargement.

She received 40 mg of furosemide, and a loading IV dose of 300 mg of amiodarone was begun with a maintenance IV dose of 900 mg

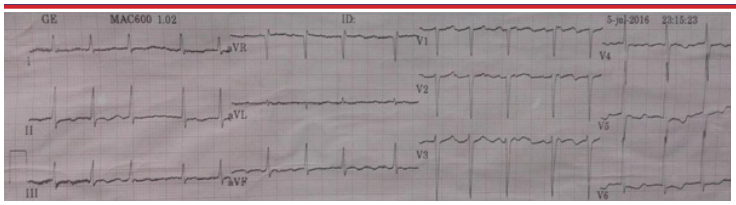

Figure 1: The 12 lead electrocardiogram shows atrial fibrillation with rapid ventricular response, narrow QRS complexes with normal values of QT and QTc intervals

for 24 hs. After 12 hs of amiodarone infusion she developed a sudden third degree atrioventricular block with narrow QRS junction escape and polymorphic premature ventricular contractions with R on T phenomenon (Figure 2). In addition, there was an extreme QT interval prolongation, the QT interval prolonged from 320 ms to 670 ms, and the QTc interval from 416 ms to 685 ms. There was no signs of acute ischemia, neither electrolyte disturbances. Blood tests were within normal limits including cardiac enzymes. There was no hemodynamic alteration. She remained conscious with no symptoms related to the bradiarrhythmia. The amiodarone infusion was immediately suspended and a Holter ECG monitoring was

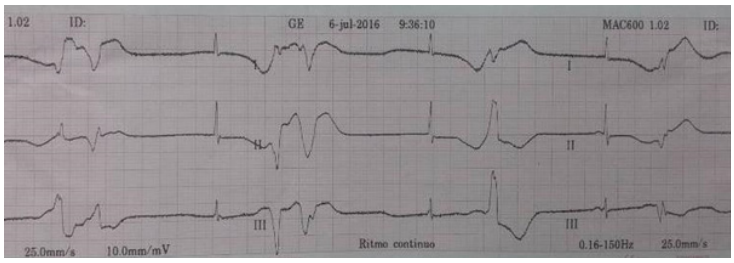

Figure 2: The rhythm trace electrocardiogram shows a sudden third degree atrioventricular block with narrow QRS junction escape and polymorphic premature ventricular contractions with R on T phenomenon. In addition, there is an extreme QT interval prolongation of 670 ms, and the QTc interval is 685 ms

installed. A few hours later she regained sinus rhythm with a low heart rate of 46 bpm, with persistent extreme QT interval prolongation with diffuse repolarization abnormalities (Figure 3). The same day she developed torsade des pointes that began with an R on T phenomenon, and degenerated to ventricular fibrillation which responded well to a DC shock with 200 joules (Figure 4). The Holter ECG monitoring revealed several non-sustained episodes of atrial fibrillation, frequent premature ventricular contractions and several episodes of non-sustained torsade des pointes. A coronary angiogram revealed only irregularities and non-significant stenosis of the left and right coronary arteries. An implantable cardioverter-defibrillator was installed, and the patient was discharged on optimal medical therapy for her heart failure, but without antiarrhythmic drugs because of persistent QT interval prolongation. One month later, while being in her house she received an appropriate shock due to ventricular fibrillation (Figure 5). A low oral dose of amiodarone was begun and she remains asymptomatic 3 months later in her follow-up visits.

Discussion

Amiodarone, a class-III antiarrhythmic drug, is considered as the most efficient agent for ventricular arrhythmias even in heart failure patients with severe left ventricular systolic dysfunction.[7] Amiodarone results in a rapid phase-III-repolarization and does not increase dispersion of repolarization. These electrophysiological findings are present in healthy hearts and are preserved in heart failure contributing to its low pro-arrhythmic potential.[8] Although, intravenous amiodarone is generally regarded as a safe medical treatment, there are several reports on pro-arrhythmia inducing torsade des points under certain conditions including electrolyte imbalance.[9-12] We report this unusual case of an elderly woman who developed serious abnormalities of the conduction system and torsade

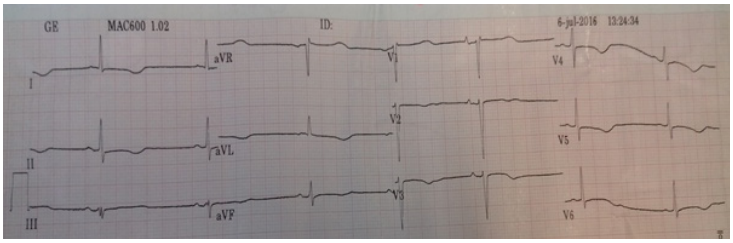

Figure 3: The 12 lead electrocardiogram shows sinus rhythm with a low heart rate of 46 bpm, with persistent extreme QT prolongation with diffuse repolarization abnormalities

des pointes in association with intravenous infusion of amiodarone during the acute treatment of paroxysmal atrial fibrillation. To the best of our knowledge, this is the first case showing intravenous amiodarone-induced third degree atrioventricular block and extreme QT interval prolongation generating torsade des pointes in an elderly patient with paroxysmal atrial fibrillation who required an implantable cardioverter-defibrillator.

Amiodarone is broadly utilized in our emergency department of outpatient clinics, and it is by far the most used antiarrhythmic drug for wide complex tachycardias in our hospital. It is well known that the electrophysiological effect of amiodarone is different when it is administered orally or intravenously.[2] While being on oral amiodarone, our patient did not have the abnormalities of the

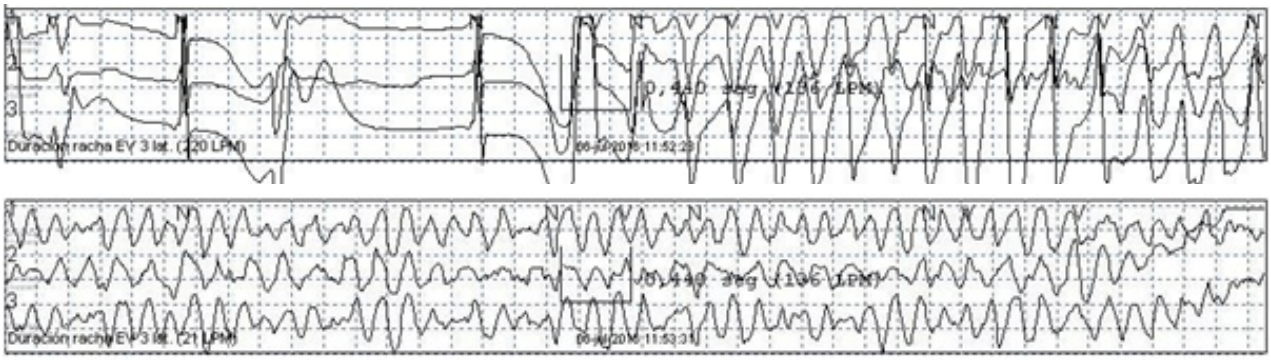

Figure 4: A: The Holter ECG recording shows the initiation of a sustained episode of Torsade des pointes that began with an R on T phenomenon. B: The Holter ECG recording shows the sustained episode of Torsade des pointes which begins degeneration to ventricular fibrillation

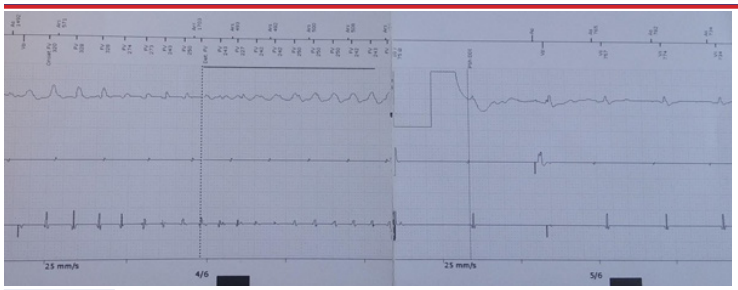

Figure 5: Representative electrograms obtained upon device interrogation. The device recorded tracings show stored atrial and ventricular intracardiac electrogram signals depicting an episode of ventricular fibrillation which subsides with an appropriate shock

conduction system mentioned earlier, neither the lethal ventricular arrhythmias that she presented in this hospitalization. However, the story was different with intravenous amiodarone. We searched for other causes that could explain this outcome. She did not present signs of acute ischemia, neither electrolyte disturbances, and other blood tests were within normal limits. Since she had diffuse hypokinesia of the left ventricle with an ejection fraction of 48%, a coronary angiogram was performed which revealed only irregularities and non-significant stenosis of the epicardial coronary arteries ruling out ischemic heart disease.

Amiodarone is the most potent antiarrhythmic agent in the prevention of lethal ventricular arrhythmias and demonstrates a very low incidence of torsade de pointes. Several randomized, controlled, clinical trials like, CHF-STAT, CAMIAT, and EMIAT trials showed that amiodarone lacked proarrhythmia and reduced the incidence of VT and arrhythmic death in high-risk patients.[12-18] It was demonstrated that amiodarone has a low proarrhythmic potential in normal hearts due to a fast phase-III repolarization, a low incidence on dispersion of repolarization, a lower potential to induce early after depolarizations, and a weak effect on reverse-frequency dependence.[18] In addition, amiodarone does not seem to increase the risk of proarrhythmia or sudden cardiac death despite marked QT-prolongation.[16] However, our elderly patient had an organic heart disease, and with the extreme QT prolongation in association with intravenous amiodarone presented an episode of torsade des pointes that required electrical cardioversion. Although proarrhythmic effects of amiodarone are rare, some patients occasionally develop polymorphic VT of torsade de pointes.[3,4] Although amiodarone blocks multiple ion currents in the heart,[17] the electrophysiological effects by which amiodarone exerts its strong antiarrhythmic action and its low proarrhythmic effects are not well understood. Intravenous amiodarone inhibits sodium channels, inward L-type calcium channels, and has noncompetitive beta-blockade effect. In addition, it also has potassium channel blockade effect which becomes more apparent after long-term oral therapy. The extreme QT interval prolongation can be explained by potassium channel blockade effect of intravenous amiodarone. There is a growing need for antiarrhythmic pharmacological drugs to prevent episodes of ventricular arrhythmias and frequent appropriate discharges of implantable defibrillators. Since amiodarone has been shown to reduce the burden of arrhythmic events and ICD-shocks,[2] we initiated oral amiodarone in the follow-up visit after documenting an ambulatory ventricular fibrillation and an appropriate ICD shock which saved her life. Although, intravenous amiodarone began all the serious abnormalities of the conduction system and the torsade des pointes in our patient with paroxysmal AF, we decided to begin low oral dose of amiodarone and she remains asymptomatic 3 months later in her follow-up visits after the appropriate ICD shock.

Conclusions

Currently, amiodarone is still one of the few remaining treatment options for the medical therapeutic management of ventricular arrhythmias and to reduce the incidence of atrial fibrillation without increasing mortality or sudden cardiac death rates in heart failure patients like our elderly present patient.[1] Nevertheless, we have to keep in mind that intravenous amiodarone may generate serious abnormalities of the conduction system and lethal ventricular arrhythmias in certain patients. In conclusion, despite the safe proarrhythmic profile of amiodarone, we described an unusual case showing intravenous amiodarone-induced third degree atrioventricular block and extreme QT interval prolongation generating torsade des pointes in an elderly patient with paroxysmal atrial fibrillation who required an implantable cardioverter-defibrillator.

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Strategies to Improve Safety and Efficacy of Atrial Fibrillation Ablation Using Electrode Multipolar Phased RF PVAC™ Catheter: a Case Report

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Abstract

Phased radiofrequency ablation with a single catheter technique, using a 9-electrode circumferential catheter, is a viable approach to pulmonary vein isolation for the treatment of atrial fibrillation. However, creating effective transmural lesions with such technique, while avoiding serious complications like atrioesophageal fistula, can be difficult. This case illustrates a challenging scenario, where catheter maneuvers fail to allow safe radiofrequency delivery, due to esophageal temperature rise, despite extensive navigating maneuvers. Changing the bipolar-to-unipolar ratio of energy delivery, from 2:1 to 4:1, allowed the creation of effective lesions, avoiding excessive increase in esophageal temperature.

Introduction

Atrial fibrillation (AF) is the most common supraventricular tachyarrhythmia in clinical practice. Pulmonary veins (PVs) isolation is an effective treatment for recurrent, symptomatic, drug-refractory AF. The most widely used approach, with point-by-point ablation at the PV antrum, is a complex and time-consuming procedure. A single catheter technique, with phased radiofrequency (RF) delivery using a 9-electrode circumferential catheter (PVAC), has emerged as a viable alternative.[1] Despite the advantages of this approach, creating permanent, transmural lesions, while avoiding serious complications like atrioesophageal fistula, can be challenging.

Case Report

A 72-year-old female was referred to catheter ablation due to symptomatic paroxysmal AF, refractory to amiodarone. Her CHA_2DS_2VASc score was 3 and the procedure was performed under general anesthesia and therapeutic anticoagulation with warfarin (INR value ≥ 2). After a single venous femoral access, heparin was administrated (100U/kg bolus) before left atrium access, and continued throughout the procedure, to maintain ACT levels ≥350 s. A single transeptal puncture was performed, guided by fluoroscopy and intracardiac echocardiography. Luminal esophageal temperature (LET) was continuously monitored with a multi-sensor esophageal temperature probe (Circa Scientific, Park City, UT, USA). Electrical isolation was achieved in all four PVs using the multipolar circular ablation catheter PVAC™ Gold and the GENius generator (Phased RF system, Medtronic Ablation Frontiers, Carlsbad, CA, USA). The RF generator delivered duty-cycled unipolar and bipolar energy between the selected electrodes pair, targeting each PV antrum, in a temperature-controlled, power-limited fashion (60°C, maximum 10 W). During ablation of the left superior PV, RF delivery was limited by consistent elevation of LET (35.7 to 38.5°C). After many attempts of repositioning the catheter (Fig.1), complete isolation was achieved by increasing the bipolar-to-unipolar ratio of energy from 2:1 to 4:1 at the electrode pair associated with LET rise, which remained below 37.8°C throughout ablation.

Discussion

This case illustrates a challenging situation, common to most approaches to AF ablation, but with aspects specific to this new technology. Although there is still a debate regarding its utility to avoid esophageal damage, monitoring of LET is used by most electrophysiologist to titrate RF energy or reduce delivery duration. We used a multi-sensor esophageal temperature probe, that enhances esophageal coverage with 12-point temperature sensing.[2]

Once an area of LET increase is identified, maneuvers to navigate the PVAC aiming to find safer positions (steering, rotating, pulling

Key Words:
Multipolar, Phased, PVAC, Ablation.

Disclosures:
None.

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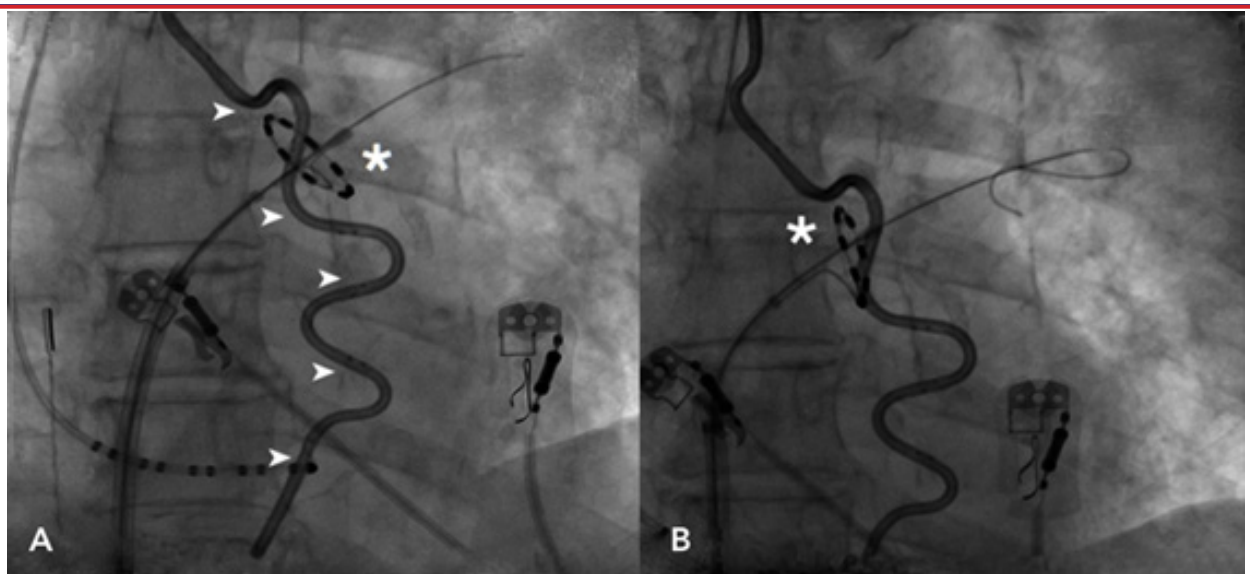

Figure 1: **Fluoroscopy shows the PVAC catheter at the left superior PV antrum (asterisk), in two different positions and orientations (A and B). After several maneuvers (rotating, pulling and pushing, sliding), RF delivery still caused consistent elevation of esophageal temperature, up to 38.5°C, monitored by the multi-sensor esophageal temperature probe (arrowheads)**

and pushing, sliding) are tried first. If this fails, changing the energy settings by delivering RF in different bipolar-to-unipolar ratio, can reduce the lesion depth while assuring transmural lesion (fig. 2). This can be explained by the fact that unipolar RF current flows from the electrode to the reference patch, causing deeper lesions, while bipolar current flows between two adjacent electrodes, creating more superficial lesions.[3,4] In our case, changing the ratio from 2:1 to 4:1 enabled us to safely isolate the left superior PV.

Conclusions

Multipolar phased PVAC catheter ablation is a feasible and safe option for PV isolation. Monitoring of esophageal temperature is important to minimize the risk of esophageal injury. When catheter maneuvers fail to allow safe RF delivery due to esophageal temperature rise, changing the bipolar-to-unipolar ratio to 4:1 can influence the depth of lesions, enabling the creation of more superficial yet effective lesions.

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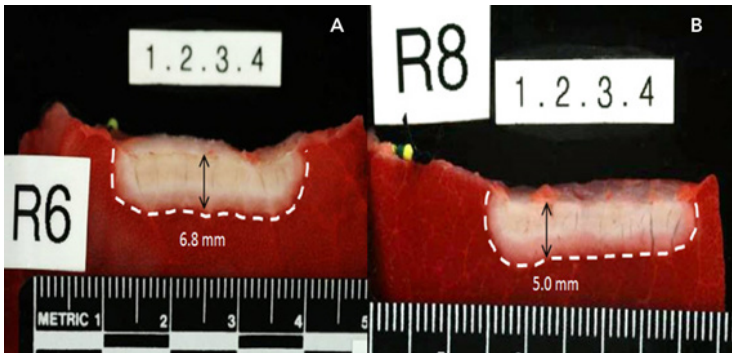

Figure 2: **Different lesion depth on porcine thigh muscle preparation with energy delivered on a 2:1 bipolar-to-unipolar ratio (A) and 4:1 ratio (B). Courtesy by Medtronic**

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Mobitz Type 2 AV Block Dissolved With Contrast Injection

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Abstract

There are many cases in the literature concerning the occurence of atrioventricular block in acute myocardial infarction. The prevelance and management of AV block in the setting of chronic myocardial ischemia remains unclear. Our case presented with stable angina pectoris. Treadmill test revealed Mobitz Type 2 AV block which disappeared with contrast injection and re-occured after injection during PCI.

Introduction

Coronary artery disease (CAD) is the underlying mechanism of high degree atrioventricular (AV) block in 40% of patients.[1] However, the prevalence and management of AV block in the setting of chronic myocardial ischemia remains unclear. Here, we report a Mobitz type 2 AV block patient due to chronic ischemic heart disease which was successfully treated by percutaneous coronary intervention (PCI).

Case

A fifty-five years old male admitted to our hospital with stable angina pectoris. There are hypertension, diabetes mellitus and PCI of obtuse marginal branch of left circumflex coronary artery (LCx OM) on his background. Electrocardiogram (ECG) showed sinus ryhthm with incomplete right bundle branch block (RBBB) and rate of 65/min. A transthoracic echocardiography (TTE) revealed hypokinesia of inferolateral wall of left ventricle and ejection fraction was 50% .Treadmill test was normal in means of ischaemic changes but Mobitz Type II block occured during exercise and disappeared in recovery period. Mobitz Type II block was also occurred transiently after treadmill exercise test and the rhythm was Mobitz Type II block when the patient was taken to catheterization lab. Coronary angiography (CAG) revealed 80% restenosis of Cx OM stent. Mobitz type 2 AV block disappeared with contrast injection to left coronary system and re-occurred after contrast injection (Figure 1). So, we thought block was associated with ischemia related to CX OM stent restenosis and restenosis was treated by balloon angioplasty (Figure 2). After balloon angioplasty the rhythm was totally normal. After three days of intervention, the electrophysiological study was normal and after ten weeks AV block was not found on the surface ECG, exercise test or 24 hours holter ECG. After 1years the patient was hospitalized due to syncope and the ECG revealed Mobitz type II block again. We performed CAG and Cx stent restenosis was revealed. After it was treated with drug eluting balloon angioplasty the rhythm was normal sinus rhythm.

Discussion

Although ischaemic ECG changes are well established risk factors for long term cardiovascular end points, occurrence of AV block during treadmill test is an area of uncertainty. In our patient, Mobitz Type II AV Block (occurred during treadmill test and disappeared with contrast injection) dissolved after PCI. This may be related to ischemia of AV node which is supplied by the RCA in 90% of general population, and by the LCx in 10% of population.[2] Dissolving of AV block with contrast injection and occurring again after contrast injection in LCx may indicate that AV node is supplied by LCx in this patient.

Yildiz et al[3] examined four patients presenting with second or third degree AV block not related to acute or previous myocardial infarction and vasovagal syncope. Angiography revealed single vessel coronary artery disease with a critical stenosis in the proximal segment of the RCA, which was the dominant artery. They have performed stent implantation to RCA and AV block was reversed to sinus rhythm.

Arterial supply to the AV nodal territory is usually abundant.[3] Even in the presence of lesion in the RCA or LCx, from which AV nodal artery originates, there was alternate anatomical supply to the AV node, ischemia induced AV block was rarely seen.

In our case during CAG, AV block was disappeared with contrast injection. According to our hypotheses the blood flow in the stenotic vascular bed was restored with the compressive contrast injection. Because of the sufficient blood flow to ischemic myocardium was

Key Words:
Atrioventricular Block, Coronary Artery Disease, Percutaneous Coronary Intervention, Stable Angina Pectoris.

Disclosures:
None.

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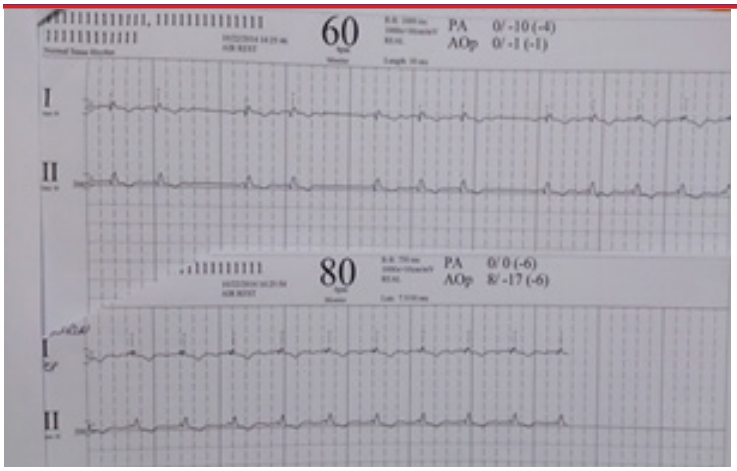

Figure 1: **Mobitz type 2 AV block disapperaed with contrast injection to left coronary system and reoccured after contrast injection**

supplied with contrast injection, AV block was disappeared. After contrast injection stenotic coronary artery was not able to supply enough blood to territory of Cx artery, the rhythm was again Mobitz Type II AV block.

Conclusions

In the light of our case and previous case reports; patients with intermittan AV block should undergo an evaluation of ischemia and permanent pacemaker implantaion may be deferred until the results of coronary angiography.

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Atrial Fibrillation Triggered By Drug-Induced Bradycardia

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Abstract

Atrial fibrillation (AF) is the most frequently observed arrhythmia in clinical practice. Many causative factors have been identified from well-known structural heart disease to less understood triggers. Both sympathetic and parasympathetic (vagal) stimuli are able to trigger paroxysms of AF. Vagally mediated AF is especially observed in young healthy subjects and especially during nights when the heart rate is considerably slow. Tachycardia induced AF is demonstrated and the possible mechanisms are explained. However, a case of bradycardia induced AF, thus far, hasn't been reported. Here we present a case of AF induced by severe bradycardia which was triggered by concomitant use of beta-blockers and diltiazem.

Introduction

Atrial fibrillation (AF) is the most common arrhythmia encountered in cardiology practice. AF is associated with increased risk of all-cause mortality (approximately twofold) and 4- to 5-fold increase in the risk of stroke.[1] Major risk factors for AF are mainly structural heart disease (hypertensive heart disease, ischemic heart disease, mitral valve disease, cardiomyopathies) and pulmonary hypertension. The most common reversible or temporary causes are hyperthyroidism, cardiothoracic surgery, acute myocardial infarction, myocarditis and pericarditis. AF is sometimes triggered by tachycardia. Especially AV nodal reentrant tachycardia and Wolff-Parkinson-White syndrome are reported to trigger AF. Here, we report an unusual case of bradycardia induced AF, which was triggered by concomitant use of carvedilol and diltiazem and converted to sinus rhythm by atropine.

Case

A 70-year-old man admitted to cardiology clinic with complaints of dizziness and fatigue. Physical examination was normal except for bradyarrhythmic pulse and borderline hypotension; 90/60 mmHg. History revealed concomitant use of carvedilol 6.25 mg and diltiazem 120 mg per day. His prior electrocardiography (ECG) was within normal limits. The admission ECG showed atrial fibrillation with slow ventricular response with a pulse of 45/min (Figure 1). The patient was hospitalized for symptomatic bradycardia, monitorized and soon atropine 1 mg was given intravenously. The patient's rhythm immediately converted to sinus rhythm with a pulse of 90/min and first-degree atrioventricular block (PR duration of approximately 240 ms) (Figure 2). The patient was monitorized for one day and sinus rhythm persisted. The next day he was discharged and outpatient follow-up visits confirmed the persistency of normal sinus rhythm.

Key Words:
Atrial Fibrillation, Bradycardia, Beta Blockers.

Disclosures:
None.

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Discussion

Atrial fibrillation is the most common arrhythmia and there are many reports indicating different triggers. Triggering and maintenance mechanisms may differ substantially. Along with well-known structural heart diseases, obesity and obstructive sleep apnea are independent risk factors for incident AF.[2] AF is sometimes triggered by tachycardias. First, the observation that elimination of atrioventricular nodal reentrant tachycardia (AVNRT) and atrioventricular reentrant tachycardia (AVRT) by radiofrequency catheter ablation also eliminates AF in many patients led to the conclusion that AF, at least in these patients, is triggered by tachycardia.[3] Since bradycardia induced AF, according to our search, has not been reported yet, its underlying mechanisms remain unclear. However, it is well known that vagally mediated AF exists in young healthy individuals especially during episodes of bradycardia (e.g. during sleep). Attacks usually start at night, lasts for a few hours and in the morning the rhythm usually converts to sinus rhythm.[4]

In our case, severe bradycardia associated with concomitant use of a beta-blocker with diltiazem can be considered to share common properties with vagally induced AF, which is also observed during episodes of bradycardia. Management is different from adrenergically mediated and other forms of AF. Beta-blockers and digoxin are especially harmful and must be avoided. In our patient, withdrawing the offending agents was enough for maintenance of normal sinus rhythm. Outpatient follow-up confirmed that the patient was on sinus rhythm and free of symptoms.

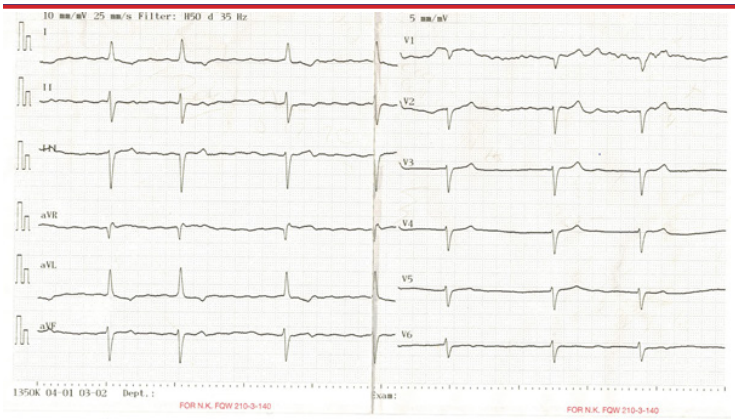

Figure 1: **Admission ECG showing atrial fibrillation with a slow ventricular response (heart rate approximately 45 beat per minute)**

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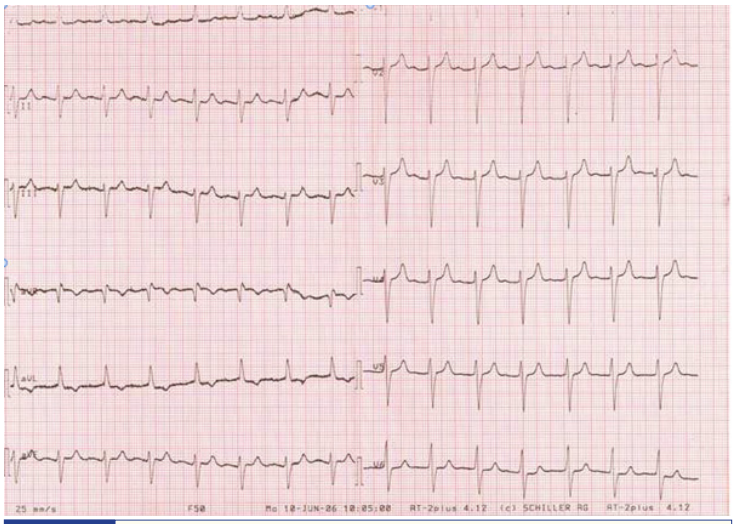

Figure 2: **ECG obtained after administering intravenous atropine showing sinus rhythm with first-degree atrioventricular block**

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Emergency Covered Stent Implantation For Rupture Of A Pulmonary Vein After Balloon Angioplasty For Postinterventional Pulmonary Vein Stenosis

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Abstract

Pulmonary vein (PV) stenosis is a known complication of PV isolation procedures for atrial fibrillation. We describe in this report a case of emergency covered stent implantation for rupture of a PV after balloon angioplasty for postinterventional PV stenosis occlusion. Focus is on stent implantation and on a novel aspect of magnetic resonance imaging for postprocedural outcome evaluation. A focused review of the current literature regarding ongoing limitations of PV stenosis treatment is provided.

Introduction

With the rise of radiofrequency ablation for atrial fibrillation pulmonary vein stenosis (PVS) has become an important complication to consider. Event rates vary considerably depending on post-procedural screening and pulmonary vein isolation (PVI) technique. In recent publications event rates were reported to be as low as 0.5-2%.[1,2] Historically treatment has often been associated with less than desirable outcome. More recently an interventional approach has been described[3,4] which caters for some but not all procedural difficulties. Furthermore there are some complications, which can occur during dilatation of the pulmonary vein. Here we describe one of these complications, rupture of the pulmonary vein, the management of this problem by stenting and considerations for follow-up by CMR angiography.

Case Report

A 43 year old male patient was referred to our hospital for balloon angioplasty (BPVA) of a recurrent stenosis of the left inferior pulmonary vein (LIPV) stenosis as diagnosed by MR angiography (Figure 1a-b). He had undergone a BPVA procedure 3 month previously for pulmonary vein stenosis after pulmonary vein isolation for atrial fibrillation. The patient was symptomatic with severe dyspnea on exertion and hemoptysis. Angiography of the LIPV following fluoroscopy-guided transseptal puncture and placement of a steerable sheath (Agilis, St. Jude Medical) confirmed subtotal stenosis. We then performed balloon dilatation (6x20mm balloon at 16atm for 20 seconds and 8x20mm balloon at 14atm for 14 seconds, Maverick, Boston Scientific). Shortly thereafter, the patient developed acute pericardial tamponade (Video 1) due to rupture of the LIPV (Figure 2a,d; Video 2). Pericardial effusion was confirmed by echocardiography and treated by pericardial drainage. The patient stabilized under continuous autotransfusion and catecholamine support. A covered stent (Advanta V12 Atrium 10x38mm) was deployed (Figure 2c,f) in the LIPV. Subsequent angiography showed no further contrast extravasation (Video 3). Postinterventional course was uneventful. MR angiography after 2 days and six weeks confirmed a patent LIPV. The implanted stent type resulted in artifacts on CMR cine-imaging (SSFP sequence, Figure 3a,c) but allowed evaluation of stent patency on contrast-enhanced CMR angiography (Figure 1c, Figure 3b,d).[5]

For prevention of stent-thrombosis and stroke the patient received dual antiplatelet therapy (clopidogrel 75mg and aspirin 100mg o.p.d.) and novel oral anticoagulant (apixaban 2,5mg o.p.d).

Six weeks after the procedure CMR angiography revealed a patent stent and the patient had markedly improved (Video 4).

Discussion

PV stenosis is an increasing problem and rupture of PVs during BPVA may result in potentially lethal bleeding and hence, interventionalists must be prepared to handle such an emergency

Key Words:
Pulmonary Vein Stenosis, Balloon Angioplasty, Pulmonary, Vein Rupture, Pericardial Effusion, Covered Stent, MR Angiography.

Disclosures:
None.

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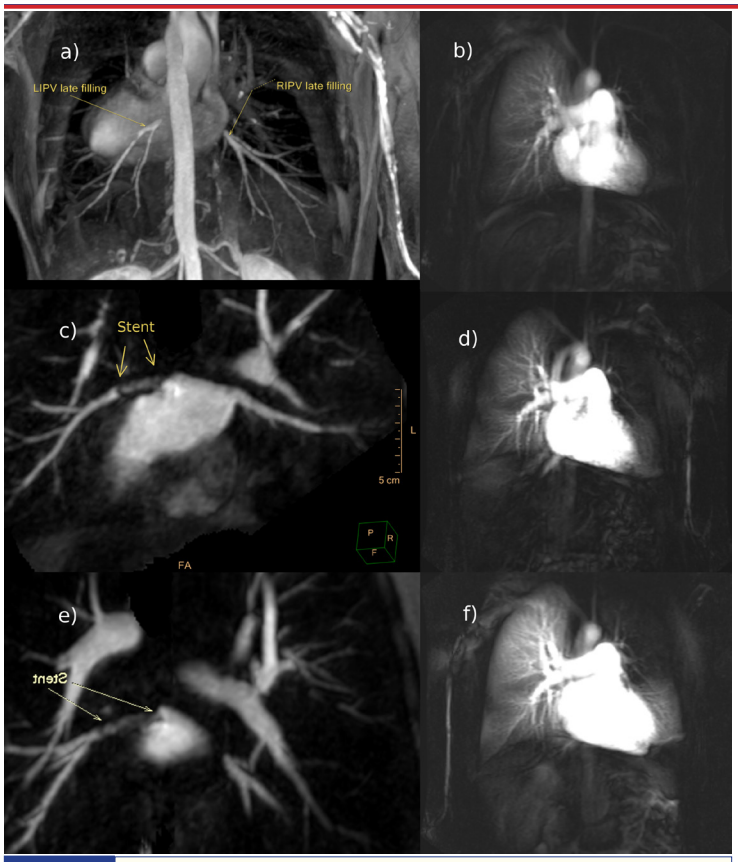

Figure 1: CMR-angiography before and after the procedure. Before the procedure the left inferior and right inferior pulmonary vein show very late filling (a). Realtime bolus tracking of the contrast medium (b) demonstrated significantly earlier filling of the right compared to the left lung vessels/parenchyma (bright) thereby indicating limited drainage via the left inferior pulmonary vein. After stenting (day 2: c,d; after six weeks: e,f) the left and right inferior vein fill simultaneously indicating improved lung perfusion/drainage. Note the lack of perfusion of the left upper lobe resulting from a chronically occluded LSPV. The covered stent in the left inferior pulmonary vein is clearly visible (c,e)

situation. Balloon angioplasty for treatment of PVS with or without stent placement for prevention of restenosis[6] as well as covered stent implantation for rupture of the ascending aorta after balloon angioplasty[7] has been reported. However, currently no data regarding the use of covered stents in the setting of pulmonary vein rupture are available. Treatment of PV rupture with a covered stent not only provides a treatment option for the complication but can potentially help maintain vessel patency. However stent availability is limited and point of care availability of covered stents with the correct dimensions can decide the fate of a patient.

No standard treatment for PVS exists. Especially subtotal or total occlusions are difficult to manage. Balloon dilatation - alone or in combination with stent placement - has evolved as recommended treatment. There is few data for stents (bare-metal or drug-eluting) regarding the safety and the potential to withstand restenosis. In the low flow system of the PVs stents smaller then 1cm seem to be at higher risk of occlusion.[6] There is no hard evidence that would support a preference of DES in this setting. However experimental data shows that PTA with a drug eluting balloon immediately following intentional ablation of the PV ostia reduces PV stenosis compared to ablation without DE-balloon treatment. Clearly randomized trials

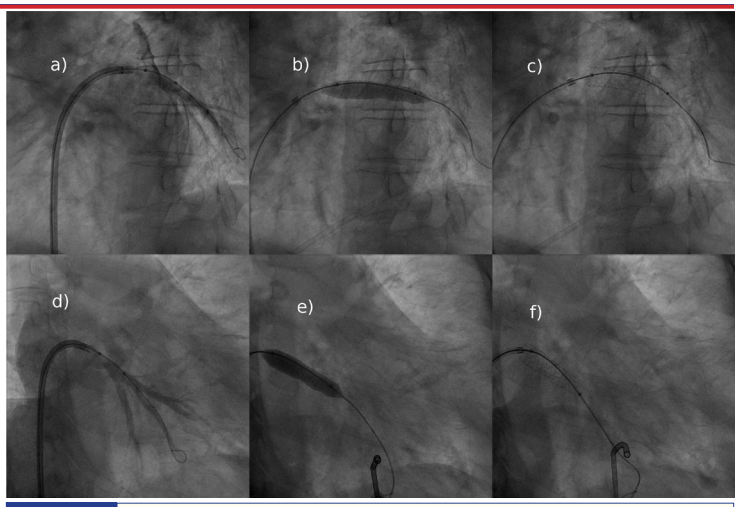

Figure 2: Left anterior oblique (a-c) and right anterior oblique projection with caudal angulation (d-f)) Selective angiography of the left inferior pulmonary vein (LIPV) revealing contrast extravasation at the site of pulmonary vein rupture immediately after balloon dilatation (a, d). Implantation of a stent (b, e) and final stent position (c, f) are shown. Also note pericardial drainage (e, f)

are needed. Besides the high incidence of unfavorable outcomes (e.g. restenosis or recurring occlusion) one has to keep in mind that these procedures are associated with a significant risk of procedural complications. Stent placement can result in stent thrombosis which potentially leads to a stroke. Anticoagulation regimens in this setting are a constant matter of debate.

CMR-based follow-up to detect restenosis or occlusion is recommended over CT-angiography or even direct fluoroscopic evaluation. CMR angiography is less invasive and contrast media is usually well tolerated even in patients with impaired renal function. Careful stent selection is important as imaging artifacts caused by stents made from stainless steel tend to obscure the stent lumen. Stents made from tantalum or nitinol usually allow for the evaluation of the stent lumen.[5] As observed in our case not only stent material but also imaging sequence plays a role in stent visibility.

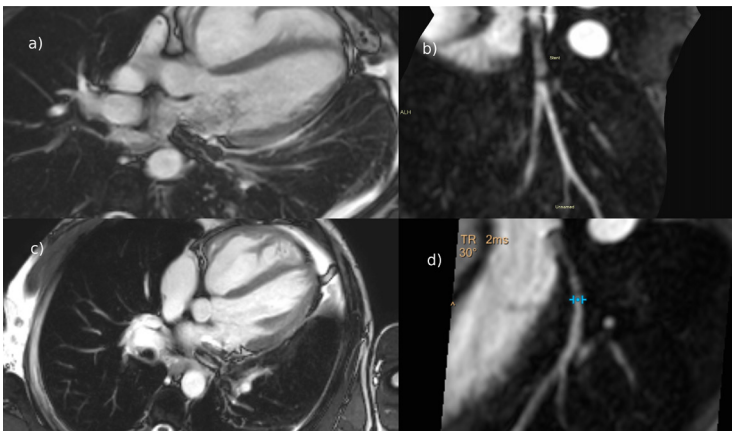

Figure 3: Cardiac magnetic resonance imaging on day 2 after stent placement (a-b) and during six-weeks-follow-up (c-d): imaging artefacts related to the covered stent of the left inferior pulmonary vein vary with the imaging sequence used and may allow for only limited in stent lumen visibility (SSFP-cine sequence, a, c). On contrast enhanced CMR angiography however, luminal visibility was improved and together with depiction of peripheral pulmonary vein branches revealed a vastly patent stent at follow up (day 2, b; six weeks after the procedure, d)

Conclusions

Several viable options for the treatment of pulmonary vein stenosis exist. In the event of periprocedural PV rupture placement of a covered stent has the potential to avoid cardiac surgery. Exact knowledge of the PV's diameter is of utmost importance for the selection of an appropriate stent. The issue of anticoagulation in this setting is largely unsolved and warrants further studies. CMR imaging may be used to effectively diagnose PV stenosis and postinterventional angiographic success.

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Brugada Syndrome:Risk Stratification And Management

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Abstract

The Brugada syndrome (BrS) is an arrhythmogenic disease associated with an increased risk of ventricular fibrillation and sudden cardiac death. The risk stratification and management of BrS patients, particularly of asymptomatic ones, still remains challenging. A previous history of aborted sudden cardiac death or arrhythmic syncope in the presence of spontaneous type 1 ECG pattern of BrS phenotype appear to be the most reliable predictors of future arrhythmic events. Several other ECG parameters have been proposed for risk stratification. Among these ECG markers, QRS-fragmentation appears very promising. Although the value of electrophysiological study still remains controversial, it appears to add important information on risk stratification, particularly when incorporated in multiparametric scores in combination with other known risk factors. The present review article provides an update on the pathophysiology, risk stratification and management of patients with BrS.

Introduction

Brugada syndrome (BrS) is an inherited arrhythmogenic disorder characterized by an elevated ST-segment and J-point in the right precordial leads of an electrocardiogram (ECG) in the absence of structural heart disease, and it may cause sudden cardiac death due to ventricular fibrillation (VF).[1] Currently, BrS is diagnosed using criteria from the second consensus report, which was released in 2005.[2] According to the report, the new diagnostic criteria require typical ECG changes in one precordial lead.

Since BrS was described in 1992, a tremendous number of BrS cases have been reported,up to 1–5/10,000 worldwide.[3-4] Mastuo et al. investigated 4,788 subjects (1,956 men and 2,832 women) who were < 50 years old in 1958 and had undergone biennial health examinations, including electrocardiography, through 1999. The prevalence and incidence of the BrS ECG pattern were 146.2 in 100,000 persons and 14.2 persons per 100,000 person-years, respectively.[5] The average age at presentation of BrS was 45 ±10.5 years, with a peak at 30-40 years of age, and the incidence was nine times higher among men than women.

The implantation of cardiovertor defibrillator (ICD) is the only reliable therapeutic modality to prevent sudden cardiac death from cardiac arrest (CA).[6-8] ICD is clearly indicated for those with prior CAof VF. However, for asymptomatic patients with BrS, a risk stratification is needed. This article reviews the current status of risk stratification for BrS and management of the patients.

Key Words:
Brugada Syndrome, Risk Stratification, Electrophysiological Study, Sudden Cardiac Death.

Disclosures:
None.

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History Of CA

BrS patients with a history of CA carry the highest risk for recurrence of CA (Figure-1), and implanting ICD is considered a necessary precaution.[6-8]

In the first report by Brugada et al.[9] in 1998, VF recurred in 34% of symptomatic patients with previous CA or syncope during a follow-up period of 34 months with 12 % recurrence per year. In their subsequent report in 2002,[10] 12 (62%) out of 71 patients who presented with CA developed new arrhythmic events during a mean follow-up period of 54 months (13.8% per year). In the study of Eckhardt et al.,[11] the arrhythmic event rates of patients with aborted sudden death was lower: 5.1% per year. The risk of recurrent VF among patients presenting with CA can be estimated as 10% at 4 years,[12,13] and >40% at 7 years.[14-15] The mean time from presentation to VF recurrence was 1.5-2 years,[15-16] but late recurrence (>5 years after the initial event) was not rare. Similar event rates were observed in studies from Japan: 8.4 % to 11.6% per year.[16-18]

VF storms defined as ≥ 3 separate VF episodes within 24 hours have occured before and after ICD implantation in up to 24 % of the patients with appropriate ICD shocks.[15,16,19] In the series with the longest follow-up ≥5 years for 75% of the patients,[20] VF storms occurred in 12 % of those initially presenting with CA. Of the 22 men with BrS who presented with VF storms, 12 patients (54.5%) suffered VF recurrences at 21 ± 24 months after the first arrhythmic storms whereas only 1 (5.9 %) out of 17 patients with a history of a single VF episode suffered VF recurrence.[19] Spontaneous type I ECG patterns and J waves were found in 77.3% and 36.4 % of patients with VF storms vs. 28.2 % (P < 0.0001) and 9.1 % (P=0.0007) in age- and sex-matched controls of BrS patients without VF storms,

respectively. Patients with ES are at risk of VF storm recurrence.[15,16,19]

Patients with a personal history of aborted sudden death have a substantial risk for recurrence of arrhythmic events and the implantation of ICD is indicated as Class I.[6-8]

Syncope

Arrhythmic (or malignant) syncope is suspected in the absence of prodromes and specific triggering circumstances when a brief loss of consciousness occurs with a rapid return. Sacher et al.[20] defined syncope based on a clinical impression as "probably arrhythmic," "probably vagal," or "syncope of unclear mechanism" in 40%, 30%, and 30% of patients, respectivel, including 57 BrS patients. VF occurred during follow-up in 22% of the patients with presumed arrhythmic syncope but in none of the other patients.

In another study of 118 patients with syncope,[21] 12% of those presumed to have arrhythmic syncope, but none of those with "non-arrhythmic syncope", developed VF during the follow-up period 4.5 years. Take et al.[22] studied 84 patients with type 1 electrocardiograms and syncope (41 patients with prodrome and 43 patients without prodrome), and followed the patients for 48 ± 48 months. Syncope due to VF recurred in 13 patients among patients with unexplained syncope and was more frequent in the non-prodromal group than in the prodromal group. Blurred vision (hazard ratio [HR] 0.20) was negatively associated with VF occurrence and abnormal respiration (HR 2.18) or fragmented QRS (HR 2.39) was positively associated with VF occurrence.

Vagal syncope can occur in patients with BrS with concomitant accentuation of the ECG pattern in BrS.[23] A detailed clinical history at the time of syncope is essential to distinguish benign syncope from malignant syncope.

Priori et al. analyzed risks of cardiac events in 200 patients withy BrS;130 probands and 70 affected family members, and observed that the association between syncope and spontaneous ST-segment elevation was the strongest risk for cardiac events,[24] and this was confirmed by other workers: a risk for recurrence of arrhythmic events that ranges from 2.6-6.4% with an annual rate of 1.4-4.0 % per year as shown in Figure-1.[11,12,16-19,25-29] Some investigators propose syncope in patients with spontaneous type 1 ECG or fragmented QRS is a predictor of arrhythmic events,[24-27] whereas others do not believe there is enough evidence to support the connection denied by others.[30-31]

In BrS, ICD implantation can be considered useful in patients with a history of syncope judged to be likely caused by ventricular arrhythmias.[8]

ECG Markers

A diagnosis of BrS is confirmed by the presence of a type 1 pattern, which is a coved-type ST elevation (≥ 2 mm) descending slowly and emerging into a negative T with little or no isoelectric separation, in ≥ 1 precordial leads (V1 to V3) at the 4th, 3rd, 2nd intercostal spaces, either spontaneously or following administration of sodium channel agents.[2] In addition to its diagnostic value, some ECG markers have been studied as risks for arrhythmic events in asymptomatic BrS.

Spontaneous Type 1 ECG Pattern

In the FINGER study,[13] 1,090 patients were recruited from 11 tertiary centers in 4 European countries (745 men; 72%) with a median age of 45 (35 to 55) years. The inclusion criteria consisted of a type 1 ECG present either at baseline or after drug challenge. During follow-up up of 31.9 (14 to 54.4) months, the cardiac event rate per year was 7.7% in patients with aborted CA, 1.9% in patients with syncope, and 0.5% in asymptomatic patients. The aforementioned symptoms and spontaneous type 1 ECG were predictors of arrhythmic events, whereas gender, a familial history of SCD, the inducibility of ventricular tachyarrhythmias during electrophysiological study, and the presence of an SCN5A mutation were not predictors.

Curio et al.[32] studied 64 subjects who were diagnosed with BrS from ECGs with high intercostal spaces. The mean age from the last follow-up was 42±11 years. A typical ECG pattern was recorded at baseline in 4 subjects before a drug-challenge with sodium-channel blockers. Of those 4 subjects with spontaneous abnormal ECG, 3 experienced cardiac events.

Drug-Induced Type 1 ECG Pattern

In the PRELUDE study,[26] none of the asymptomatic patients with drug-induced type I ECG developed arrhythmic events during the 3 years of follow-up, regardless of VF inducibility at EPS. Curio[32] observed that none among the 60 patients with drug-induced ECG pattern from high intercostal spaces experienced cardiac events. Thus, patients with spontaneous type I ECG consistently have twice the risk of arrhythmic events than patients who develop a type 1 ECG pattern when challenged with a sodium-channel blocker.[13,14] ICD implantation was not indicated in asymptomatic BrS patients with a drug-induced type I ECG in the expert consensus statement.[8]

Fragmented QRS

Fragmented QRS complexes (f-QRS) are defined as ≥ 4 spikes in the QRS by Morita et al.[33] or as ≥2 spikes in the QRS of V1, V2, or V3 by Priori et al.[26] Morita[33] noted that f-QRS was more frequent in patients with BrS than in controls with right bundle branch block (RBBB) (43% vs. 3%), and particularly among BrS patients with CA (85%). Its presence was associated with an increased risk of arrhythmic events. In the PRELUDE study,[26] a prospective evaluation of 308 patients without CA (including 65 with syncope and 243 with no symptoms) revealed that patients with f-QRS were

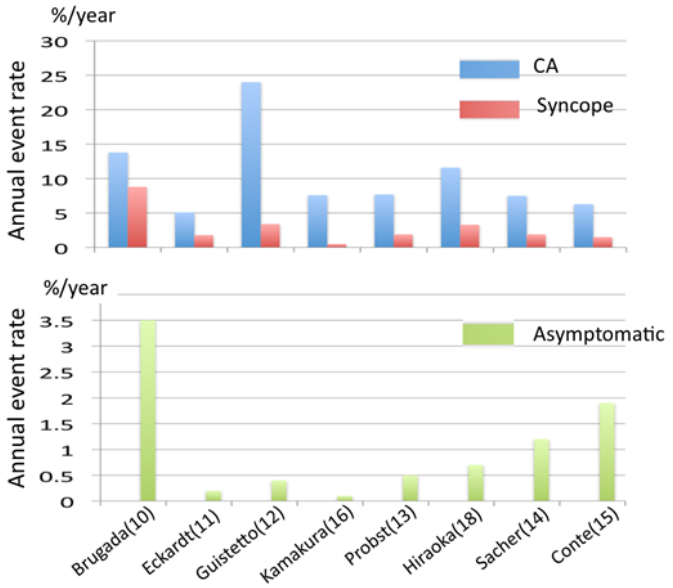

Figure 1: **The averaged annual rate of arrhythmic events in Brugada syndrome (BrS) from the literature**

Upper column. The annual event rates of BrS patients with prior cardiac arrest (CA) (blue) and those with syncope (red). Lower column. The event rates of pateints with asymptomatic BrS. Sacher and Conte are providing the event-rates after ICD implantation. The numericals in the parenthesis is the reference number in the text.

associated with a 9 times higher risk for VF recurrence. f-QRS is a promising predictor for arrhythmic events,[26,33-35] but may needs a further study before it can be declared a criterion for justifying ICD implantation in asymptomatic patients with BrS.[8]

Early Repolarization Pattern (ERP)

Notch or slur at the terminal part of the QRS complex often represents early ERP. ERP was observed in 3 of the 8 patients with idiopathic VF in 1993,[36] and recently the association was confirmed by a larger study by Haissaguerre et al.[37] The dynamic characteristics of ERP were also shown in idiopathic VF patients[38] ERP can be observed in healthy individuals, and ERP with horizontal or down-sloping ST was cennected to the malignant type of ERP.[39,40]

ERP can coexist with BrS, and Sarkozy et al.[41] observed that 15% of patients with BrS had ERP in the inferolateral leads. Kamakura et al.[16] observed a similar prevalence of ERP in BrS. ERP was associated with a 4-fold increased risk of VF recurrence. Similarly, Takagi et al.[42] reported that the risk was 11 times higher in BrS when the patients had inferolateral ERP with horizontal pattern. Some researchers have suggested inferolateral ERP is a risk for VF recurrence,[16-43] but other researchers do not support this view.[44] Patients with VF storms were associated with a higher prevalence of ERP:36%.[19] During the follow-up of 22 patients presenting VF storms, 44% had recurring VF storms within the mean follow-up time of 21±24 months. When ERP is found in patients with BrS, either ERP or BrS can be a trigger of VF. Recently, we experienced a patient with BrS combined with prominent slurs, and marked and transient ERP was considered a trigger for VF storm.[45]

Other ECG Signs

A wide QRS in lead V2 (≥ 120 ms);[46] the duration of the S-wave in lead I,[47] the r-J interval in lead V2 ≥ 90 ms and the QRS width in V6 ≥ 90ms;[48] aVR sign[49] or Tpe interval[50] were found to be good predictors of VT/VF, but these factors need to be confirmed by a larger study. Complete RBBB may coexist with BrS and unmasks the ECG pattern of BrS.[51] The prevalence and prognostic significance as well as the pathophysiology of this comorbidity needs to be explored.

Late potentials in a signal-averaged ECG are often found in BrS,[52,53] but the predictive value is considered limited. An increased TWA at night was observed more frequently among Brugada patients with a history of CA,54 but its prognostic significance was limited.[54,55]

Electrophysiological Study

VF has been induced in 68-83% of symptomatic and in 33-39% of asymptomatic patients with BrS, and earlier studies suggested that the inducibility of VF during EPS is a risk for VF occurrence during follow-up.[10-12,56-59] However, other studies showed a negative or limited value for VF induction.[8,13,14,16,26] The VF inducibility might be affected by four factors:

1. The site of stimulation.
2. The number of extrastimuli.
3. The coupling intervals of extrastimuli and
4. The use of antiarrhythmic agents.

Site Of Stimulation

When the hearts of the patients with BrS was stimulated, a bigger conduction delay occurs in the right ventricle compared to the left ventricle,[60] and a conduction delay within the ventricle begins at longer coupling intervals of premature stimuli in BrS compared to non-BrS patients.[61] These findings support the existence of electrophysiological heterogeneity within the heart of BrS, and this heterogeneity may affect the responses to electrical stimulation during EPS.

To avoid non-specific results, some workers prefer the apex of the right ventricle for stimulation. Sieira et al.[59] updated their long-term follow-up data in 273 patients with asymptomatic BrS who underwent EPS only from the RVA and were followed for up to 15 years. The positive and negative predictive values of VF induction from the RVA for foreseeing arrhythmic events were 18% and 98%, respectively. However, the association between the site of VF induction (RVA vs. RVOT) and subsequent arrhythmic events was not evident in the studies of Makimoto et al.[62] and Kamakura et al.16

Number Of Extrastimuli

An increase in the number of extrastimuli will increase the rate of VF inducibility, and using two extrastimuli improved the sensitivity of the test from 50% to 75% with a low positive predictive value (13%) but a good negative predictive value of PES in asymptomatic non-inducible individuals (99%).[57]

Makimoto et al.[62] reported that 2 out of 17 patients (12%) who had VF induced by 1-2 extrastimuli developed VF, but none of the 14 non-inducible patients by 3 extrastimuli or the 11 patients with no inducible arrhythmias developed VF during the 6 years of follow-up. In a pooled analysis of 1,312 patients with BrS but without CA by Sroubek et al,[28] the mean age at the electrophysiology study was 44.9±13.3 years. Of those patients, 1,034 (79%) were male, 429 (33%) presented with syncope, and 696 (53%) had a spontaneous type 1 ECG pattern. Ventricular arrhythmia was induced in 527 of 1,247 (42%) as follows: 22 with a single extrastimulus, 231 with double extrastimuli and 274 with triple extrastimuli. The individuals induced with single or double extrastimuli rather than more aggressive stimulation protocols were associated with an increased risk for CA. However, Takagi et al.[63] reported that none of the 30 patients who had VF induced by 1-2 extrastimuli developed spontaneous VF during the 3 years of follow-up. In the PRELUDE study, no differences were observed in the VF-free survival curves between the 63 patients without prior CA who had VF induced by 1-2 extrastimuli and the 245 patients who were either non-inducible or had VF induced with 3 extrastimuli.[26]

Coupling Intervals

Patients with BrS might have a shorter ventricular effective

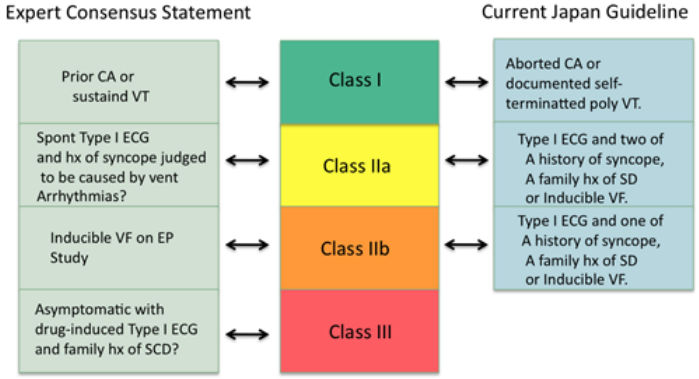

Figure 2: **Indications of ICD for patients with Brugada syndrome (BrS)**

In the expert consensus statement (left) patients should have spontaneou type I ECG pattern of BrS when considering an implantation of ICD. In the Japan guideline (right), prior cardiac arrest or documentation of self-terminating polymorphic venticular tachycardia is requried for Class I indication. ICD may be recommended as Class IIA if patients have two of three risks factors, and as Class IIB if patients have one risk factor in addtion to spontaenous or drug-induced type I ECG pattern for BrS.

refractory period (VERP) compared to non-BrS patients.[64] The short VERP < 200 ms during basic ventricular pacing at 600 ms correlated with an increased incidence of spontaneous VF in the PRELUDE study.[26] This outcome differs from the data of Makimoto et al.[62] which showed that the VF-free survival curves of 81 patients with inducible VF were identical whether VF was induced with a coupling interval < 200 ms.

Antiarrhythmic Agents

Some antiarrhythmic agents are known to prevent VF recurrence in BrS. The study by Belhassen et al. showed that the EPS-guided selection of IA antiarrhythmic agents, which prevent VF induction, was beneficial.[65] However, such studies are not routinely performed.

Familial And Genetic Background

The inheritance of BrS occurs via an autosomal dominant mode of transmission, and 12 responsible genes have been reported thus far.[66] Either a decrease in the inward sodium or calcium current or an increase in one of the outward potassium currents has been shown to be associated with the BrS phenotype. Some mutations may develop a more severe phenotype,[67] but in many cases, there is complex interplay between mutations and polymorphisms.[68-72] No associations have been observed between a family history of sudden cardiac deaths or mutations in the SCN5A gene, and the risk of VF in larger studies. Furthermore, SCN5A mutations were found only in 30% or less of BrS patients. This low yield is a limiting factor of genetic studies in BrS.

Managements Of BrS

As acute managements of VF storms, both oral quinidine and intravenous isoproterenol are effective.[8,73-75] Quinidine blocks transient outward current and rapid delayed rectifier currents and isoproterenol augments L-type calcium current.[76]

For long-term management, ICD is the main therapy (Figure 2). In the expert consensus statements,[8] ICD implantation is considered a class IIB indication for asymptomatic patients with inducible VF. Whereas in Japan, Class IIA or Class IIB indication is determined from the number of risk factors: a history of syncope, a family history of sudden death and inducibility of VF (Class IIA for the patients with two risks factors and Class IIB for those with one risk factors.[77] However, the current recommendation of ICD is still debated.

Quinidine is effective for prevention of VF in BrS,[65,73,74] but it may be intolerable in some patients. In a smaller number of patients, bepridil[78,79] or cilostasol[80] have been shown to be efficacious and promising. As new option, catheter ablation was shown to be effective in controlling VF storms by eliminating the VF triggering premature beats[81,82] or by modulating the arrhythmogenic substrate in the epicardial side.[83]

Conclusions

Current status of risk stratification of BrS and its managements were reviewed. For patients presenting with aborted sudden cardiac death or malignant syncope, ICD is recommended. However, risk stratification in asymptomatic BrS patients is still controversial and indication of ICD may vary from a country to another. Additional progress through the accumulation of pathophysiology data and genetic mutation data as well as clinical evidence are needed.

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Catheter Ablation for Persistent and Long-Standing Persistent Atrial Fibrillation

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Abstract

Persistent and long-standing persistent atrial fibrillation evolves from complex arrhythmogenic substrate and sources. Multiple studies have shown improved freedom from arrhythmia recurrences if sinus rhythm had been restored during the index ablation; however, such harder procedural endpoint requires laborious stepwise approach almost invariably pursuing non-pulmonary-vein sources. Longer-term conversion of persistent atrial fibrillation into sinus rhythm is associated with significant improvement in major indices of hemodynamic and functional status; these indices also represent major predictors of cardiovascular mortality. Optimal ablation techniques and strategies preserving most of the individual potential for functional improvement need to be established.

Introduction

Catheter ablation for persistent and long-standing persistent atrial fibrillation (LSPAF) is often considered as a low yield endeavor. This is a consequence to generally worse ablation outcome and concerns about detrimental effects of extensive left atrial (LA) or bi-atrial ablation on top of advanced atrial structural remodeling.[1-3] Serious symptoms including dyspnea, fatigue, and incapacity may be misinterpreted or attributed to aging or other conditions, in particular in the face of preserved left ventricular (LV) systolic function. Quality of life (QoL) associated with persistent AF/LSPAF was previously shown to be poorer than that in paroxysmal AF[4] or in other cardiovascular populations, including those with significant coronary artery disease who are older, have worse LV function, and require major intervention.[5] Growing evidence of significant improvement in LV ejection fraction (LVEF), maximum oxygen consumption at exercise testing (VO_2 max), and brain natriuretic peptide (BNP) after successful ablation for all persistent AF types[6-9] has been sinking in only slowly, although these indices also represent major predictors of cardiovascular mortality. Their amelioration suggests that the ablation impact on survival may be more profound and sooner detectable in high-mortality LSPAF population than in low-mortality patients with paroxysmal AF.[10]

This review focuses on efficient abolition of persistent AF substrate and sources and hemodynamic and functional benefit from restored sinus rhythm (SR).

Key Words:
Atrial Fibrillation, Persistent, Long-Standing Persistent, Catheter Ablation.

Disclosures:
None.

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Substrate and Sources of Persistent AF

The substrate of persistent AF/LSPAF is complex due to advanced atrial dilation and remodeling in terms of scar or amyloid deposits.[2,11,12] Natural three-dimensional atrial myocardial architecture[13] modified by structural changes, and modulated by cardiac autonomic nervous system[14] give rise to heterogeneous AF mechanisms and sources. Localized sources within the antra of pulmonary veins (PV sources) have been widely acknowledged. Localized sources (distinct areas of localized reentry or ectopic foci) outside the PVs remain a matter of dispute.[15] Participation of macro-reentry circuits (i.e. peri-mitral, roof-dependent, peri-tricuspid) in the background is clear in many AF instances. Heterogeneous, unstable, and entirely random patterns of activation[16,17] may also base the AF mechanism, particularly in LSPAF continuous for years.

PV sources and macro-reentry circuits can be effectively abolished by circumferential or linear ablation validated with clear lesion-specific endpoints. In persistent AF; however, such "schematic" ablation was of little efficacy in restoring SR and more extensive lesions were required to achieve this endpoint.[18-20] Specifically in LSPAF, the immediate impact of PV isolation on AF termination was rather low.[21,22] In our experience with the last 101 patients ablated for LSPAF, in whom 77% rate of AF termination and 69% rate of SR restoration was attained (Figure 1), left PV isolation terminated AF directly into SR in only 3 patients, and left and right PV isolation converted AF into intermediate atrial tachycardia (AT) in additional 4 and 5 patients, respectively (unpublished data).

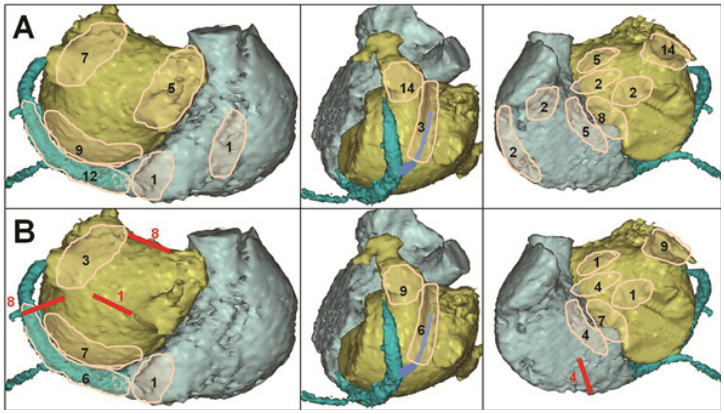

Figure 1: **Sites of termination of atrial fibrillation and restoration of sinus rhythm by ablation at the index procedure for long-standing persistent atrial fibrillation**

Left-to-right panels show posterior, left lateral, and left anterior oblique views of both atria. Count of events in a specific region is schematically depicted as a number in pink translucent area. Atrial fibrillation was terminated (Panel A) in 78/101 patients: into intermediate atrial tachycardia (n=68), or directly into sinus rhythm (n=10). Direct conversion of atrial fibrillation into sinus rhythm occurred during left pulmonary vein encircling (n=2), at low posterior LA wall along the course of coronary sinus (n=2), during ablation within proximal coronary sinus (n=2), at low left atrial ridge (n=1), left atrial roof (n=1), left-side of limbus of oval fossa (n=1), and right side of limbus of oval fossa (n=1). Sinus rhythm was restored (Panel B) in 70/101 patients, directly from atrial fibrillation in 10 patients (see above) and from intermediate atrial tachycardia in 60 patients. The dominant regions of conversion of atrial fibrillation into sinus rhythm or atrial tachycardia, and of conversion of intermediate atrial tachycardia into sinus rhythm included the low posterior left atrial wall (endocardial aspect of coronary sinus), coronary sinus with ligament/vein of Marshall, left atrial ridge, base of appendage, and interatrial septum. Red lines with counts show instances of sinus rhythm restoration from intermediate peri-mitral (mitral isthmus), roof-dependent (roof or posterior wall), or peri-tricuspid (cavo-tricuspid isthmus) macro-reentry tachycardia/flutter

Gradual AF organization and conversion into one or more types of intermediate AT during systematic stepwise ablation pursuing SR restoration as procedural endpoint support the existence of non-PV localized sources perpetuating persistent AF. In addition, more than half of the intermediate or recurrent ATs arise from localized sources.[3,15,18-21,23] The non-PV sources may be also present in paroxysmal AF, however, their prevalence is higher in persistent AF/LSPAF, and their number individually increases with the duration of continuous AF to up to the median of 7 in LSPAF.[3,24,25] Correspondingly, the efficacy in persistent AF termination by selective ablation of the localized sources identified by body-surface panoramic mapping or by possible additional lesions gradually declined with a dramatic shift to worse results in LSPAF.[3] The location of non-PV sources may depend e.g. on individual structural changes, yet a majority of them cluster at several LA, coronary sinus (CS), and right atrial (RA) regions,[3,15,18-21,23] which partly overlap the areas with rich autonomic innervation.

In our 101 last patients ablated for LSPAF (see above), the dominant regions of AF conversion into AT/SR or subsequent AT conversion into SR included low posterior LA wall, CS with ligament of Marshall, ridge between left PVs and LA appendage, appendage itself, confluence of left upper PV antrum - LA roof - LA appendage, and inter-atrial septum (Figure 1). Intermediate macro-reentry ATs preceded restoration of SR in 30% of initial procedures. At first repeat procedure (n=37), AT represented 84% of the recurrent arrhythmias, and the majority of localized AT sources (either primary recurrent or converted from recurrent AF by ablation) were found to originate from similar regions along CS/LOM, ridge, appendage and septum.

Ablation Strategies and Endpoints

Results of different ablation strategies employed in persistent AF/LSPAF are difficult to compare, and even similar lesion design may be of limited value if immediate ablation impact on the arrhythmia mechanism/sources was diverse. On the contrary, achievement of hard procedural endpoint such as SR restoration or even subsequent noninducibility of any AF/AT may serve as a more appropriate measure of immediate ablation efficacy independent of specific lesion design or sequence. Strategy consisting of PV isolation followed by direct current cardioversion and subsequent completing of LA roof a mitral isthmus conduction block may miss the non-PV localized sources, and relying on reverse remodeling and dying out of unaffected sources of AF may be conceptually misleading.

The concept of tailored stepwise ablation (Figure 2) was recently doubted by the results of STAR-AF II study,[26] which was; however, limited by the study protocol not allowing combination of ablation strategies necessary to eliminate all potential AF/AT sources. Correspondingly, the reported efficacy in AF termination (8%, 22%, and 45% for PV isolation, PV isolation + linear ablation, and PV isolation + complex fractionated electrogram ablation) was low with presumably significantly lower rates of SR restoration (data was not published). The study confirmed only moderate efficacy of PV isolation alone in cure of patients with persistent AF (of whom 21% were in SR prior to index ablation), and the fact that extensive ablation failing to achieve harder procedural endpoint may be rather proarrhythmic and counterproductive when compared with PV isolation alone. In this respect, some data suggest that the risk of arrhythmia recurrence may be higher in case of extensive stepwise ablation finished with cardioversion from converted AT as compared to extensive ablation finished with cardioversion from AF significantly organized but not converted into AT.[27]

The role of mandatory LA roof and mitral isthmus lines at the index procedure for persistent AF is not clear. Avoiding linear ablation because of concerns about proarrhythmic effect of incomplete lesion may be double-edged. The propensity of remodeled LA for the development or peri-mitral or roof-dependent reentry AT after the index procedure that avoided any linear ablation may not significantly differ from the risk of incomplete or recovered linear lesions. Some data suggested sooner or later need for linear ablation in nearly 90% of patients to achieve long-term freedom from recurrent AT.[28]

Growing body of evidence favors restoration of SR by the index ablation as an independent predictor of improved long-term rhythm control. The predictors of AF termination included the following variables: shorter duration of continuous AF,[29] smaller LA size,[30] shorter long-axis LA diameter,[21] better LA appendage mechanical function,[31,32] preserved LVEF,[33] longer AF cycle length,[21,29,30,33,34] or lower proportion of high voltage LA sites.[21]

Overall, restoration of SR at the index ablation for persistent AF/LSPAF - disregard of the sequence of ablation steps - can be interpreted as permanent or temporary suppression of all active AF/AT sources, and should be pursued as a fundamental procedural endpoint on the way to long-term SR maintenance. Patient-specific ablation with minimum unnecessary damage to the atrial tissue is desired, and may be facilitated by novel body-surface or basket-catheter-based panoramic AF mapping systems.

Long-Term Maintenance of Sinus Rhythm

Even in case of standardized ablation approach with similar immediate efficacy, outcomes may be difficult to compare between persistent AF populations disparate in terms of underlying atrial structural remodeling[2,35] or clinical characteristics such as duration of

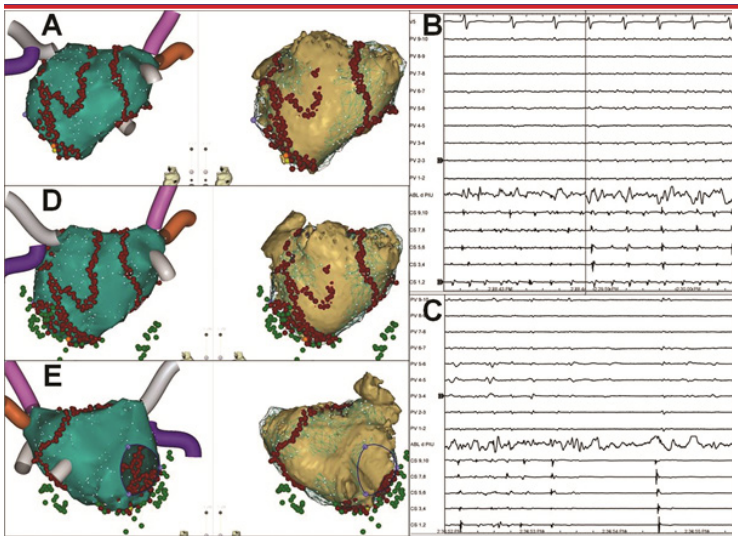

Figure 2: **Example of stepwise ablation with mandatory pulmonary vein isolation as the first step**

Posterior (panels A,D) and anterior (panel E) view of electroanatomic (left) and computed tomography (right) left atrial maps. Following pulmonary vein isolation, atrial fibrillation was converted into transient atrial tachycardia (Panels A,B) and subsequently into sinus rhythm (Panels A,C) (yellow and orange dots) by electrogram-guided ablation targeting the low posterior left atrial wall (endocardial aspect of coronary sinus). Mitral isthmus, left atrial roof, and cavo-tricuspid isthmus conduction blocks with coronary sinus isolation (green dots) were completed after restoration of sinus rhythm (Panel D,E). Noninducibility of any atrial tachyarrhythmia was eventually confirmed by atrial pacing up to 300 bpm, isoproterenol, and adenosine. No septal, left atrial anterior wall or appendage ablation was required in this case (see anterior view of the left atrium in Panel E), and timely left atrial appendage activation was preserved along with restoration of the appendage outflow velocity from peak 0.42 m/s during atrial fibrillation to 0.66 m/s during sinus rhythm. Patient's / procedure characteristics: male, age 60 years, 108 kg, 196 cm, continuous atrial fibrillation for 24 months, history of temporary hypothyroidism induced by amiodarone, prior failure to convert atrial fibrillation by direct current cardioversion, left atrial volume by the CARTO system 170 ml, procedure, fluoroscopy, and radiofrequency energy delivery times 270, 11, and 120 minutes respectively

continuous AF or resistance to antiarrhythmic drugs before ablation.

Freedom from AF/AT after single ablation as the hardest outcome measure is commonly low, but can be markedly improved by repeat ablation.[21,36-38] PV isolation alone was associated with only moderate AF/AT-free outcome in patients with persistent AF[26] or LSPAF.[39] "Good arrhythmia control" as a more clinically relevant outcome measure is usually favorable and can reach acceptable ~90% after stepwise/repeat ablation.[21,36,37] Most of repeat procedures are usually performed within the first two years, although late AT recurrences due to evolving substrate may gradually reduce the long-term outcome and require delayed repeat ablation.[37,38] Of our last 101 patients with LSPAF and 69% SR restoration rate at the index procedure (see above), 92% patients remain in stable SR at the end of 49±23 month follow-up and after 1.4 procedures/patient (84% were off class I/III AADs; 81% were free from any AF/AT recurrence after the last ablation).

Pre-procedural factors of better AF/AT-free survival after single or repeat ablation for persistent AF/LSPAF included smaller LA size,[36,40] shorter continuous AF duration,[21,29,36,39-41] younger age,[30,42] male gender,[40] absence of congestive heart failure,[40] absence of hypertension,[30] higher LA appendage outflow velocity,[21,32] LA systolic strain and LAA wall velocity[44] or AF cycle length.[21,29,30,45] Restoration of SR at the index ablation appeared as a powerful predictor of outcome in multiple studies.[21,27,30,32,33,36-38,40,41,44] The predictive value of restored SR at the initial ablation was shown to extend beyond repeat procedures.[21,30,40,44]

Noninducibility of AF/AT, suggesting non-transient effect on distinct AF/AT source(s), is intuitively superior to simple restoration of SR. Although unrealistic in many initial procedures, noninducibility is feasible in a majority of re-do cases. We have recently demonstrated the predictive value of AF/AT noninducibility at repeat ablation for long-term arrhythmia-free outcome in patients with LSPAF; when it was not attained despite termination of recurrent AF/AT, the outcome was significantly worse.[21]

Overall, achievement of SR restoration by ablation and subsequent arrhythmia noninducibility serve as more reliable procedural endpoints; however, do not guarantee 100% arrhythmia-free outcome, because no current tool can discern between the desired ablation -induced tissue necrosis (future scar) and injured but surviving myocardium that may recover to resumption of existing AF/AT source(s) or proarrhythmic effect, in addition to the natural disease progression and evolution of new AF/AT sources.

Hemodynamic and Functional Benefits from Successful Ablation

Improvement in QoL has been emphasized as the major incentive for catheter ablation of paroxysmal AF. Insidiously progressive symptoms of LSPAF have been recently shown to impair baseline QoL even more than episodic palpitations related to paroxysmal AF.[4] Consequently, the magnitude of improvement 3 years after the index ablation was greater in patients with LSPAF, which resulted in comparable absolute post-ablation QoL levels in both paroxysmal AF and LSPAF populations.[4] In addition to QoL improvement, several recent studied assessed the hemodynamic and functional effects of catheter ablation for persistent AF and LSPAF in greater detail. Two randomized studies demonstrated superiority of catheter ablation over medical rate control in the subjects with persistent AF and LV systolic dysfunction.[6,7] These studies reported consistent post-ablation VO_2 max improvement contrasting with further deterioration on rate control therapy. Post-ablation LVEF significantly improved in both studies, compared with borderline increase or further significant decrease in the rate control arms.[6,7] The magnitude of improvement in BNP and Minnesota Living with Heart Failure Questionnaire Score was significant in ablated patients, but less prominent or insignificant in patients with rate control.[6,7]

The benefits in heart failure patients are not surprising given the LV systolic function is frequently derpessed by the arrhythmia itself. There is a paucity of data on functional benefit in non-heart

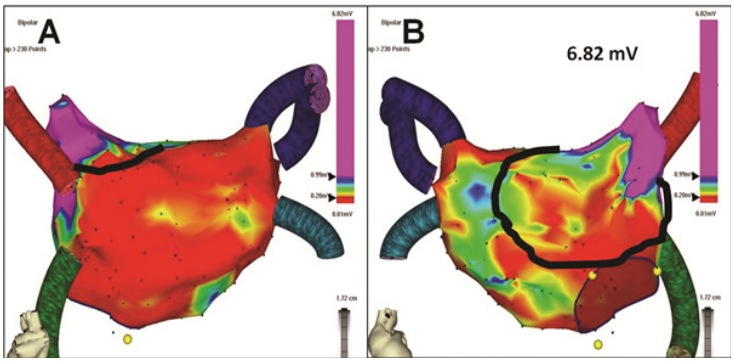

Figure 3: **Characteristic pre-ablation voltage pattern in long-standing persistent atrial fibrillation**

Prior to any ablation, the electroanatomic left atrial mapping (A = posterior view, B = anterior view) reveals low voltage (≤0.2 mV coded in red color) across the whole posterior wall, while favorable voltage (≥1 mV coded in purple color) is present in the appendage (maximum voltage 6.82 mV). Black line circumscribes the amount of surviving atrial myocardium that would be lost as a result of indiscriminate appendage isolation and complete anterior linear lesion with possible consequences for global left atrial transport function

failure patients. We have recently found a significant post-ablation improvement in VO_2 max, LVEF, NT-proBNP, and QoL in 160 patients (including ~20% with baseline LVEF ≤40%) undergoing catheter ablation for LSPAF resistant to amiodarone therapy and cardioversion.[8] In another study, patients with LSPAF designated as asymptomatic experienced a significant post-ablation improvement in VO_2 max (+3.7±10 mL/kg/min) and in physical component score, which was not present in patients with failed procedures.[9] The study included ~13% patients with the diagnosis of congestive heart failure, which implied that the selection of patients based on symptoms may not exclude subjects who got used to live with AF.[9] To address a more homogenous LSPAF population with preserved LV systolic function, we have compared functional benefits in 155 LSPAF patients with no prior history of LV systolic dysfunction (i.e. LVEF consistently ≥50%) vs. 41 LSPAF patients with LVEF consistently ≤40% for 23±20 pre-ablation months (unpublished data). In the latter group,LVEF increased 12 months after index ablation by 22±8% and 85 % of these patients experienced LVEF normalization to ≥50%. The magnitude of VO_2 max improvement was 3.0±4.4 in patients with LVEF ≥50% vs. 3.9±5.1 mL/kg/min in patients with LVEF ≤40%. Of note, near two-fold elevation of NT-proBNP over the pathological cut-off value (942±625 pg/mL) and its subsequent 12-month post-ablation decrease by 711±562 pg/mL in patients with normal baseline LV function corroborated severe adverse hemodynamic effects of LSPAF also in this population.

In summary, recent data show a significant hemodynamic and functional benefit from SR restored by successful catheter ablation of persistent AF/LSPAF. Limited data suggests that the LSPAF-related loss of exercise capacity (VO_2 max) corresponds to at least 3 mL/kg/min even in asymptomatic and/or non-heart failure patients. Elevated (NT-pro)BNP might help the clinicians to attribute insidiously progressive dyspnea, fatigue, and incapacity to the arrhythmia itself and advice the patients about catheter ablation.

Left Atrial Appendage – Sacrifice or Protect?

A significant proportion of non-PV sources maintaining persistent AF/LSPAF are located within the LA appendage and abutting ridge and ligament of Marshall. Selective ablation of these sources is laborious and has to be often repeated. Isolation of these sources by peri-ostial LA appendage ablation,[46] or by LA anterior line supplementing complete left PV isolation and mitral isthmus and LA roof lines[47] without doubt improves ablation efficacy; however, possible adverse effects of these seductive steps have yet to be understood. Increased thromboembolic risk of electrically isolated non-contracting LA appendage has been already shown.[47] Appendage occlusion/exclusion may rectify this adverse effect, but does not solve possible hemodynamic consequences. It is known that the contribution of active LA transport to the LV filling increases with exertion to up to 40%. It is also obvious that severe structural remodeling in patients with persistent AF/LSPAF typically involves the main LA body and specifically the posterior wall, while the appendage as the only trabecular LA structure seems to be better protected against major myocyte changes and interstitial fibrosis[48] (Figure 3). Consequently, LA appendage mechanical depression due to AF can reverse upon restoration of SR,[8,49,50] and its relative contribution to the active LA transport and LV filling may be greater as compared to subjects with healthy LA.[51] Therefore, restored LAA emptying and resulting favorable post-ablation active trans-mitral flow may be of particular importance for global hemodynamic and functional status particularly in active subjects without major comorbidities. Some surgical studies suggested adverse effects of the LA appendage exclusion on the LA transport function.[52,53]

In addition to complete LA appendage isolation, the consequences of LA appendage activation/outflow delay (i.e. partial or complete appendage emptying against closed mitral valve) are even less well understood. Detrimental effects of the LA anterior line on the LA transport function have been recently challenged; however, the study did not address the issue adequately by failing to document the appendage outflow delay in a majority of patients at follow-up.[54] We have recently found association between delayed LA appendage outflow (interval between the onset of LA appendage outflow and the onset of QRS complex <50 ms on 12 month post-ablation transesophageal echocardiography) and lesser increase in the LA appendage outflow velocity (7±25 vs. 20±18 cm/s; P <0.00008) or lower peak A wave velocity of trans-mitral flow (35±11 vs. 39±12 cm/s; P =0.04) as compared to patients with early appendage outflow (interval between the onset of LA appendage outflow and QRS complex ≥50 ms). Moreover, when relative improvements in VO_2 max, LVEF, NT-proBNP, and EQ-5D were summed into a composite score reflecting change in global hemodynamic and functional status,

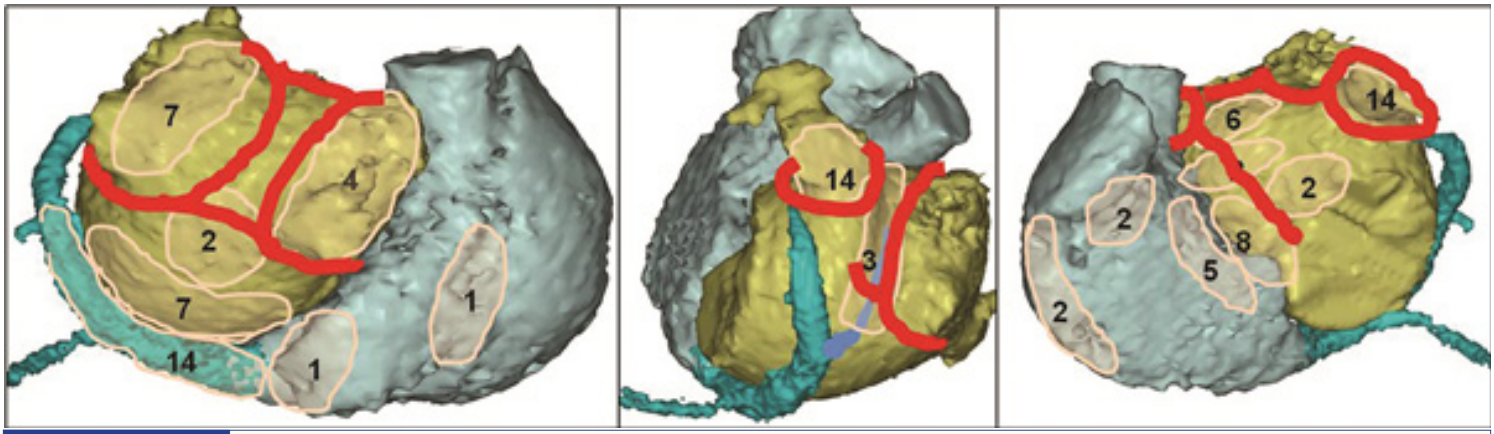

Figure 4: **Schematic depiction of common lesions / appendage exclusion during thoracoscopic epicardial ablation**

In relation to the prevalent sites of atrial fibrillation termination and sinus rhythm restoration during catheter ablation shown in Figure 1, the effect of epicardial box lesion on perpetuators of long-standing persistent atrial fibrillation may be limited. Appendage exclusion and anterior linear lesion eliminating multiple non-PV sources and both macro-reentry circuit may significantly contribute to the ablation efficacy; however, this "added value" may be negated by complete loss of the only remaining functional left atrial myocardium (see Figure 3) and its contribution to the left atrial transport function. Non-pulmonary vein sources located within the coronary sinus and inter-atrial septum are not suitable or accessible to the epicardial radiofrequency ablation

the LA appendage outflow delay (along with older age, female gender, continued antiarrhythmic drugs, and lower LA appendage outflow velocity) was adversely related to the improvement in this score.[55]

Overall, restoration of AF-related LA appendage mechanical dysfunction in patients with persistent AF/LSPAF may have undervalued salutary effects on global LA transport of blood and global functional status, and may warrant a more selective approach to the AF/AT sources originating within the LA appendage. More studies are needed to assess the hemodynamic role of the LA appendage specifically in severely structurally remodelled LA.

Surgical (Hybrid) vs. Catheter Ablation

Efforts and expertise unavoidable for successful systematic catheter ablation in patients with persistent AF/LSPAF spurred on proliferation of "hybrid" thoracoscopic epicardial and endocardial catheter ablation performed either simultaneously or in sequence. In the face of increased risks of serious complications, true advantages of thoracoscopic epicardial ablation should be confronted with true reasons or sources that underlie the efficacy of hybrid approach. In the context with distribution of sites where LSPAF and subsequent intermediate ATs were terminated by catheter ablation (shown in Figure 1), mere epicardial radiofrequency box lesion seems to be of limited "added value", because it misses a majority of non-PV sources (Figure 4). True advantages of epicardial ablation may include direct destruction of ligament of Marshall and epicardial approach to thick myocardial structures (e.g. LA roof) or ganglionic plexi (although recent AFACT trial presented at Cardiostim/Nice 2016 showed no further improvement in outcome after extra ganglionic plexi ablation at the expense of increased rate of complications). The efficacy of "hybrid" approach most likely consists in the LA appendage exclusion and ablation of LA anterior wall; (non)inclusion of these steps appeared to be responsible for diverse outcomes in multiple studies.[56,57] These steps can eliminate frequent localized sources and both LA macro-reentry circuits; however, at a price of loss of the only remaining contractile LA structures with unclear impact on functional status specifically in younger active subjects (see above, Figures 3,4).

Most importantly, thoracoscopic approach has been associated with high prevalence of serious complications including early post-procedural death.[58,59] Simultaneous surgical and catheter ablation will always struggle with peri-procedural anticoagulation and balance between the risk of thromboembolism and bleeding. Finally, sequential hybrid ablation automatically means two procedures per patient, with possible further repeat procedures in long-term follow-up.

Overall, the major principal limitations of thoracoscopic epicardial ablation include inaccessibility to many non-PV sources within the septum or inability to safely apply radiofrequency energy to the CS sources, and hence failure to cure a high proportion of LSPAF patients with a single procedure. In addition, "schematic" surgical ablation unable to individualize patient-specific lesions may result in unnecessary destruction of atrial tissue responsible for hemodynamic and functional benefit from restored SR. Such a concept may relieve the electrophysiologists of tedious systematic search for AF sources, but goes against the quest for more selective ablation and maximized functional improvement.

Conclusions

Ablation for persistent AF and LSPAF evolves amid the gaps in our understanding of the arrhythmia mechanisms and sources, their evolution in timeline and detection by mapping, and fine balance between ablation safety and efficacy. Significant hemodynamic and functional effects of successful catheter ablation may reflect the magnitude of reversible hemodynamic and functional impairment related to the arrhythmia itself. This functional deterioration, which is often underrated by the clinical judgement, may insidiously progress into heart failure and increased mortality that has not improved over the last 20 years despite nearly optimal anticoagulation. Therefore, functional and potential mortality benefits may encourage catheter ablation of persistent AF/LSPAF in high proportion of patients up to now destined to lifelong rate control and oral anticoagulation. An increasing body of evidence indicates that favorable outcome requires elimination of all arrhythmic sources including the sources of intermediate AT; however, such procedures are laborious and lengthy with current mapping and ablation tools. Therefore, novel mapping and ablation technologies along with further insight into the AF pathophysiology are desired to facilitate faster selective abolition of non-PV sources, and by minimizing unnecessary atrial myocardial damage allow maximum individual functional benefit from restored SR.

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Management of Patients with Atrial Fibrillation: Focus on Treatment Options

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Abstract

Atrial fibrillation (AF) is leading cardiac arrhythmia with important clinical implications. Its diagnosis is usually made on the basis on 12-lead ECG or 24-hour Holter monitoring. More and more clinical evidence supports diagnostic use of cardiac event recorders and cardiovascular implantable electronic devices (CIED). Treatment options in patients with atrial fibrillation are extensive and are based on chosen rhythm and/or rate control strategy. The use and selected contraindications to AF related pharmacotherapy, including anticoagulants are shown. Nonpharmacological treatments, comorbidities and risk factors control remain mainstay in the treatment of patients with AF. Electrical cardioversion consists important choice in rhythm control strategy. Much progress has been made in the field of catheter ablation and cardiac surgery methods. Left atrial appendage occlusion/closure may be beneficial in patients with AF. CIED are used with clinical benefits in both, rhythm and rate control. Pacemakers, implantable cardioverter-defibrillators and cardiac resynchronization therapy devices with different pacing modes have guaranteed place in the treatment of patients with AF. On the other hand, the concepts of permanent leadless cardiac pacing, atrial dyssynchrony syndrome treatment and His-bundle or para-Hisian pacing have been proposed. This review summarizes and discusses current and novel treatment options in patients with atrial fibrillation.

Introduction

Atrial fibrillation (AF) is the most prevalent cardiac arrhythmia with important clinical implications.[1] In 2010, AF affected 33.5 million of individuals globally and was described as 'growing epidemic'.[1] AF decreases health related quality of life[2] and substantially contributes to cardiovascular morbidity and mortality especially in women.[3] Variety of possible causative risk factors and diseases, comorbidities, as well as possible complications resulting from AF require comprehensive assessment and management of patients with atrial fibrillation (Fig 1). It refers also to screening of general population and especially subjects at risk of atrial fibrillation.[4,5] Screening of patients ranges from simple pulse assessment, through various forms of electrocardiography monitoring (including symptom event monitors and looping memory monitors), to active search of atrial high rate episodes (AHRE) in patients with cardiovascular implantable electronic devices (CIED).[6] Especially after cryptogenic stroke insertable cardiac monitors represent reasonable AF diagnostic approach.[7] CIED as well as AF ablation techniques are more and more accessible in current clinical practice and possess great potential in the treatment of patients with AF. Their application will be the focus of current review.

Key Words:
Atrial Fibrillation, Treatment, Ablation, Pacemaker, ICD, CRT.

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None.

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Overview of Clinical Management of Patients with Atrial Fibrillation

In non-emergency clinical situations before choice of clinical strategy patient clinical characteristics, risk factors, comorbidities, cardiac structure and patient preferences should be assessed and each patient should be managed individually (Fig. 1). It should be accompanied with knowledge of specific contraindications, proarrhythmic effects and noncardiovascular toxicities of antiarrhythmic drugs.[8] Especially reversible AF causes should be targeted. In the assessment of the risk of AF progression HATCH (**H**ypertension, **A**ge ≥75 years, previous **T**ransient ischemic attack/stroke [2 points], **C**hronic obstructive pulmonary disease and **H**eart failure [2 points]) scale may be utilized.[9,10]

Adequate rhythm and ventricular rate control prevent hemodynamic disturbances. Based on AF symptoms frequency „pill-in-the-pocket" (propafenone or flecainide added to beta blocker or nondihydropyridine calcium channel antagonist) may be the choice of treatment especially in the early phase of AF, in patients without advanced structural heart disease, once revealed to be safe in a monitored setting.[11,12] Patients with severe heart failure should

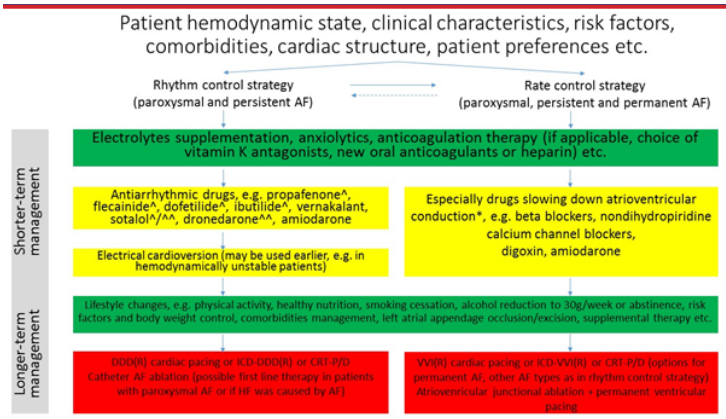

Figure 1: Overview of clinical management of patients with atrial fibrillation

AF, atrial fibrillation; HF, heart failure; DDD, dual chamber pacemaker; ICD, implantable cardioverter-defibrillator; CRT-P/D, cardiac resynchronization therapy-pacemaker/defibrillator. ^ not recommended in left ventricular hypertrophy >15mm or ≥14mm (ibutilide). ^^ not for cardioversion. * some of these drugs should not be used in decompensated heart failure and/or in patients with pre-excitation

be treated with amiodarone. Using amiodarone the pharmacological cardioversion to sinus rhythm is achieved later than in the case of class Ic drugs.[13] Electrical cardioversion, when compared to pharmacological cardioversion is more effective, particularly in persistent AF.[13] On the other hand AF symptoms duration ≥ 48 hours (or of unknown duration), patients requiring anticoagulation therapy, remain contraindications (not in hemodynamically unstable patients) to both pharmacological and electrical cardioversion if anticoagulation was not introduced at least 3 weeks earlier or left atrial thrombus was not excluded.[12,14] In patients assessment echocardiography has an important role which it not only helps to guide management strategy, but also the choice of drugs.

The rate control strategy focuses on slowing down atrioventricular conduction. The drugs used in this strategy include beta-blockers, nondihydropyridine calcium channel blockers, digoxin and especially in resistant to treatment subjects amiodarone. The resting heart rate target of <80 beats per minute (bpm) or <110 bpm during moderate exercise (or resting if lenient rate-control strategy is applicable) should be achieved.[12,15] However, we should take into account that ventricular rates <70 bpm may be associated with a worse outcome and current European Society of Cardiology guidelines for patients with heart failure (HF) and AF recommend resting heart rate of 60-100 bpm as optimal target value.[16]

Thromboembolic and bleeding complications prevention is one of the most important goals in treatment of patients with AF. Scales important in their risk assessment include CHA_2DS_2-VASc (**C**ongestive heart failure/ left ventricular dysfunction, **H**ypertension, **A**ge ≥75 years [2 points], **D**iabetes mellitus, **S**troke/ transient ischemic attack/thromboembolism [2 points], **V**ascular disease (prior myocardial infarction, aortic plaque or peripheral artery disease), **A**ge 65-74 years, **S**ex **c**ategory [female gender])[17] and HAS-BLED (uncontrolled **H**ypertension, **A**bnormal renal/liver function [1 or 2 points], **S**troke previous history, **B**leeding history or predisposition [anemia], **L**abile international normalized ratio [INR], **E**lderly [> 65 years], **D**rugs/alcohol use [1 or 2 points])[18] scores. These scales calculate risk of stroke/peripheral embolism/pulmonary embolism or risk of major bleeding, respectively. Moreover, inclusion of persistent form of AF and renal impairment, beside CHA_2DS_2-VASc score, may be considered and may lead to achievement of greatest area under the curve.[19,20] Based on balance in risk stratification of thromboembolic and bleeding complications anticoagulation therapy use must be considered. One should take into account, that new, promising players appear and become more and more common on the stage of anticoagulation therapy.[21,22] On the other hand in patients with high thromboembolic risk and contraindications to oral anticoagulation therapy left atrial appendage (LAA) percutaneous occlusion may be considered.[14] LAA occlusion may be performed using endocardial percutaneous intracardiac occlude (WATCHMANTM, Amplatzer Cardiac Plug) and epicardial left atrial appendage ligation via pericardiac sack (LARIAT, AtriClip®).[23,24] According to recently published data, LAA occlusion may eliminate significantly the risk of thromboembolic complications.[24,25] Its exclusion may be considered in patients undergoing cardiac surgery, including surgical AF ablation.[14,24] Extracardiac LAA ligation may be performed via thoracoscopy or percutaneously.

In both AF treatment strategies upstream therapies should be considered. Intensive risk factors management, including hyperlipidaemia, hypertension, diabetes, smoking and obstructive sleep apnoea may increase clinical success rates.[26] Moreover exercise and alcohol abstinence (or reduction to 30g per week) should also be taken into consideration.[26] As mean body mass index (BMI) among patients with AF is elevated,[27,28] importance of weight management needs to be emphasized. In a study by abed and colleagues, in patients with obesity and symptomatic AF, with a median follow up of 15 months duration it was found that weight management with intensive management of cardiometabolic risk factors (intervention group) was superior to intensive management of cardiometabolic risk factors and general lifestyle advice in achieving weight reduction and reduction of AF symptom burden and severity scores, number of episodes and cumulative duration.[29] Interestingly in both studied groups reduction of interventricular septal thickness and left atrial area were observed and were more pronounced in the intervention group.[29] Long-Term Effect of Goal directed weight management on Atrial Fibrillation Cohort: A 5 Year follow-up (LEGACY) study revealed that in patients with AF and BMI ≥27kg/m^2 sustained (particularly with evasion of weight fluctuation), long-term weight loss associates (in a dose dependent manner) with AF burden reduction and maintenance of sinus rhythm.[30] Furthermore, these changes associate with beneficial alterations in risk factors and cardiac remodeling.[30]

Ablation in The Treatment of Atrial Fibrillation

Atrial fibrillation ablation eliminates the arrhythmogenic triggers, substrate and/or improper impulses propagation. Promising effects of new ablation devices influence increase in number of candidates for AF ablation and lead to decrease in complications rate. Taking into account patients preferences as well as outcomes associated with catheter AF ablation, it should be considered in selected patients with symptomatic paroxysmal AF (as first-line therapy) and in cases of ineffective pharmacological treatment of persistent AF (Fig. 2).[14,80] It is generally indicated in symptomatic recurrences of paroxysmal AF during antiarrhythmic drug therapy. Moreover in management of AF patients AF Heart Teams have been proposed.[12,80] Tachycardiomyopathy is another clinical situation in which AF ablation may be performed before use of antiarrhythmic pharmacotherapy.[14] This recommendation seems to be in line with results of recent clinical trial, which has shown, that catheter ablation of persistent AF in patients with HF was found to

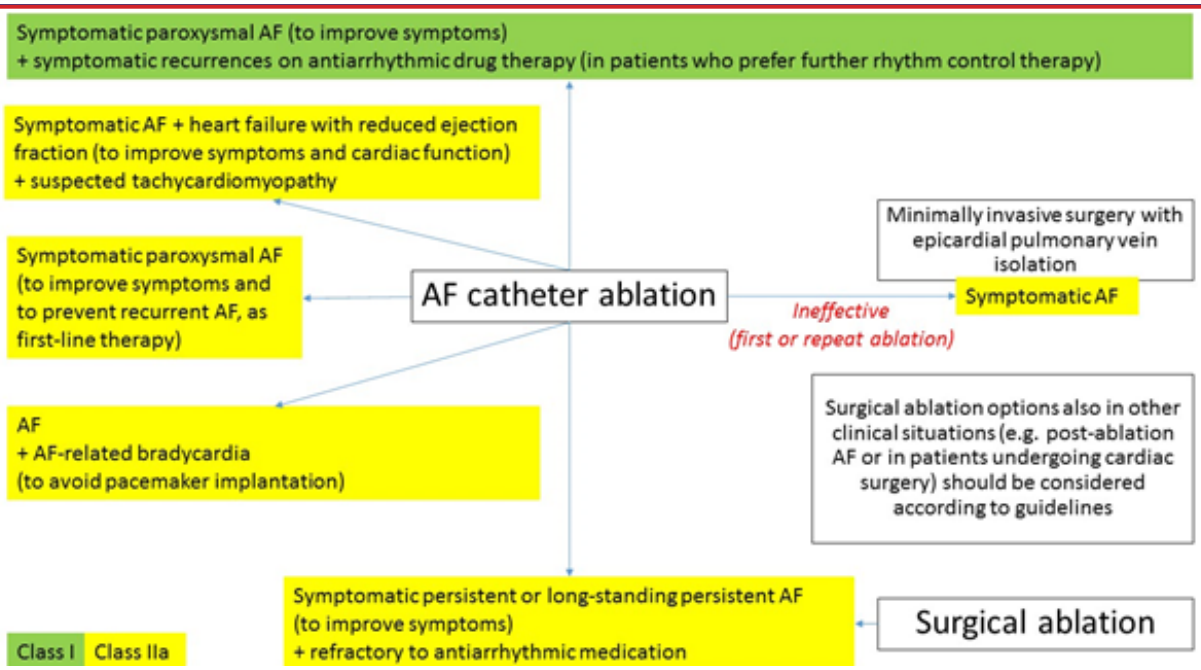

Figure 2: **Overview of atrial fibrillation ablation indications**

AF, atrial fibrillation

be superior to amiodarone in achieving no AF recurrence at long-term follow-up and reduction in unplanned hospitalizations and mortality.[31] Catheter or surgical ablation of AF should be considered in symptomatic patients with persistent AF or long-standing, persistent AF refractory to antiarrhythmic medication (Fig. 2).[80] Healthier, younger individuals may benefit more from ablation than elderly patients with multiple comorbidities. However, benefits of AF ablation in patients ≥ 75 years old were shown to be effective in reducing mortality and stroke risk.[32] AF arrhythmogenic substrate location is often poorly defined so its targeting has probalilistic nature. The most common AF origins are, atrial muscle sleeves extending to pulmonary veins (ca. 80%), left atrial posterior wall, superior caval vein, oblique vein/ligament of Marshal, terminal crest, coronary sinus and interatrial septum.[33] AF ablation may be performed from the endocardial side using catheters introduced via femoral vein and transseptal puncture. Alternatively, epicardial ablation by open heart surgery (often performed in conjunction with other cardiac surgery) or via a thoracoscopic or mediastinal approach. Moreover the hybrid procedures are also performed. The most common techniques in AF ablation is pulmonary veins isolation (PVI) without or with lines and/or complex fractionated atrial electrogram (CFAE) ablation.[34] Regarding to freedom from total tachyarrhythmia during long-term

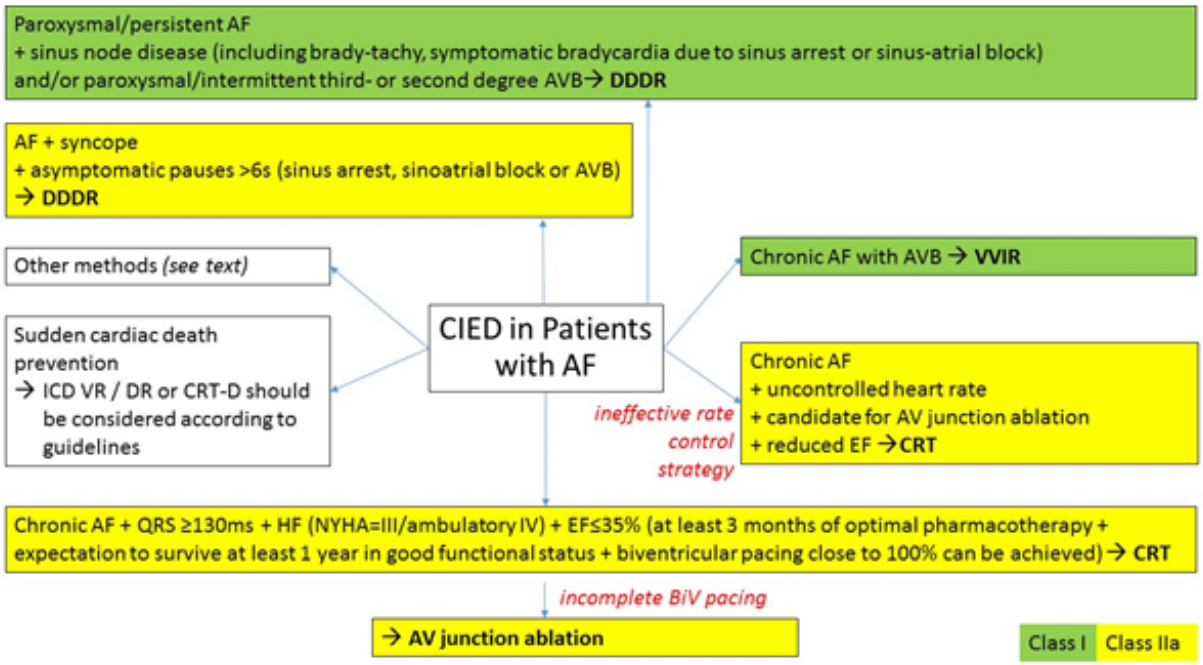

Figure 3: **Overview of current options and/or guidelines recommendations for cardiovascular implantable electronic devices use in patients with AF**

AV, atrioventricular; AVB, atrioventricular block; CIED, cardiovascular implantable electronic devices; EF, ejection fraction; NYHA, New York Heart Association; BiV, biventricular; other abbreviations as in Fig. 1

follow-up, it was shown, that wide antral circumferential ablation (WACA) approach (ablation ≥1.5 cm away from PV ostium) in PVI is more effective than ostial PVI.[35] Some of the most frequent lines in catheter AF ablation are the "roof line", the "mitral isthmus line" and anterior linear lesion.[36,37] In patients with history of cavotricuspid isthmus dependent atrial flutter or if it was induced during EP testing additional linear lesion at the cavotricuspid isthmus is also placed.[37]

Atrial fibrillation ablation may be performed using radiofrequency energy, cryothermy, laser, ultrasound or microwave energy, some of them remain still at the initial stage.[38] Recent clinical trial (The FIRE AND ICE Trial) revealed that cryoballoon ablation was noninferior to radiofrequency ablation (the most common method, with the use of electroanatomical mapping system) in patients with drug-refractory paroxysmal atrial fibrillation.[39] The recommendations regarding atrial fibrillation ablation by PVI technique point that electrical PV isolation should be the goal and entrance block into PV should be demonstrated. Moreover reconduction assessment 20 minutes following initial procedure should be considered.[37]

Cardiovascular Implantable Electronic Devices in Management of Atrial Fibrillation

Many clinically interesting cardiovascular implantable electronic devices functions were shown to have significant impact on the course of AF and clinical management of patients with AF. CIED play important role both in the diagnosis and treatment of atrial fibrillation. Incidence of pacemaker-detected AF may reach 50% and its burden is associated with increased stroke risk.[40,41] However, it was found that patients with subclinical pacemaker-detected AF are significantly less frequently treated by anticoagulants than patients with clinical AF.[40] On the other hand remote control of CIED enables early detection of AF and/or optimization of treatment.[42]

Cardiac implantable electronic devices in treatment of AF are generally reserved for clinical situations in which lifestyle changes and pharmacological and/or ablation treatments are ineffective. Choice of pacing mode in patients with AF is very important. In patients with paroxysmal or persistent AF and concomitant sinus node disease and/or atrioventricular (AV) conduction disturbances atrioventricular rate – responsive pacing (DDDR) is indicated (rhythm and rate control). Ventricular rate responsive cardiac pacing (VVIR) is used in patients with advanced AV conduction disturbances in the course of permanent AF (heart rate control), Fig. 3.[12,14] Importantly permanent leadless cardiac pacing may possess valuable treatment option especially in this group of patients.[43]

Atrial fibrillation is frequent in patients with heart failure (HF).[44,45] There are two groups of indications for CIED implantation in patients with AF and HF. The first group includes patients with AF and HF, who are often characterized by prolonged ventricular depolarization (especially QRS ≥ 130ms) and decreased left ventricular ejection fraction (EF≤35%)[81] and the second, in which left ventricular dysfunction results from long standing fast heart rate. Patients in both clinical categories may benefit from improved heart rhythm and/or heart rate control. MUltisite STimulation In Cardiomyopathies (MUSTIC) study evaluated the effects of biventricular pacing in HF patients in New York Heart Association (NYHA) class III and intraventricular conduction delay. It revealed clinical benefits according to improved 6-min walked distance, quality of life and NYHA class, also in patients with AF.[46] In the Ablate and Pace in Atrial Fibrillation (APAF) trial 'Ablate and Pace' therapy for severely symptomatic chronic AF was tested.[47] In this study cardiac resynchronization therapy (CRT) was superior to apical right ventricular pacing in reducing clinical manifestations of HF in patients undergoing AV junction ablation.[47] On the other hand subgroup analysis of the Resynchronization–Defibrillation for Ambulatory Heart Failure Trial (RAFT) revealed, that in patients with permanent AF or atrial flutter, HF (NYHA class II-III), a LVEF ≤30% and an intrinsic QRS ≥120ms or a paced QRS ≥200ms, who received an CRT-D device did not differ from those who received implantable cardioverter-defibrillator (ICD) alone, when death or HF hospitalization were taken into account (composite primary outcome).[48] Therefore indications to implant CRT in patients with permanent AF and without significant bradyarrhythmias is discussed, especially because large registry data have shown, that atrial tachycardia/AF was the most prevalent reason for CRT pacing loss.[49]

However, systematic review revealed that patients with AF undergoing CRT for symptomatic heart failure and left ventricular dyssynchrony, after AV nodal ablation compared with medical therapy aimed at rate control, had significantly reduced all-cause and cardiovascular mortality as well as had improved NYHA class.[50] On the other hand, we have to keep in mind, that patients after AV nodal ablation are pacing device dependent.

Patients with AF and increased sudden cardiac death (SCD) risk may benefit from implantable cardioverter-defibrillators as SCD preventive therapy. However, after ICD implantation for primary or secondary prevention, during median follow-up of 3 years, about 21% of patients suffer from inappropriate ICD shocks and 60% of them result from AF.[51] Moreover multiple (≥2) ICD shocks due to AF are associated with worse prognosis, while single shock resulting from AF or shocks due to lead failure are not.[51] It is crucial in ICD programming to know discrimination algorithms, including interval stability and atrioventricular association discriminator in dual-chamber ICD differentiating AF from fast ventricular rhythms.[52]

Moreover, in selected patients with AF, especially with concomitant heart failure, requiring permanent cardiac pacing, His-bundle or para-Hisian pacing may possess a therapeutic option.[53-56] However, this mode of pacing limitations include intraventricular conduction disturbances.

Overview of current options and/or guidelines recommendations for CIED implantation in patients with AF are shown on Fig. 3.[57,58]

Permanent Cardiac Pacing and Reduction of AF

Influence of pacing mode on AF was tested in Canadian Trial Of Physiologic Pacing (CTOPP).[59] Results of CTOPP have shown, that patients who underwent physiologic (atrial based) pacing (AAI or DDD) were less likely to develop chronic AF, than patients who underwent ventricular-based pacing.[59] Similar results were also found in our study, in which we have found that DDD pacing mode was associated with lower rate of AF de novo than VVI pacing mode.[60] Surprisingly, subgroup analysis of CTOPP revealed, that in patients with myocardial infarction/coronary artery disease or abnormal left ventricular function, there was no benefit regarding chronic AF development resulting from physiologic pacing.[59] The current look, takes into account the detrimental effect of high right ventricular pacing percentage and enables us to assess the results of the CTOPP study differently.[61,62]

In patients after total AV junction ablation, without antiarrhythmic

therapy, DDDR cardiac pacing, compared with VDD pacing (PA3 Trial) did not prevent paroxysmal AF.[63] This data also suggest, that ventricular pacing (also in synchronous mode) promotes AF.[64] Therefore, DDD(R) pacemakers with programmed algorithms promoting spontaneous AV conduction should be prefered in most pacemaker patients without permanent AF and significant AV conduction abnormalities.[65]

Cardiac resynchronization therapy may influence atrial fibrillation and possess antiarrhythmic effects.[66-68] Gasparini and colleagues, found that end-diastolic diameter ≤65 mm, left atrium ≤50 mm, post-CRT QRS ≤150 ms and atrioventricular junction ablation appear to be predictive of spontaneous sinus rhythm resumption in heart failure patients with permanent AF after CRT introduction.[68] However, in the CArdiac REsynchronisation in Heart Failure (CARE-HF) trial, CRT did not reduce the incidence of AF.[69] It should be emphasized that in the Management of Atrial fibrillation Suppression in AF-HF COmorbidity Therapy (MASCOT) trial it was revealed that the atrial overdrive pacing did not lower the 1-year incidence of AF in a group of CRT recipients.[70]

Interestingly, the interaction between electrical impulses in the right and left atrium may be important to sustain AF.[71] Electrical activation between atria occurs by preferential conduction pathways, such as Bachmann's bundle, fossa ovalis rim and coronary sinus.[71] Atrial conduction disturbances due to primary disease, AF recurrences and/or AF ablation may lead to atrial dyssynchrony and be a risk factor for atrial fibrillation.[72,73] It may therefore be targeted by atrial resynchronization through multisite atrial pacing (including Bachmann's bundle area and coronary sinus ostium pacing), atrial septal pacing, coronary sinus or biatrial pacing.[72,74-79] However, concept of atrial dyssynchrony syndrome treatment needs more research evidence before it could be widely used in clinical practice.[72]

Conclusions

Treatment options in atrial fibrillation are extensive and are based on chosen rhythm and/or rate control strategy. Indications for anticoagulation therapy must be considered in all AF patients. Nonpharmacological treatments, comorbidities and risk factors control remain mainstay in the treatment of patients with AF. Electrical cardioversion consists important choice in rhythm control strategy. Much progress has been made in the field of catheter ablation and cardiac surgery methods. Left atrial appendage occlusion/closure may be beneficial in patients with AF. CIED are used with clinical benefits in both, rhythm and rate control. Pacemakers, implantable cardioverter-defibrillators and cardiac resynchronization therapy devices with different pacing modes have guaranteed place in the treatment of patients with AF.

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Idiopathic Paroxysmal Atrio-Ventricular Block. What is The Mechanism?

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Abstract

Idiopathic paroxysmal atrioventricular (AV) block poses a true diagnostic challenge. What is clear about this entity is the confusion about its definition and consequently about its etiology. According to certain sources, the diagnosis of this block requires the lack of a structural cardiac pathology that justifies the observed manifestations and an absence of electrocardiographic disorders prior to an episode. The clinical presentation of idiopathic paroxysmal AV block does not differ from that of another cardiogenic syncope or of a vasovagal syncope with a significant cardioinhibitory component. With respect to the mechanism that explains this block, it has been postulated that patients with low basal adenosine levels exhibit hyperaffinity of the A2 receptors of the AV node. Variations in plasma adenosine levels may favor episodes of paroxysmal AV block. The diagnosis of this block is complex and can require years to determine. Routine electrophysiological examination of these patients is not cost effective due to the low sensitivity and specificity of this approach. Numerous groups have supported the use of an implantable loop recorder to substantiate AV block paroxysms and assess their clinical correlations. Permanent stimulation devices are utilized to reduce syncopal recurrence.

Introduction

In daily clinical practice, cardiologists can encounter true diagnostic challenges. Nevertheless, this fact can be satisfying to physicians, who will be induced to investigate challenging cases to determine accurate diagnoses. The transient loss of consciousness associated with syncope represents an example of a diagnostic challenge. It is useful and necessary to classify the etiology of syncope as follows: reflex (neurally mediated) syncope, syncope due to cardiac causes, orthostatic hypotension and unexplained syncope.[1] The final category includes forms of syncope for which extensive investigation does not reveal an underlying cause; this phenomenon occurs in cases of idiopathic atrioventricular (AV) block. The definition and etiology about idiopathic paroxysmal AV block are confusing. Certain authors consider idiopathic AV block to be a new clinical entity as a cause of recurrent unexplained syncope.[2] This type of AV block is defined as a paroxysmal third-degree AV block that exhibits abrupt onset, with no other rhythm disturbances before or during the block, and occurs in patients with a normal ECG and a normal heart.[3] The clinical and electrophysiological features of this type of block differ from those of both intrinsic AV block due to AV conduction disease and extrinsic vagal AV block.

In contrast to idiopathic AV block, intrinsic AV block typically occurs in patients with underlying heart disease[4] and is frequently initiated by atrial, His or ventricular extrasystole; increased heart rate (tachycardia-dependent AV block or "phase 3 paroxysmal AV block"); or decreased heart rate (bradycardia-dependent AV block or "phase 4 paroxysmal AV block").[5] The clinical and ECG characteristics of the patients with idiopathic AV block are shown in table 1. In a general population of patients with paroxysmal AV block these clinical and ECG conditions are present in about 30% of patients.[4]

The extrinsic vagal AV block due to vagal nervous effect over the conduction system, include the gradual slowing of the sinus rate and AV conduction prolonging the PR interval (Figure 1).[6]

The prevalence of idiopathic AV block is unclear; however, this type of block is likely underdiagnosed due to poor recognition, its unpredictability and the typical lack of an obvious marker for AV conduction disease between episodes. The International Study on Syncope of Uncertain Etiology 2 (ISSUE 2)[7] was a prospective investigation; in this study, for subjects with an implantable loop recorder, the incidence of AV block (of type 1C according to the study's classification system[8]) was 15% among patients with ECG-based documentation of syncope.

Diagnostic Approach To Suspected Idiopathic Paroxysmal AV Block

No specific tests exist to diagnose idiopathic paroxysmal AV block; therefore, this block should be considered in all patients who present

Key Words:
Atrioventricular Block Idiopathic, Syncope, Adenosine Plasma Level.

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None.

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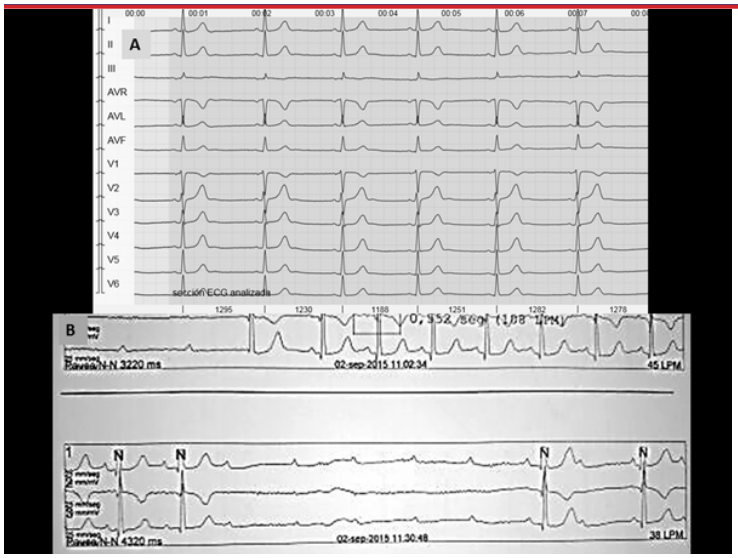

Figure 1: **Extrinsic vagal AV block. The figure shows an extrinsic vagal AV block in implantable loop recorder monitoring. (A) Histogram is shown the typical mechanism of vasovagal syncope. There is an increased heart rate followed by a gradual slowing of the sinus rate and AV conduction prolonging the PR interval to cause AV block. (B) Another event in the same patient. Baseline electrocardiogram is shown a sinus bradycardia at 42 beats per minute, gradual increase in cycle length to block**

with unexplained syncope or sudden cardiac arrest. However, before idiopathic paroxysmal AV block is diagnosed, we must exclude the possibility that the observed symptoms were caused by drug treatment (with beta blockers and/or calcium antagonists) or certain other structural cardiac diseases. In elderly, the degeneration of the His-Purkinje system and/or a degenerative valvular heart disease are the most frequent causes of AV block. Paroxysmal AV block has been reported in acute coronary syndromes caused by inferior or anterior myocardial infarctions.[9] Less frequent causes of paroxysmal AV block that we must nevertheless consider include various diseases other than Lev-Lenègre disease; immunological disorders (for instance, systemic lupus erythematosus); infections such as acute rheumatic fever and bacterial endocarditis with cardiac abscess formation; congenital defects; surgery; and sarcoidosis.[10] Finally, anecdotes have indicated that congenital disorders such as an aneurysmal membranous septum may be an exceptional cause of paroxysmal AV block[11] (Figure 2).

Table 1: **Patients clinical and ECG characteristics of patients with idiopathic AV block reported by Brignole et al (3). RBBB (right bundle branch block); LBBB (left bundle branch block). LAH (left anterior hemiblock**

Characteristics	N patients 18
Age (years)	55
Sex: male (%) Female (%)	9 (50) 9 (50)
Normal ECG, no (%)	18 (100)
Mean QRS duration (msec) <=120 >120	--
RBBB RBBB alone Bifascicular (RBBB+LAH) Bifascicular + long PR	0
LBBB	0
Intraventricular conduction delay	0
PR interval (msec)	-
Asystole duration (sec)	9 +-7
Left ventricular ejection fraction <35% (%)	0
AV block with abrupt onset	12 (66)

In addition, to exclude structural cardiopathy, a patient's electrocardiogram must exhibit the absence of disturbances or alterations prior to the manifestation of the AV block, such as the gradual slowing of the sinus rhythm (the PP interval) or the prolonging of the PR interval.[4,12]

To achieve a diagnosis of idiopathic paroxysmal AV block, it is necessary to perform a series of complementary tests that allow for the exclusion of other causes of syncope. A tilt table test is frequently used to assess syncope with vasovagal etiology, but this approach is not useful for reproducing an AV block due to this test's non-specific response in cases of suspected idiopathic paroxysmal AV block.[7]

An electrophysiological study of a patient who is suspected of having idiopathic paroxysmal AV block could be considered to exclude intra-Hisian blocks that may not produce abnormalities in basal electrocardiograms.[13] However, it is well known that an electrophysiological study has limited specificity and sensitivity for detecting alterations in AV conduction.[14] Brignole et al.[3] examined 18 patients who satisfied the criteria for idiopathic paroxysmal AV block and had presented with unexplained repeated syncopal episodes. An electrophysiological study was performed, and ajmaline was administered; normal results were obtained for 12 out of the 15 patients who agreed to undergo these procedures. These data likely do not support the routine performance of an electrophysiological study in cases of suspected idiopathic paroxysmal AV block.

A useful tool in the study of recurrent syncope is an implantable loop recorder. First, this continuous electrocardiographic monitoring system enables analyses of an episode's clinical correlations with the electrical trace at the time of the syncope and therefore allows hypotheses regarding causality. Second, this system permits assessments of whether certain previously discussed alterations occurred prior to the AV block; such determinations would enable the classification of an AV block as idiopathic. Third, the use of this system allows the adoption of a therapeutic approach based on a

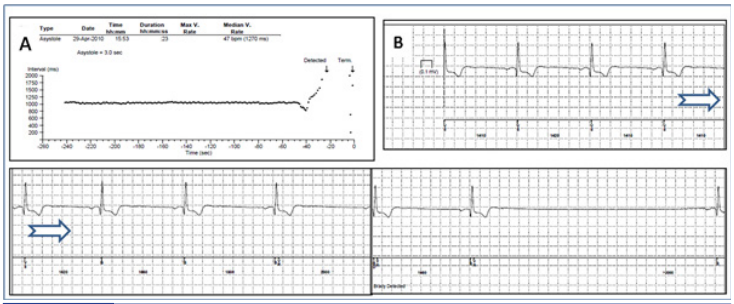

Figure 2: **Baseline electrocardiogram, sinus bradycardia at 48 beats per minute, normal axis, PR normal, narrow QRS with no repolarization abnormality. External monitoring, third-degree atrioventricular block with delay of 4320 ms and QRS escape of similar morphology to the baseline electrocardiogram. As can be seen, the paroxysmal third-degree AV block does not exhibits abrupt onset, prolonging the PR interval. So, this is not an idiopathic paroxysmal AV block. This record shows just how problematic this clinical entity**

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patient's findings; for example, a permanent stimulation device could be implanted to prevent syncopal recurrence in cases involving the substantiation of an idiopathic paroxysmal AV block.[15] Numerous groups support the use of an implantable loop recorder[16,17,18,19] in research and in daily practice.

Permanent stimulation devices, which are not used in cases involving vasovagal syncope,[20] can be employed to prevent and avoid the recurrence of syncopal episodes in patients with idiopathic paroxysmal AV block,[3] improving morbidity. Similarly, the prognosis for these patients are not unfavorable, given the paroxysmal nature of the AV block and the low probability of degeneration into permanent forms of AV block.[3] However, no monitoring data collected over a period longer than a year exist to support this assertion.

Hypothesized Mechanism

The mechanism associated with idiopathic paroxysmal AV block is unknown. Studies have examined the role of plasma adenosine in the development of idiopathic AV block. Brignole et al.[3] considered the possibility that low plasma levels of adenosine could explain repeated syncopal episodes in the profiles of patients with idiopathic paroxysmal AV block. This statement, which lacks significant scientific evidence due to the absence of powerful supporting studies, can serve as a hypothesis regarding a possible mechanism. The aforementioned researchers examined 18 patients and observed that the only common element among these patients was a low level of plasma adenosine relative to the corresponding level in 81 healthy adults (0.33 micromole vs. 0.49 micromole). Following the intravenous administration of adenosine triphosphate (18–20 mg), a significant nodal pause was provoked in 88% of the included patients (with pauses falling between 3.3 and 25 seconds). Given these findings, Brignoleet al.developed a hypothesis involving hyperaffinity of adenosine receptors, which are found in high numbers in the AV node.[23,24] Thus, a transient increase in endogenous adenosine may be sufficient to produce an AV block in patients with low basal levels of adenosine and free or unoccupied high-affinity A1 receptors. Similar research has been conducted previously in patients with vasovagal syncope profiles;[25] although no clear and specific results were obtained, certain similarities between such patients and patients with idiopathic paroxysmal AV block may exist. Carrega et al.[26] examined adenosine receptor (A2A) levels in a group of patients who had suffered repeated syncopal episodes and had positive tilt table test results and found an elevated number of this receptor in the patients relative to healthy subjects. Subsequently, Saadjian et al.[27] examined a similar population and identified a polymorphism in the gene encoding the A2A receptor that was more common in patients who had suffered unexplained syncopal episodes than in 121 healthy subjects; this result could lead to the reorientation of hypotheses regarding these receptors' potential role in idiopathic paroxysmal AV block.

Conclusions

Idiopathic paroxysmal AV block poses a true diagnostic challenge. Although it is true that the clinical presentation does not differ from that of another cardiogenic syncope, the diagnosis of this block requires the lack of a structural cardiac pathology that justifies the observed manifestations and an absence of electrocardiographic disorders prior to an episode. For diagnosis, it is useful the implantable loop recorder to substantiate AV block paroxysms and assess their clinical correlations.

The mechanism associated with idiopathic paroxysmal AV block is unknown. It has been postulated that patients with low basal adenosine levels exhibit hyperaffinity of the adenosine receptors of the AV node. No relevant data have been reported, so it´s necessary that more studies are needed to confirm this hypothesis.

The prognosis of idiopathic paroxysmal AV block is favorable, given the paroxysmal profile of the AV block and the low probability of degeneration into permanent forms of AV block. Permanent stimulation devices can be employed to prevent and avoid the recurrence of syncopal episodes in patients with idiopathic paroxysmal AV block.

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Catheter Ablation of Incisional Atrial Tachycardia

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Abstract

Tachycardias after atrial incisions represent frequent and serious problem. The majority of them are based on a re-entry electrical activation around a combination of anatomic and surgically created obstacles. Considering significant progress of cardiovascular surgery during the last decade along with potential large amount of open-heart procedures in the near future the number of incisional tachycardias has a tendency to increase. The aim of this work was to quantify the magnitude of the problem, characterize the tachycardias after different surgical operations and to analyze possible interventional treatment strategies. Nowadays evolution of mapping and ablation technologies may contribute to radically treatment of this type of arrhythmias while there are still a lot of issues that should be solved to improve the results of interventional treatment of incisional tachycardias.

Introduction

Atrial incisional arrhythmias represent a common complication of cardiovascular surgery. The term incisional atrial tachycardia (intraatrial re-entry tachycardia) is used when the re-entry zone is localized around postoperative scar. Considering significant progress of cardiovascular surgery during the last decade along with potential large amount of open-heart procedures in the near future the number of incisional tachycardias has a tendency to increase. Beyond that, heart surgery associated with manipulation inside the atria, such as correction of congenital malformations, valve interventions or "maze" procedure may appear the common cause of atrial tachycardia. Such atrial arrhythmias are caused by myocardial damage and mostly demonstrate macro-re entry mechanism.[1-4] We can't also underestimate the role of atrial fibrosis, pericardial inflammation and high blood pressure in cardiac chambers. These factors cause a dispersion of myocardial refractory and sinus node dysfunction and contribute to atrial conduction delay that may predispose to the formation of re-entry. Cardiopulmonary bypass surgery, metabolic and electrolyte disturbances, increased adrenergic tone and use of inotropic agents contribute to high risk of arrhythmias during perioperative period. Studies demonstrated that small body weight, young age, prolonged cardiopulmonary bypass time, the complexity of the surgery and the residual defect were the risk factors of early postoperative arrhythmias.[5,6] According to experts opinion, incisional atrial tachycardia occurs in 10-30% of patients after magistral vessels transposition and in 20-37% of patients undergoing the Fontan operation.[1-4] According to data of M.Gelatt et al., up to 14% among 478 patients after Mustard procedure presented incisional atrial arrhythmias while 1% demonstrated ectopic tachycardias. Overall prevalence of incisional tachycardias during 20 years of follow up was 24%.[7] Atrial incisions performed during surgical correction of Fallot's tetralogy also predispose to further incisional tachycardia where 10% of patients experience atrial arrhythmias, 11% demonstrate sustained ventricular tachycardia and 8% of patients die suddenly.[8-10] The loss of coordinated atrial activity and the increase of rate frequency may be accompanied by severe disorders of systemic hemodynamics. It was reported that atrial arrhythmias leading to deterioration of ventricular function were associated with increased overall risk of death including sudden cardiac death.[11,12] It was shown that right atrium surgery during septal defects closure or correction of other congenital heart anomalies represent another major cause of atrial re-entry arrhythmias.[13-20] Such tachycardias tend to have various localization due to individual anatomical features and surgical technique as well as the severity of atrial fibrosis. Incisional tachycardia can occur both during early and late postoperative period. Early postoperative arrhythmias often require correction of electrolyte balance along with pharmacological and non-pharmacological interventions. Late postoperative arrhythmias are associated with numerous risk factors, including direct injury of cardiac conduction system, the surgical "scars" that contribute to conduction abnormalities; and a combination of hemodynamic, anatomical and electrical disturbances in patients with structural heart disease. Modified Fontan procedure and prior early atrial tachycardia are also considered to be independent predictors of late

Key Words:
Catheter Ablation, Incisional Tachycardia, Electroanatomical Mapping, Substrate Mapping.

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incisional arrhythmias.[21]

Patients with sinus node dysfunction also demonstrate high prevalence of atrial tachycardias. Both early and late postoperative arrhythmias represent an important risk factor for morbidity and mortality after cardiac surgery. Typical (isthmus-dependent) atrial flutter is the most common arrhythmia in patients undergoing heart surgery, often combined with incisional atrial tachycardias, forming several re-entry zones or complex dual-loop (figure-eight) re-entry circuit.[22,23] Right atrial re-entry mechanisms are more frequent compared to left atrium.[1,24,25] According to W.Anne et al., the majority of patients selected for atrial incisional tachycardia ablation presented right-side arrhythmias including typical atrial flutter (62%) while only 49% of overall rate were associated with atriotomy. However, left-sided arrhythmias were reported to be more common among the patients with acquired valvular disease.[26] Atrial ectopic tachycardia may also complicate the postoperative period after heart surgery. Unlike atrial re-entry tachycardia, it has different cycle lengh, usually starts and ends slowly, and does not respond to stimulation in «overdrive pacing» mode.[23] The prevalence of postoperative ectopic tachycardia varies according to different authors from 1 to 50%.[27-30] Most often, it occurs after correction of Fallot's tetralogy or interventions near atrioventricular node.[31] Thus, data from A. Dodge-Khatami et al. showed 11% rate of atrioventricular ectopy after correction of congenital heart defects whereas overall mortality was reported about 3%.[29-31] The exact cause of ectopic nodal tachycardia is unknown, but it can be assumed that the increase of His automatism is associated with its surgical damage. Meanwhile, direct correlation between the ectopic nodal tachycardia and young age along with lack of magnesium in the postoperative period was revealed.[32]

Due to variety of potential arrhythmias after cardiac surgery it is sometimes difficult to adequately differentiate them from each other. In most cases, the absence of distinct atrial activity on the ECG leads to confusion and misdiagnosis of atrial fibrillation. Large P-waves on the surface electrocardiogram are often mistaken for typical atrial flutter. Unlike the classical type flutter with saw-toothed P-waves and heart rate about 300 beats per minute, atrial incisional tachycardias often demonstrate slow rhythm with different P-waves pattern. These deviations correlate with different excitation wavefront spreading and scar location in the atria. Sometimes P-waves during incisional tachycardia may be similar to typical pattern of isthmus-dependent atrial flutter.[1] In some cases, it is difficult to identify the P-wave on the surface ECG, which is probably due to small scar size and short circle of re-entry. Thus, diagnostic intracardiac electrophysiological study is required. However, it is generally possible to identify incisional atrial tachycardia on surface ECG. It is important that re-entry zone is associated with scars as result of surgery. Functionally, they represent lines of conduction block. It should be noted that functional blockade doesn't always correlate with anatomical substrate as confirmed by autopsy. Area of functional block is characterized as full electric "silence" or fragmented and low voltage electrograms. The number of possible re-entry circles is clearly associated with the number of isolated "channels". It was shown by H.Nakagawa et al., that patients after Fontan procedure had much more myocardial "channels" in contrast to those after intratrial septal occlusion or Fallot's tetralogy interventions and this fact predisposes to multiple atrial re-entry tachicardias.[2]

In other single center study M.N.S. De Groot et al. analyzed the voltage of intracardiac electrograms in patients with congenital heart anomalies compared to healthy individuals. It was found that the amplitude of atrial potential in case of congenital structural diseases was significantly lower than in normal hearts. Localization of low-amplitude electrograms correlated with re-entry zone.[33] B. Love et al. reported association between some electrical parameters (double potentials, electrical "silence" region) and central re-entry circuit in patients with congenital heart anomalies during sinus rhythm, atrial pacing and during tachycardia.[33] Therefore, a correlation between electrical activity and localization of tachycardia is demonstrated. However, data about electrical and histopathological correlation in patients with atrial incisional tachycardias are lacking, due to technical difficulties and short follow up period.

During surgery interventions, atriotomy, cannulation or other manipulations may lead to postoperative scar formation, usually in lateral wall of right, while re-entry wavefront circulates around the incision.[2] Linear ablation from the bottom edge of scar to inferior vena cava or tricuspid valve, or from the top edge of scar to superior vena cava provides re-entry circuit interruption.[34-35] Sometimes scar heterogeneity leads to "channel" formation between high-density areas resulting into slow and fragmented electrical activity that is necessary for re-entry mechanism. When there are a lot of "channels", various forms of tachycardias may be induced. Thus, termination of "channels" activity leads to the elimination of tachycardia.[2] Atrial electroanatomical mapping often identifies areas with low amplitude of atrial potentials, including distant sites far from surgical lesions. This fact may indicate large zone of myocardial damage or atrial wall infarction while definite etiology of "atrial myopathy" remains unclear. It possibly can be explained by the interruption of atrial blood supply and the lack of protection during cardioplegia. The use of antiarrhythmic drugs and atrial pacing didn't demonstrate effectiveness in the incisional tachycardia treatment.[36,37] Furthermore, drug therapy is limited by potential organotoxic complications and risk of pro-arrhythmic activity. Antitachycardia pacing is usually used for re-entry arrhythmia termination but in case of atrial incisional tachycardias may often induce atrial fibrillation with subsequent deterioration of hemodynamics.[37] Only intracardiac electrophysiological study and radiofrequency ablation may potentially modify the vulnerable section of re-entry circuit and prevent arrhythmia recurrence. Several studies on young patients after surgical correction of congenital heart anomalies demonstrated average efficacy of radiofrequency ablation from 12 to 50% during more than 2 years of follow-up.[2,14-16]

The lack of randomized clinical trials is the main limitation when the effectiveness of incisional tachycardia treatment is estimated. The termination of arrhythmia during ablation doesn't always represent adequate clinical point of radical treatment. The problem of frequent recurrence after successful ablation of tachycardia requires further evaluation and formation of additional predictors of effectiveness.[38]

Non-fluoroscopic ablation without atrial activation mapping may provide tachycardia termination but doesn't allow to estimate conduction block inside the vulnerable re-entry zone. According to the North American Pediatric Registry of radiofrequency ablation, the effectiveness of procedure was only 55% in the mid-1990s while other centers reported up to 78% efficacy.[34,35,39-42] During 2-year follow-up after successful tachycardia ablation 50% rate of arrhythmia recurrence was demonstrated.[38]

As reported by W.Anne et al., using of Halo catheter with the possibility of registering more than 20 endocardial electrograms

allowed to identify re-entry zones and improve the efficiency of tachycardia ablation up to 94%. But at the same time the rate of post-operative recurrence was 29% that could be explained by new re-entry zones formation. There was direct correlation between the number of re-entry curcuits and risk of arrhythmia recurrence after first ablation procedure. Long-term success rate depends on number of different types of tachycardia and corresponds with other literature data.[18,35] More frequent recurrence of atrial incisional arrhythmias (33-53%) in early studies was associated with inability to identify all potentially vulnerable areas of re-entry, especially in patients with multiple "scars" in the myocardium.[4,35,37,42]

Radiofrequency ablation of incisional atrial re-entry tachycardia is complicated by several factors and requires:

1. Identification of vulnerable tachycardia zones.
2. Formation of effective transmural lesions.
3. Verification of bidirectional conduction block.
4. Confirmation the lack of recurrent episodes during long-term follow-up.

A detailed understanding of the incisional tachycardias mechanisms, and therefore, successful treatment is obtained using nonfluoroscopic mapping systems with real-time analysis and graphic 3D visualization of myocardial activation. Contemporary navigation systems provide high-accuracy data (estimated error no more than 1 mm) on three-dimensional geometrical reconstruction of the heart chambers and electroanatomical mapping. It is safe and informative technique for atrial activation visualization in patients with complex incisional atrial arrhythmias, which contributes to diagnosis of both focal and incisional atrial reentry tachycardia. Analysis of activation map may help to identify critical area of slow conduction, contributing to successful catheter ablation. Visualization of surgical scars and anatomical structural barriers within the three-dimensional electroanatomical map simplifies the process of linear lesions creation.[43] Electroanatomical mapping allows to differentiate ectopic and re-entry tachycardia. This method is wide practically used and represents a systematic approach to the incisional tachycardia treatment Long-term outcome of ablative therapy of post-operative atrial tachyarrhythmias in patients with tetralogy of Fallot: a European multi-centre study.[44-46]

Electroanatomical mapping during sustained tachycardia helps to identify zones scar in the myocardium, "channels" of slow conduction or the phenomenon of "snake biting its own tail", which is characterized as persistence of the earliest and most recent activation in the tachycardia circuit. After failing to induce the tachycardia or in cases of unstable tachycardia or various cycle length, mapping can be performed during atrial pacing, to detect slow conduction "channels" between scars and normal anatomical structures. Radiofrequency energy should be delivered at specific sites demonstrating "abnormal" voltage, isthmus of a circuit, or slow conduction zones.[47] The main principle of procedure is modifying the arrhythmogenic substrate connecting scar/abnormal myocardium to natural anatomical barriers (upper and lower vena cava, tricuspid and mitral rings) or another scar with tachycardia elimination. Main criteria of transmural necrosis during ablation include low amplitude (up to 80% of baseline) or fragmentation of unipolar atrial potential, registered with map catheter.[2] Potential complications of ablation procedure include phrenoplegia, caused by phrenic nerve damage, and thromboembolic events after conversion to sinus rhythm. More rarely occur hemopericardium, cardiac tamponade and atrio-esophageal fistulas.

Comparative study at Boston Children's Hospital demonstrated significant increase of incisional tachycardia ablation efficacy using electroanatomical mapping.[48] If entrainment pacing was not performed, it didn't reduce effectiveness of the procedure.[2,37] Under 3D mapping guidance the rate of successful ablation is over 90%.[2,49]

Conclusions

Therefore, improved surgical techniques during last decades contributes to better prognosis in patients with congenital heart anomalies and acquired valvular disease while the risk of incisional atrial tachycardias is progressively increasing. On the other hand, growing number of patients with repeated surgical procedures leads to multiple scars formation in the atria and consistently escalates risk of arrhythmias. High rate of postoperative arrhythmias and their complications stimulates the development of new interventional techniques. Understanding the electrophysiological mechanisms and evolution of mapping and ablation technologies will contribute to radically treatment of this type of arrhythmias. However, there are still a lot of issues that should be solved to improve the results of surgical treatment of incisional arrhythmias.

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