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- **Routine use of Intracardiac Echocardiography for Atrial Flutter Ablation is Associated with Reduced Fluoroscopy time, but not with a Reduction of Radio frequency Energy delivery time.**
- **Resolution of AV Block after Ablation for Atrial Fibrillation. Post-Ictal Transient Atrial Fibrillation as a Rare Manifestation of Grand Mal Seizure.**
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Atrial Fibrillation Awareness – Empowering the patient

Dear Colleagues

Welcome to the Fall issue of the Journal of Atrial Fibrillation. Thank you for your fight against the global epidemic of Atrial Fibrillation (AF). September was the AF month with several activities organized all over the world. There were educational lectures, awareness walks, yoga sessions and many other activities to raise the AF awareness in the community. A lot of you have been part of this mission with single goal of eliminating AF.

Congratulations are to the Global AF Alliance (GAFA) Foundation, Heart Rhythm Society (HRS) and ACC for launching a very effective campaign last month. HRS did an excellent Twitter Question and Answer session with an expert panel. A wide variety of clinical management issues have been discussed. Controversial areas were covered and debated. GAFA and ACC did a patient oriented Webinar on AF Management. In addition to this Apple along with Alive or launched a massive online AF awareness program as well. While some people viewed this as a marketing gimmick, it still brings a tremendous value to the core mission of spreading the knowledge and improving patient engagement. What Coronary artery disease (CAD) was thirty years ago is AF today. It takes unfettered commitment from all fronts to fight this 21st century epidemic.

While our understanding of AF and its maladies continue to improve the tools to manage them are slowly but steadily becoming better. AF ablation remains a very important tool in out therapeutic armamentarium. Our ability to tackle non-paroxysmal AF has been limited. In addition to the pulmonary vein isolation several adjunctive strategies have been tested and failed. Complex fractionated electrograms, linear lines, rotor ablation and more have been tried without much success. Our ability to understand the pathophysiology and substrate evolution with the progressive AF will remain the next best hope. Several new options in the form of left atrial appendage (LAA) occluders for anticoagulation eligible high-risk patients have proven to be very promising.

This issue of the journal has several interesting original and review articles worth spending time on. We once again appreciate your support to the journal and look forward to your contributions to the field.

Have a great summer.
Best wishes

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A Simplified Trans-Septal Puncture Technique using a Needle Free Approach for Cryoablation of Atrial Fibrillation

Shohreh Honarbakhsh[1], Ben O'Brien[2], Richard J Schilling[3]

[1]This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.[2]This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.[3]This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

Abstract

Background: Trans-septal puncture (TSP) is routinely performed during treatment of atrial fibrillation (AF) and other electrophysiology procedures. The purpose of this retrospective observational study was the analysis of a novel needle free technique employed to gain access to the left atrium (LA).

Methods: The SafeSept Needle Free guidewire was delivered, using no needle, to the interatrial septum via a standard cryoablation sheath and dilator under transoesophageal guidance. The wire was then advanced into the LA with position confirmed by fluoroscopy. All cases were performed under general anaeasthetic (GA).

Results: The novel procedure was performed in 43 patients (38 paroxysmal AF (88.4%) and 5 persistent AF (11.4%)) with 100% success rate in accessing the LA. The procedure times (51.70 ±18.18) and fluoroscopy times (2.75 ± 3.35) were recorded. There were no complications seen in the cohort.

Conclusions: Using SafeSept Needle Free wire for TSP had a high success rate and resulted in no complications, with the potential to reduce procedure and fluoroscopy times.

Introduction

The origins of trans-septal puncture (TSP) lie in its use for left heart catheterization. However, studies for the evaluation of valve disease or percutaneous mitral balloon valvuloplasty indicate that it is now more commonly performed to access into the left atrium (LA) for catheter ablation of arrhythmia[1][2]. The original technique first described by Ross et al. in 1960[3] has evolved over the subsequent years. This means that while the use of ultrasound imaging has increased, the techniques and technologies used are not specifically designed for the purpose they are being put to today[4]. An increase in atrial fibrillation ablation procedures facilitated the development of specific techniques and the adoption of new technologies to assist TSP such as the RF needle[5]. However, it is well known that TSP is related to some life-threatening complications. This is especially true in the presence of challenging interatrial septal anatomy[2]. We sought to investigate whether a novel TSP puncture wire, the SafeSept Needle Free guidewire (SafeSept™ Pressure Products, San Pedro, CA, USA), could be used through a cryoablation sheath to reduce procedural steps such as sheath and wire exchanges.

Key Words

Atrial Fibrillation, Cryoablation, Trans-septal puncture, Needle-Free, Safe-Sept.

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Patients and methods

In this retrospective observational study, a total of 43 consecutive patients undergoing pulmonary vein isolation using cryoballoon were analysed. TheTSP procedures were performed under general anesthetic using the SafeSept Needle Free guide wire (SafeSept™ Pressure Products, San Pedro, CA, USA) with Transoesophageal (TOE) guidance without interrupting oral anticoagulation therapies.

Seldinger technique was used to gain femoral venous access and introduce a cryoablation sheath (Flexcath Advance™ Steerable Sheath, Medtronic, Minneapolis, USA) with the tip placed in the SVC under TOE guidance (no fluoroscopy was used for this part of the procedure). No problems were encountered advancing the sheath with the support of the guidewire. A second 7F sheath was used to introduce a pacing wire into the SVC to pace the phrenic nerve during right pulmonary vein freezes. The guide wire was withdrawn from the cryoablation sheath and a SafeSept wire advanced to the mid portion of the sheath and dilator. The SafeSept wire is a 150cm, 0.0315" nitinol guidewire with a sharp tip and a radio-opaque distal coil. When unsupported by sheath and dilator it has a pre-formed J-shaped tip, a feature designed to render it atraumatic when inside thevasculature [Figure 1]. A bend of 300 was placed on the cryoablation sheath and dilator and they were then slowly withdrawninferiorly under TOE guidance. When the tip of the dilator was seen to drop into the fossa ovalis the SafeSept wire was advanced and used to puncture the septum [Figure 2]. Heparin was

Table 1: Demonstrates the baseline characteristics

	SafeSept Needle Free
Age y, mean ± SD	59.5 ±10.8
Sex M (%)	34 (79)
Hypertension, n (%)	13 (30)
IHD^, n (%)	2 (4.7)
Diabetes, n (%)	2 (4.7)
Echocardiography Normal LV function n (%)	40 (93)
Normal valvular function n (%)	41 (95.3)

^Ischaemic heart disease

given as per local protocol at this juncture. The position of the wire was confirmed on fluoroscopy as being in the left upper pulmonary vein. The sheath and dilator were then advanced through the septum under fluoroscopic guidance and the needle and dilator removed. The cryoablation procedure proceeded as described before[6].

Procedure time was defined as time from initial venous puncture to removal of sheaths and measured in minutes. Duration of fluoroscopy was also measured in minutes. Patients were monitored overnight and followed up in clinic 3 months post procedure. They were assessed for standard major and minor complications of AF ablation during these times.

Normal left ventricular function was defined as an ejection fraction above 55%; with normal valvular function defined as no pathological stenosis or regurgitation. Out of those with abnormal LV function all were mildly impaired.

Results

From July 2015 to April 2016 the SafeSept Needle Free guidewire was used to perform TSP in 43 consecutive patients. Baseline characteristics are demonstrated in [Table 1].

The majority of patients in the cohort were undergoing ablation for paroxysmal atrial fibrillation (PAF); 38 PAF, 88.4% and 5 early persistent AF, 11.6% [Table 2]. None had had a prior TSP performed. Most patients had preserved left ventricular systolic function (40/43, 93%; [Table 2]).

In all patients, the TSP was successful with no complications. Procedure data is shown in [Table 3].

Discussion

Given the expansion in electrophysiology procedures a variety of techniques designed to improve efficacy and safety of the TSP have been employed[7]. Radio frequency delivery to the inter-atrial septum has been applied with success in cases in which standard techniques have failed [8][5]. A recent study has demonstrated a benefit to deep inspiratory maneuvers[2].

Our study demonstrates for the first time that a specifically designed trans-septal wire can be used without a trans-septal needle

Table 2: Demonstrates the indication for catheter ablation, extra procedures performed and the echocardiographic features

Indications	SafeSept Needle Free
Persistent AF, n (%)	5 (11.6)
Paroxysmal AF n (%)	38 (81.4)
Extra Procedures	
CTI^ Line n (%)	11 (25.6)
EPS* n (%)	2 (4.7)

^Cavotricuspid isthmus
*Electrophysiology study

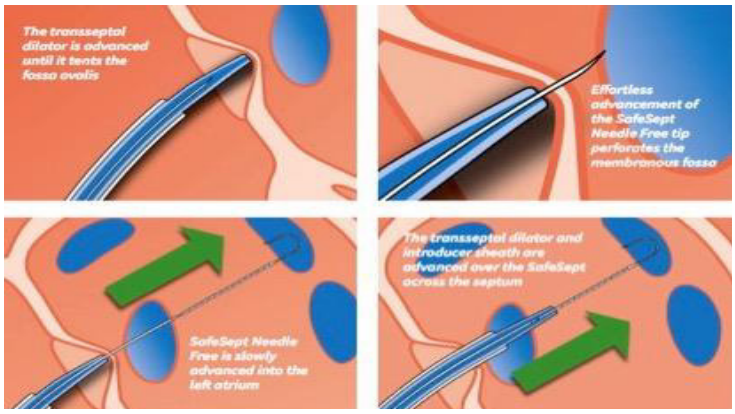

Figure 1: Schematic view of the use of the Needle Free SafeSept wire to cross the atrial septum

to successfully perform TSP; with LA access achieved in all patients. The use of a SafeSept guide wire has been previously described [9],[10], with the larger of these cohorts consisting of 210 patients. These groups' technique differs from that employed here, using a different model of the guide wire that requires introduction via the lumen of a standard Brockenbrough needle. Successful performance of the TSP occurred in 97.6% the larger cohort and in all 19 patients in the smaller study.

Table 3: Demonstrates the procedural data

	SafeSept Needle Free
Successful TSP n (%)	43 (100)
Procedure time min ± SD	51.70 ±18.18
Fluoroscopy time min ± SD	2.75 ± 3.35
Complications n (%)	0

In this cohort of patients, we experienced no complications and this indicates the technique to be safe in this group. Lower fluoroscopy times when compared to those reported in other studies[6], could be due to no fluoroscopy being used until the LA is accessed. This improvement also applied to total procedure time[6], with the simpler work-flow, avoiding the need to exchange sheaths and wires making the procedure more efficient. It may also improve safety, as sheath exchange is one point in the procedure where there is the potential to produce air embolism or lose position of the wires/sheaths.

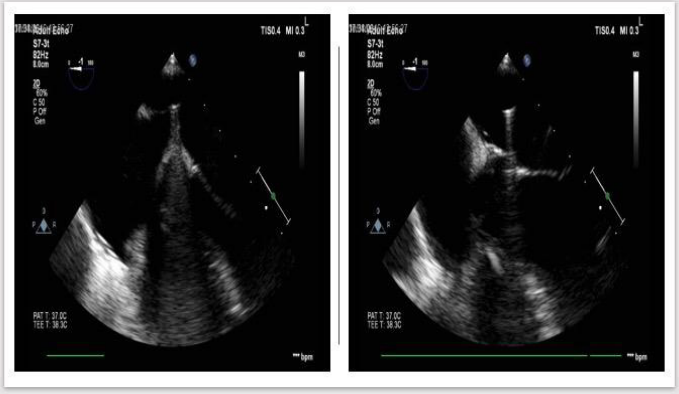

Figure 2: Transoesophageal echocardiography views demonstratetenting of the inter-atrial septum (left) and subsequent advancement into the left atrium (right)

Limitations

This study is limited due to it being a retrospective analysis. A larger randomized controlled study would be necessary to conclusively evaluate its validity. Furthermore, we have measured fluoroscopy time and procedure time, which are influenced by the length of the procedure post TSP. Any further evaluation of this technique should focus on fluoroscopy time and procedure duration from RFV sheath insertion to TSP.

Conclusions

Our technique, whilst requiring further evaluation, offers promise of streamlining the trans-septal puncture and potentially reducing procedure and fluoroscopy times with no obvious compromise to safety.

Conflict of Interests

None.

Disclosures

None.

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Feasibility and Usability of a Mobile Application to Assess Symptoms and Affect in Patients with Atrial Fibrillation: A Pilot Study

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Abstract

Background : Atrial fibrillation (AF) is the most prevalent arrhythmia leading to hospital admissions. The majority of patients with AF report symptoms that are believed to be associated with the arrhythmia. The symptoms related to AF traditionally are collected during a clinic visit that is influenced by biases associated with recalling the experience over a limited period of time.

Purpose: We designed this pilot study to assess the usability and feasibility of a mobile application to assess symptoms in patients with AF.

Methods : We designed a mobile application (miAfib) to assess symptoms (chest pain, palpitation, shortness of breath, fatigue, dizziness/lightheadedness), positive affect (happy, excited, content) and negative affect (worried, angry, sad) on multiple occasions throughout the day based on iOS platform. We performed a four-week feasibility trial to examine user adherence, acceptance and experiences with the mobile application. We administered questionnaires to assess factors affecting usage and self-reported acceptance of the application based on a five-point Likert scale with zero representing strongly disagree and 5 representing strongly disagree with.

Results : We included ten patients with paroxysmal and persistent AF. The mean number of completed assessments each day was 2.81 ± 1.59 with 94.7% of days with at least one assessment. The users found the application easy to use (4.75±0.46), intended to use it in the future (4.37±1.06) and found it easy to integrate into daily routine (4.5±1.07).

Conclusions : In this pilot study, we found participants in this four-week trial reliably used the application and were able to use the app to report their daily symptoms and affect regularly. Participants reported that they found the application easy to use and would consider using the application in the future.

Introduction

Atrial fibrillation (AF) is the most prevalent arrhythmia leading to hospital admissions.[1] Its incidence is associated with an increase in the risk of stroke, congestive heart failure and overall mortality.[2] The national incremental cost of AF to the health care system has been estimated to be as high as $26.0 billion.[3] The number of patients diagnosed with AF is projected to increase to more than 15 million by 2050.[4] The majority of patients with AF report symptoms believed to be associated with the arrhythmia.[5] The most common symptoms reported are dyspnea, chest pain, dizziness, fatigue and palpitations.[6] These symptoms can lead to a decrease in functional status and quality of life in many patients with AF. [7]

Symptoms related to AF are traditionally collected via recall measures that require participants to summarize their experiences over some time period (i.e. since the last clinic visit). Current approaches to the assessment of symptoms during clinical visits is problematic for several reasons. They are susceptible to several factors including recall bias, retroactive reconstruction, effort after meaning, and affect-related bias.[8] Another concern is that the assessments of symptoms, affect and functional status are not performed in patients natural settings, therefore limiting their generalizability and ecological validity.[9] This emphasis on retrospective assessment also precludes examination of the dynamic changes in symptoms over time and their interaction with heart rhythm, affect and functional status. There is a need for development of tools that allow real-time repeated assessments of symptoms and affect to capture the daily variability in symptoms and understand the potentially dynamic daily interactions between symptom and affect.

Mobile applications("apps")are software designed to operate on a smartphone or other mobile devices. In the United States, smartphones are owned by 73% of adults who use these devices in a diverse range of activities in daily life.[10] Mobile applications have become increasingly important in the management of patients across a range of medical problems. They provide a unique opportunity to collect clinically-relevant data from a patient population through collection of data in patients natural environment. As such, we developed a novel mobile application (miAfib) to assess AF-relevant symptoms and affect on multiple occasions throughout the day. This

Key Words

Atrial Fibrillation, Mobile Application, Feasibility Study.

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Figure 1: miAfib mobile application

study aimed to evaluate the feasibility and usability of this mobile application for a four-week use period in a sample of individuals with AF.

Methods

We designed a mobile application (miAfib) to assess symptoms (chest pain, palpitation, shortness of breath, fatigue, dizziness/ lightheadedness), positive (happy, excited, content) and negative (worried, angry, sad) affect on multiple occasions throughout the day based on iOS platform for iPhone available through the app store for download by study participants [Figure 1]. The beta version of the mobile application was tested extensively for user experience, data recording and transfer prior to release of the final product to the app store. We designed a study website (www.miAfib.com) to assist participants with mobile application set up and study details. For self-reported measures, we utilized the mobile application to collect the severity of AF related symptoms and affect on multiple occasions throughout the study period. Patients were identified by a unique login, which allowed for authorization with the server and tracking of their responses. The users were prompted with notifications to remind them to complete the symptoms and affect assessments four times per day every three hours starting at 9AM. When the user opened the application, it displayed the assessments to the user. The application captured the users input, which was transferred back to University of Michigan Medical School (UMMS). These web services were designed to retrieve the data and store it at a University of Michigan HIPAA compliant server. The study team performed the initial setup of the application for all participants. The research coordinator performed the background and baseline clinical measurements during the initial encounter. Data security, patient privacy and HIPPA requirements were given a premium consideration. These were addressed through using data encryption, HIPPA compliant servers and password-protected files. We included patients with paroxysmal and persistent AF who presented to University of Michigan for the management of their cardiac arrhythmia. We also included patients with persistent AF undergoing electrical cardioversion. These patients recorded their heart rhythm using an event recorder before and after the electrical cardioversion.

Mobile questionnaires

The questions for the mobile application were designed to assess symptoms most commonly associated with AF, positive and negative affect. The questions assessing symptoms consisted of a ten-point scale with zero representing no symptoms at all and 10 representing severe symptoms. The questions used to assess symptoms were: "how severe is your shortness of breath", "what is your level of fatigue", "how severe are your palpitations", "how severe is your chest pain" and "how severe is your dizziness or lightheadedness". The questions assessing affect were rated using a five-point scale with zero representing absence and 5 representing complete presence of emotion. The questions used to assess positive affect were: "how happy are you at this time", "how excited are you at this time" and "how content are you at this time". The questions used to assess negative affect were: "how worried are you at this time", "how angry are you at this time" and "how sad are you at this time". Mean symptom, positive and negative affect scores were used to summarize the results obtained from the mobile application.

Survey

A final follow up session was arranged approximately four weeks from the first session. In the final session, the research coordinator conducted a semi-structured interview with the participant over the phone. The participants completed a self-report questionnaire, consisting of five-point Likert scaled questions (one, representing strongly disagree, to five, representing strongly agree) designed to measure ease of use ('by the end of four weeks I found the app easy to use'), convenience and integration into daily routine ('by the end of the four weeks I found the app easy to use'/ had fitted into my routine') and future intentions to use the application ('I intend to use the app in the future').[11] Mean score was used to summarize the results obtained from the surveys.

Table 1: Baseline Characteristics

Age	
Sex (Female %)	5 (50%)
Paroxysmal AF (%)	5 (50%)
Hypertension (%)	4 (40%)
Diabetes (%)	1 (10%)
Obstructive Sleep Apnea (%)	5 (50%)
Congestive Heart Failure (%)	1 (10%)
Chronic Kidney Disease (%)	0 (0%)
Peripheral Vascular Disease (%)	0 (0%)

Feasibility trial

We performed a four-week feasibility trial to examine user adherence, acceptance and experiences with the mobile application.

Patient Characteristics

Patients with a history of symptomatic persistent and paroxysmal AF seen at the University of Michigan Health Center (UMHS) were eligible to be included in the study. Identification and recruitment of eligible participants was based on the physician referral and use of ICD-10 codes. Potential patients were screened for initial eligibility by a research coordinator. Written informed consent was obtained prior to study enrollment. Baseline characteristics were obtained at the initial visit. Staff recruited patients between November 2015 and February 2017. Eligibility criteria were: age > 21, diagnosis of AF and stable medical regimen for at least 30 days prior to study

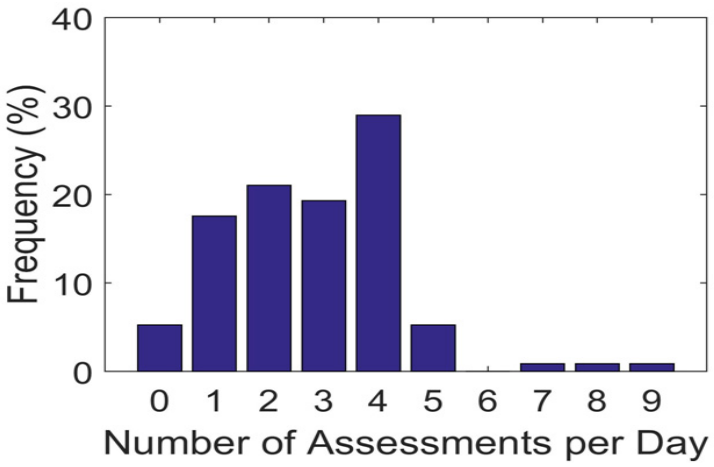

Figure 2: The distribution of completed assessments per day

inclusion. The exclusion criteria were: no symptoms associated with AF, psychiatric disorders, diagnosed neurological disorders associated with cognitive difficulties (stroke, dementia, Parkinson's disease, Multiple Sclerosis), cancer or brain tumors, chronic use of recreational drugs, alcohol abuse and moderate to severe traumatic injury, life expectancy less than one year, pregnancy, known allergic reaction to adhesives or family history of adhesive skin allergies and existing implantable cardiac rhythm devices and neuro-stimulators. The baseline characteristics of patients are summarized in [Table 1].

Our primary measures of interest were frequency of usage (measured via number of completed assessments), qualitative accounts of the effects of the application and factors affecting usage, as well as self-reported acceptance of the application (as measured in the questionnaire).

Results

The mean number of completed assessments each day was 2.81 ± 1.59 (median=3, Q1=2, Q3=4) with 94.7% of days with at least one assessment while in study. The frequency of assessments is demonstrated in [Figure 2]. The patients completed the full assessment at every instant of using the application. These results indicate that participants were able to routinely engage with the application during the trial period while also providing comprehensive data.

Descriptive statistics showed that users found the application easy to use (4.75±0.46) and intended to use it in the future (4.37±1.06). Convenience and integration into daily routinewas rated highly (4.5±1.07). While these data are supportive, these self-reported measures were obtained over a relatively brief trial period and additional measures may be needed for long term habitual use.

Four patients used the mobile application while wearing the event recorder (BodyGuardian Heart, Preventice Solutions). Patients completed mean of 3.89 ± 1.34 assessments while wearing the event recorder. Patients found that the application was easy to use (4.50±0.58) and intended to use it in the future (4.0±1.41). The participants found the application convenient and easy to integrate into daily their routine (4.0±1.41). [Figure 2] demonstrates an example of patient reported data in patients before and after an electrical cardioversion.

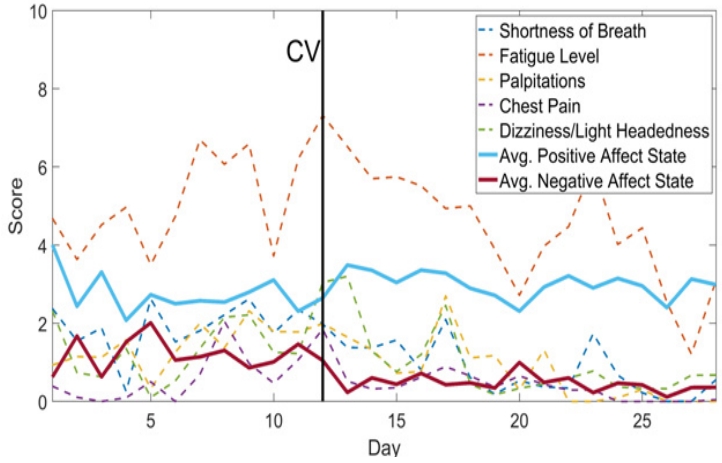

Figure 3: Symptoms and Affect Recorded by miAfib Mobile Application Before and After Electrical Cardioversion

Discussion

This was the first study to evaluate the feasibility and applicability of a mobile application to assess daily symptoms and affect in patients with AF. Participants in this four-week trial regularly used the application to report their daily symptoms and affect. Participants found the application easy to use and would consider using the application in the future.

There is growing evidence that affect is associated with cardiovascular health.[12] Negative emotional states have been associated with acute cardiac dysfunction, myocardial ischemia and increased long term cardiovascular mortality.[13] These negative emotional states and specifically anxiety and depression have also been linked to more severe symptoms in patients with AF.[12], [14]-[16] However, investigating the temporal sequence of affect and cardiac dysfunction represents significant methodological challenges that are not addressed with one-time assessments of affect during clinic visits. The prospective real-time assessments of how a person feels over a period of time have demonstrated an association between negative affect, acute cardiac dysfunction and poor long-term survival. Despite the evidence suggesting an association between affect and symptoms in cardiovascular disease, there have not been studies evaluating their relationship in patients with AF. Our mobile application allows for more accurate and time sensitive measurement of symptoms and affect in patients with AF, so that we can determine how within-subject changes in symptoms and affect influence functional status in individuals with symptomatic AF. These findings lay the foundation for future research evaluating the subjective symptoms and affect and their relationship with rhythm and functional status. This approach will provide an unparalleled window into the daily lives of patients with AF.

Limitations

Our pilot study included a limited number of patients to evaluate the feasibility of the mobile application. Larger studies are needed to determine its feasibility in a diverse group of patients with AF. Although the overwhelming majority of our patients found the mobile application easy to use, there is a need to evaluate its feasibility in different patient populations with both paroxysmal and persistent AF. Future research is also needed to determine the feasibility of personalization of the mobile application based on patient and physician preferences.

Conclusions

Our study demonstrates the feasibility of a mobile application designed to assess symptoms and affect in patients AF. Our mobile

application provides a unique opportunity to evaluate psychological and physiological correlates of symptoms in patients with AF.

Conflict Of Interests

None.

Disclosures

None.

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Postpacing Interval During Right Ventricular Overdrive Pacing to Discriminate Supraventricular from Ventricular tachycardia

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Abstract

Introduction: Failure to differentiate supraventricular from ventricular arrhythmias is the most frequent cause of inappropriate implantable cardioverter-defibrillator (ICD) therapies. We hypothesized that the postpacing interval (PPI) after overdrive right ventricular pacing may differentiate ventricular (VT) from supraventricular tachycardia (SVT) such as sinus tachycardia, atrial flutter and atrial tachycardia. This hypothesis is based on the entrainment maneuver. Reentrant tachycardia circuit for VTs would haveshorter distance to RV apex than SVTs have, and the conduction time between a ventricular pacing site and the tachycardia origin is expected to be shorter in VTs than in SVTs.

Methods: 220episodes from 38 patients with single chamber ICDs that RV overdrive pacing could not terminate or change the tachycardia cycle length (TCL) were retrospectively reviewed. Episodes were classified as VTs (n=115) and SVTs (n=105). TCLs, PPIs and PPI-TCL were compared between groups.

Results: The cycle length of VTs was shorter than SVTs (320.6±30.3 vs 366.5±40 ms, p=0.001). PPI and PPI-TCL of VTs were shorter than SVTs (504.7±128.3 vs 689.2±121.8 ms, p=0.001, 184±103 vs 322.6±106.6 ms, p=0.001; respectively). ROC curve analysis demonstrated a 525 ms cut-off value for PPI has 89% sensitivity and 57.4% specificity to predict inappropriate ICD therapies due to SVTs (AUC:0.852). Similarly, A PPI-TCL <195 ms favored VT as a diagnosis rather than SVT with a 90% sensitivity, and 51% specificity (AUC:0.838).

Conclusions: Analyzing of PPI during overdrive pacing from RV apex may discriminate supraventricular from ventricular tachycardia. This criterion may have a potential role in implantable devices that use a single ventricular lead.

Introduction

The most common cause of sudden death in patients with structural heart disease is scar related reentrant ventricular tachycardia[1]. The implantable cardioverter-defibrillator (ICD) therapy is the most powerful therapeutic tool in the treatment of ventricular tachyarrhythmia (VT) and for the prevention of sudden cardiac death[2],[3]. Atrial fibrillation or atrial tachycardia/flutter with fast AV conduction and sinus tachycardia are frequent causes of inappropriate ICD discharges due to misclassification of the tachycardia[4]. The rate of the conducted supraventricular tachycardia (SVT) may exceed the upper detection interval at which discriminators and morphology templates are programmed, leading to inappropriate shocks that are usually preceded by an episode of anti-tachycardia pacing [5]. Overdrive pacing from RV apex may successfully terminate the tachycardia in many cases. But if it is unsuccessful it may be expected to entrain the tachycardia. Entrainment maneuvers are widely used in electrophysiological studies to to differentiate between mechanisms of tachycardia. In a patient with ICD, the conduction time between a right ventricular apex and the tachycardia origin is expected to be shorter in VTs than in SVTs (provided there are no accessory AV connections). Depending on entrainment phenomenon, post-pacing interval (PPI) after unsuccessful ATP for VT should be shorter than the PPI for SVTs. Therefore, assessment of PPI on device stored EGMs may help to to discriminate between the VT and SVT.

Key Words

Antitachycardia pacing, Inappropriate shock, Discrimination.

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Materials and Methods

For this study, we retrospectively analyzed 38 consecutive patients (30 male, 8 Female) with single lead ICD, who had ICD and tachyarrhythmia therapies. Events were adjudicated by three observers (KY, EG, MA) on the basis of arrhythmia onset, EGM configuration and regularity.Clinical features, tachycardia ECG if available, electrophysiological study findings were checked after ICD-EGM analysis were checked to increase tachycardia discrimination probability. Leads implanted other than RV apical site were excluded. Tachycardia episodes were classified into VTs and SVTs (sinus tachycardia, atrial flutter and atrial tachycardia). Atrial fibrillation episodes were excluded due to impossibility of entrainment. Episodes due to any non-physiological condition such as over-sensing, were excluded. Patients who have evidence of AV conduction disorder or extranodal conduction were also excluded.

Table 1: Clinical characteristics (n=38), LVEF: left ventricular ejection fraction, CMP: cardiomyopathy.

Variable	Mean±SD or %
Age (years)	56±12
Male sex	79%
LVEF	28±17%
Ischemic CMP	63%
Beta-blockers	89%
Amiodarone	73%

Onset and stability parameters were either turned off or programmed to monitor only to allow delivering ATP therapies to supraventricular arrhythmias. After first inappropriate shock, stability and onset parameters programmed on.

PPI was considered as the interval, in milliseconds, between the last stimulus artifact of the pacing train and the first rapid deflection crossing the baseline of the first non-stimulated beat, in the ventricular EGM channel. Difference between PPI and tachycardia cycle length (PPI-TCL) was also obtained. TCL was determined the average of five consecutive cycle lengths of the ambient tachycardia rate prior to ATP. The episode is excluded, if there is 50 ms or greater change in pre- and post-ATP TCL.

All continuous variables were represented as mean±standard deviation while categorical variables were expressed as numbers and/or percentages. Data were analyzed using SPSS software. Kolmogorov Smirnov test was used to assess statistical distribution. Student t-test or Mann-Whitney U test were used to assess significance and p value less than 0.05 was regarded as significant. Receiver operator curves (ROC) were used to determine cut-off values to discriminate VTs from SVTs.

Results

Thirty-eight patients were enrolled to the study. Demographic data of the study patients was presented in [Table 1]. Mean age of the study patients was 56±12years and 30 were male. Twenty-four patients had ischemic cardiomyopathy and 14 had nonischemic cardiomyopathy. Mean LVEF was 28±17%. All the patients underwent single lead ICD implantation for secondary prevention. All defibrillators were from the same manufacturer (Medtronic Inc. Minneapolis, MN). Total 1063 tachycardia episodes that ATP therapy was delivered were reviewed. Eight hundred thirty-eight of these episodes were successfully terminated by ATP, and ATP was accelerated the tachycardia in 5 episodes. For this study, 220 tachycardia episodes that RV overdrive pacing could not terminate or change the TCL were enrolled and retrospectively classified as VT or SVT by experienced observers [Table 2]. Episodes classified as VTs (n=115) and SVTs (n=105). Hundred and five SVTs were diagnosed as follows; 25 atrial tachycardia, 55 sinus tachycardia and 25 atrial flutter.

The TCL of VTs was shorter than SVTs (320.6±30.3 vs 366.5±40 ms, p=0.001).PPI and PPI-TCL of VTs were shorter than SVTs (504.7±128.3 vs 689.2±121.8 ms, p=0.001 and 184±103 vs 322.6±106.6 ms,p=0.001; respectively). ROC curves applied to both PPI and PPI-TCL measurements [Figure 1]. ROC curve analysis demonstrated a 525 ms cut-off value for PPI has 89% sensitivity and 57.4% specificity to predict inappropriate ICD therapies due to SVTs(AUC:0.852). Similarly, PPI-TCL <195 ms favored VT as a diagnosis rather than SVT with a 90% sensitivity, and 51% specificity (AUC:0.838).Sixty-six of 115 episodes classified as VT had PPI<525 ms. And sixty-two of the episodes had PPI-TCL than 195 ms cut-off value.

Discussion

The main finding of our study is PPI and PPI-TCL after failed ATP based on discrimination seems to be safe and effective in single lead devieces. Due to inappropriate ICD therapies occur mostly due to supraventricular arrhythmias 4and affect most of the patients,ICD programming strategies aimed at reducing inappropriate ICD therapies result in significant reduction in mortality, with no increase in the risk of syncope[6]-[8]. This emphasizes the need to improve ICDalgorithms to minimize inappropriate shocks and to enhance ATPas first-line therapy. By using the atrial rhythm, dual-chamber ICDs are expected to discriminate more precisely between SVT/VTs compared with single-chamber ICDs. Kolp C et al found that in patients with dual-chamber devices, inappropriate therapies are lower than patients with single-chamber devices[9]. The reason behind the wide usage of dual-chamber ICDs may lie on the benefit

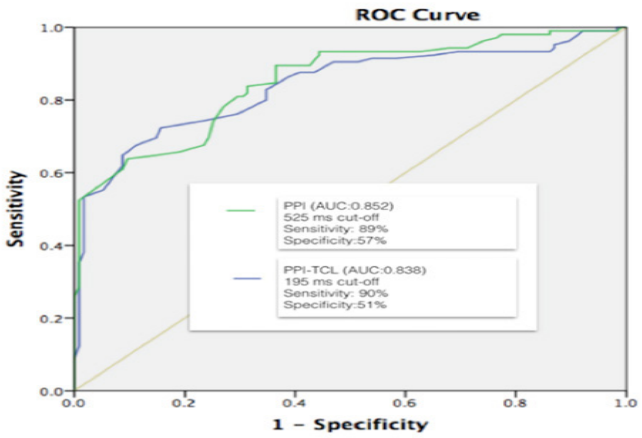

Figure 1: ROC analysis of PPI and PPI-TCL measurements

of them in SVT/VT discrimination. Peterson et al. [10]reported that, in clinical practice patients often receive dual-chamber ICDs, even without clear indications for pacing. The use of dual-chamber device compared with a single chamber device was associated with a higher risk of device-related complications and similar 1-year mortality and hospitalization outcomes. Dual-chamber devices are costlier for the initial implant and are associated with a greater risk of generator depletion. For these disadvantages of dual-chamber ICDs, several discrimination algorithms have been developed for single-chamber ICDs.

As onset and stability are nowadays the cornerstone of modern single-chamber discrimination algorithm, there are several limitations of the current algorithms. Swerdlow et al.[11]showed that the sudden onset failed to detect 0.5% of spontaneous VT episodes. Other limitation of the onset criterion is the inability to distinguish paroxysmal ATs with sudden onset. We hypothesized that the PPI following a failed episode of ATP for true VT is significantly shorter than the PPI for SVT and therefore may be used to discriminate the origin of the tachycardia, and therefore these parameters could be incorporated into ICDs redetection algorithms or a complement to the conventional algorithms. These conclusions are based on the presented statistically significant difference between PPI and PPI-TCL between VTs and SVTs.At first glance, a 90% sensitivity and

Table 2: An example of a VT episode. ATP: antitachycardia pacing, PPI: postpacing interval, TCL: tachycardia cycle length.

Variable	VT (n=115)	SVT (n=105)	p value
TCL (ms)	320.6±30.3	366.5±40	0.001
PPI (ms)	504.7±128.3	689.2±121.8	0.001
PPI-TCL (ms)	184±103	322.6±106.6	0.001

57% specificity seem to be still low in this settingand If PPI would be the sole discriminating factor, a cut-off of 195 ms would potentially miss one out of ten VTs not responding to ATP, falsely labeling it as SVT and potentially putting the patient in great danger. However, ATP is not just a discriminator it is also a therapeutic maneuver. ATP has been reported to successfully terminate VT in over 90% of cases, making this a very successful and pain free therapy in ICDs[12]. Therefore, programming strategies now use ATP as initial therapy even in fast VT episodes if the rhythm is found to be stable[13].Shock reduction can be accomplished with multiple bursts of ATP to treat fast VTs in patients with ICDs. Anguera et al.[14]compared the safety and effectiveness of a single ATP burst (Group 1) with a strategy of successive ATP sequences (Group 2) for termination of FVT episodes before shock therapy. Over a mean follow-up of 35 months, effectiveness of the 1st burst ATP in Group 1 was 73% and shocks were required in 27% of episodes. Effectiveness of the 1st burst ATP in Group 2 was 77%, and this increased to 91% with the 3rd or successive ATP bursts. Acceleration occurred in 8.9% of treated FVT episodes and 56.9% of accelerated episodes required shocks.

Even ATP failed to terminate VT episode, this can still be used to differentiate SVTs from VTs in ICDs. Using the current algorithm as a discriminator, ATP would terminate 90 of 100 VTs, and our 195 ms cut-off would successfully discriminate 9 of remaining VTs and allow further therapies. This concept of entrainment has been defined as a basic electrophysiologicalmaneuver to indicate the proximity of a rovingpacing catheter to a macro-reentrant circuit or focal tachycardia[15],[16]. Consistent with literature, our discrimination technique based on entrainment maneuver seems to be safe.

Michael KA et al.[17]postulated that the PPI and PPI - TCL would be greater in AT/AF vs. VT after episodes of failed ATP. They evaluated patients implanted with dual (DR)/biventricular (BIV) ICDs. Cut-offs of 615 ms for the PPI[AUC 0.93; 95% confidence interval (CI): 0.84–1.00; P<0.01] and 260 ms for PPI - TCL (AUC 0.86; 95% CI: 0.74–0.98; P<0.01) were identified to discriminate SVTs from VTs.Although their study did not enroll patients with single-chamber ICDs, they concluded that their results may have particular relevance in patients with single-chamber ICDs, in which atrial EGMs are not available for analysis, and in patients with chronic AF to differentiate rapidly conducted AF from dual tachycardia.Our results are concordant with the previous studies. Entrainment based discrimination algorithm has been shown to be effective in single chamber ICDs.

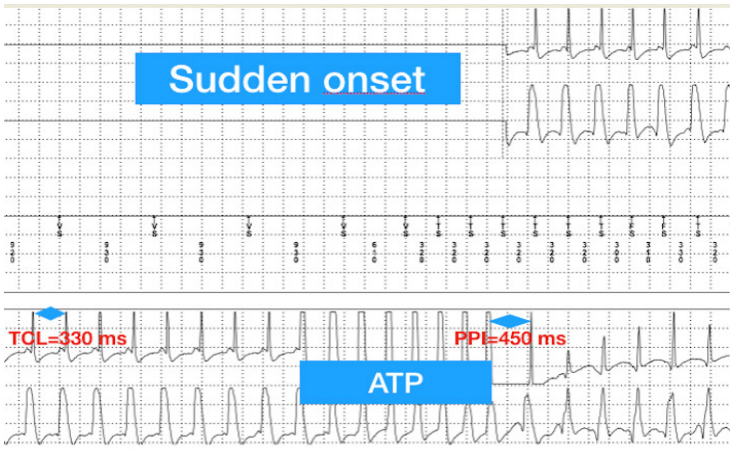

Figure 2: An example of a VT episode. ATP: antitachycardia pacing, PPI: postpacing interval, TCL: tachycardia cycle length.

In our cohort antitachycardia pacing, could terminate or differentiate the VT from SVT in 904 of 1063 episodes (85%), but accelerated only 5 episodes 0.4%. Our results confirm both efficacy and safety of ATP, and gives rise to the rationality of programming early ATP for both discrimination and therapy. The role of programming the device to deliver early ATP and combining it with other discrimination algorithms should be interest of further research.

Limitation

The sample size of this study is small and our findings need to be validated in a larger cohort of patients. No patients with dual tachycardias were included in the study and our findings are not applicable in this subgroup. Leads implanted to non-RV apical sites were not included, so the clinical significance of current algorithm in this population is unclear. Only a single manufacturer's devices were used and by this way a homogeneous patient population could be afforded and observer-related errors could be reduced. Due to single chamber devices, atrial EGM was not available to see AV relationship of the tachycardias. Simultaneous surface ECGs of the episodes was also not available for SVT/VT discrimination.The EGMs of the episodes were evaluated by experts who were blinded to study protocol. Due to lack of EP study data and surface ECGs, this may limit exact discrimination of SVTs and VTs. In patients with extensive LV scar and epicardial VTs may have probably much farther than the usual RV apical lead, and may cause misdiagnosis. The study was retrospective and criteria for ATP programming were not standardized for all patients. Although potentially useful, in our study onset and stability parameters were turned off or programmed to monitor only. The question if PPI could improve the already existing, multi-parametric, discriminating algorithms, should be further research area. Despite limitations this study is a hypothesis generating study, and will light to further studies on this field.

Conclusions

Our data strongly suggest that the PPI and PPI - TCL parameters may have the potential to be incorporated into ICDs as a method of redetection or dynamic discrimination of the underlying rhythm and a complement to the conventional algorithms. However, a larger study to validate this concept is required.

Conflict Of Interests

None.

Disclosures

None.

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Laser catheter ablation of long- lasting persistent atrial fibrillation: Longterm results

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Abstract

Catheter ablation of atrial fibrillation (AF) is a current therapeutic option but its efficacy for the treatment of long-lasting persistent AF (l-lpAF) remains suboptimal. We tested the laser method as an alternative for catheter ablation of l-lpAF by using an open-irrigated electrode laser mapping and ablation (ELMA) catheter. Laser ablation was attempted in 48 patients aged 50-81 years (69 ± 7.6 y, female = 28) with drug resistant (3.5 trials) l-lpAF (≥12 months). All of the patients had comorbidities: congestive heart failure NYHA II-III (100%), hypertension 29 (60%), coronary artery disease 19 (40%), and heart valve defect 17 (35%). None of the patients had diabetes or obstructive sleep apnea. All were in AF at the beginning of the procedure. Continuous wave (cw) 1064nm Nd:YAG laser applications at 15W/10-20s (14-26/patient) were applied via the ELMA catheter until local electrical activity displayed on the monitor in the bipolar focused local electrograms (LEG) recorded via the pin electrodes from the tip of the catheter was abolished permanently and sinus rhythm was achieved. Online monitoring of electrical potential amplitudes in the focused LEG recorded via the pin-electrodes of the ELMA catheter allowed for validation of ablation success. Procedure duration ranged from 82-175 min (118 ± 72 min), number of lesions were14-26 (19 ± 4) per patient and X-ray exposure times ranged from 15-82 min (23.2 ± 12 min). Interventions were without complications. After the ablation procedure all the patients were in sinus rhythm, off medication, however, 12 (25%) needed a repeat study for various arrhythmias. During followup of 9 months to 29.3 years (8.2 ± 6.5 years) patients' quality of life improved significantly and during final follow-up control all except two were off medication still in sinus rhythm (lifelong success rate = 96%). As compared to other catheter ablation methods the laser method is an intriguing alternative for catheter ablation of l-lpAF.

Introduction

Atrial fibrillation (AF), the most frequent clinical arrhythmia, is associated with increased risk of stroke, myocardial infarction, heart failure, and death [1]. AF is generally considered a progressive disease, typically evolving from paroxysmal through persistent to permanent forms, a process attributed to electrical and structural remodeling related to both the underlying disease and AF itself. In 2010, the estimated numbers of men and women with AF worldwide were 20.9 million and 12.6 million, respectively, with higher incidence and prevalence rates in developed countries [2],[3]. AF prevalence increases with age; starting at the age of 50, this doubles every decade of life, corresponding to a 5% prevalence in the population older than 60, and a 13% prevalence in the population older than 80. This means that 70% of cases affect people who are between 65 and 85 years old [4]. AF treatment is a very active field of novel discoveries and research with strong translational potential, often in bedside–bench–bedside reiterative cycles. Unfortunately, available drugs for AF therapy have moderate success and important limitations, particularly increasing the risk of Lifethreatening proarrhythmic events and bleeding complications [5]. To cope with these limitations, catheter ablation with pulmonary vein isolation (PVI) by means of RF current has become the gold standard, the cornerstone treatment for paroxysmal AF [6]. Worldwide, thousands of procedures have been done, and hundreds of papers published. Given this history and knowledge, one would think the best technique to ablate AF would be agreed on. However, persistent AF suggests that the electrophysiology community isn't settled on the best technique to ablate AF. Up to now, the success rate of RF ablation in the more prevalent and highly heterogeneous l-lpAF populations has been disappointing [7]. Regardless of methods of catheter ablation applied with the aim to convert l-lpAF or permanent AF into stable sinus rhythm the success rate of the first ablation procedure, taking into account a 3-month blanking period, when measured as freedom from repeat catheter ablation, from need for cardioversion, and from need for the use of an antiarrhythmic drug was 40% at one year and 34% at two years [8]. The results of these 'realworld' experiences are remarkably consistent, indicating that the one-year success of l-lpAF ablation procedures at the centers actually delivering this therapy in Europe today is well under 50%, a

Key Words

Long-lasting persistent atrial fibrillation, Laser catheter ablation, Bipolar focused local electrograms.

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Table 1: Two to 4 Comorbidities were present in all, and additional arrhythmias in 18 (37.5%) of the 48 patients candidates for laser catheter ablation of long persistent l-lpAF

Comorbidities	No		Arrhythmias	No
Congestive heart failure II-III	all	100%		
Coronary artery disease		40%		
Enlarged left atria	38	79%	Left atrial flutter	7
Ø 46-52 mm			Common AVNRT	3
High blood pressure	29	60%	Left AP	3
>160 / >95 mmHg			Atrial flutter	2
Mitral valve prolapse	16		RVOT	1
insufficiency grade 1-2		35%	SSS	1
Severe aortic valve stenosis	1		(right atrial reentry)	1
Gradient 60 mmHg at rest				

AVNRT = atrio-ventricular nodal reentrant tachycardia, AP = accessory atrio-ventricular pathway,SSS = Sicksinus syndrome, AT = atrial tachycardia, nsRVOT = ventricular outflow tract tachycardia

success rate quite a lot lower than often stated. The question raises: is complete electrical isolation of pulmonary veins the cornerstone, alone? The same group the PVI procedure was initiated from showed, that for ablation of l-lpAF a stepwise approach combining PVI with complex fractionated atrial electrograms (CAFE) and linear ablation may improve the success rate of AF ablation [9].

Our early in-vivo animal experimental studies with laser catheter coagulation of atrial myocardium in dogs showed, that the method is safe and can be performed in a controllable manner [10]. Transmural laser lesions produced in the atrial walls achieved clear cut areas of coagulation necrosis without tissue vaporization and crater formation [Figure 1]. Lesions healed to dense fibrous scars without aneurysm formation, without compromising the anatomic integrity of the atrial wall [Figure 2]. Our initial attempts at laser catheter ablation of cardiac arrhythmias in humans were promising [11], [12], [13]. Based on these results laser catheter ablation of l-lpAF was attempted in patients.

Patients

Study participants were recruited from patients scheduled to undergo laser catheter ablation procedure for drug resistant (3.5 trials) l-lpAF. From 15.03.1988 to 31.07.2003 laser ablation was attempted in a series of 48 highly selected and severely symptomatic patients, aged 52-81 (69 ± 7.6) years, (f = 28), with long-lasting (≥12 months) persistent AF. They had multiple comorbidities and complex arrhythmias [Table 1].

Congestive heart failure NYHA class II-III with decreased exercise capacity, fatigue, breathlessness and palpitations during emotional or physical stress were present in all of the patients. In their history one to 4 DC shock cardioversion failed to stabilize sinus rhythm. In addition, 4 had a permanent pacemaker implanted because of bradyarrhythmia or atrioventricular conduction disturbances, and anti-tachycardia pacing was not effective in one of the patients. Patients were anticoagulated with warfarin (CHA_2DS_2-VASc score before ablation = ≥2) that was discontinued and they were put on heparin prior to the laser ablation. Pre-interventional transthoracic 3D-Echo- Doppler and transesophageal echocardiography did not give evidence of intra-cardiac thrombus formation. Twenty nine (60%) of the patients were under treatment for hypertension, and 19 (40%) for coronary artery disease. These medications were not discontinued prior to the study. None of the patients had diabetes, obstructive sleep apnea, experienced stroke or other thromboembolic events. Their body mass index ranged from 22.2 to 28.4. One was alcohol addict that became evident first during follow-up. Five patients (10%) had an unsuccessful RF ablation attempt 13-16 months prior to the laser treatment. Antiarrhythmic drugs were discontinued prior to ablation and were not restarted after l-lpAF laser ablation.

Materials and Methods

Continuous wave 1064nm laser light from a cwMediLas 4060N fibertom, Dornier MedTech, provided with a light-guide protection system (LPS), was applied via an open-irrigated electrode laser mapping and ablation (ELMA) catheter, RytmoLas, LasCor GmbH. The proximal end of the optical fiber was connected to the laser via a Fiber Sub-Miniature Assembly (FSMA) connector [Figure 3]. The catheter tip was provided with three pin electrodes arranged symmetrically at the tip of the catheter, with interelectrode distances of ≤ 2.0 mm between each other. Each of the electrodes was connected via plugs to the manifold, for three bipolar focused local electrogram (LEG) recordings. The optical fiber had a conically shaped tip that produced a donut like illuminated spot on the targeted endocardial surface in front of the catheter end hole [Figure 4]. The development of the open-irrigated ELMA catheter I described in detail elsewhere [14].

In general, a slight sedation with phenobarbital was applied. After venous punctures in the groin (Seldinger technique) an 8F long preshaped sheath (RytmoGuide, LasCor GmbH) or a steerable introducer (Agilis™ NxT, St. Jude Medical) was inserted under X-ray control. Side selective transseptal puncture procedure was performed by using the TransLas laser puncture set [15]. The ELMA catheter was advanced via the transseptal access into the left atrium and was manipulated during continuous monitoring of electrical potential amplitudes and intermittent X-ray control of catheter position. LEGs were displayed simultaneously with 12-lead surface

Table 2: AF Laser Ablation Procedures

Ablation		Laser	
Procedure duration(min)	Xray exposure time(min)	524 Applications No per patient	Radiation per patient (s)
82-175	15-82	14-26	180-310
(118+-72)	(23+-12)	(19+-4)	(235+-75)

electrograms on the monitor. Prior to its insertion into the sheath the laser catheter was continuously rinsed with heparinized (5000 IU/L) saline at a rate of 15 mL/min. Saline flow increased automatically via the foot-switch to a rate of 30-35 mL/min during laser application.

Continuous variables are expressed as mean ± SD. The study was performed in the Laser and Applied Technologies Center, the Clinical Cardiac Electrophysiology Laboratory, 3d Medical Department, Cardiology, Hospital Harlaching, teaching hospital of the LM-University of Munich. Quality of life forms were completed prior to and following laser ablation. Clinical and electrocardiographic controls, and, only in case of need, redo procedures were performed during an intended life-long follow-up.

Study design / Ablation protocol

Study design, including the form of written informed consent, was granted a favorable ethical opinion and was approved by the Ethics Committee of the Board of Physicians of the Land of Bavaria (reference EK/h No: 95243). Written informed consent was obtained from all the 48 patients recruited to the study. In addition,

patients completed a questionnaire for quality of life (QL-form) at baseline, 12-14 months after the study, and after ≥5.2 years, in regard of exercise capacity, angina, palpitations, breathlessness, and attacks of dizziness / syncope.

After advancement of the ELMA catheter beyond the endhole of the transseptal sheath manual catheter exploration of the left atrial cavity was performed systematically. Initially endocardial areas with relative regular rapid and sharp high frequency atrial potentials in the left atrial posterior wall were targeted. The catheter tip was brought in a stable intimate contact with the endocardial surface where the highest electrical potential amplitudes were recorded from. Laser application at 15W was aimed at that area until amplitudes of electrical potentials in the LEG displayed on the monitor were abolished permanently. The catheter was then moved to adjacent sites where electrical potentials were still present and the procedure was repeated. Stepwise the entire LA posterior wall around the pulmonary veins was rendered electrically inactive, devoid of electrical potentials. When sinus rhythm was achieved burst stimulation at pacing cycle lengths (PCL) of 150-200 ms was performed. If AF recurred laser applications were stepwise aimed at the LA roof, mitral isthmus, and around the margins of the left atrial appendage until local electrograms, including CFAE or torsade were abolished.

If AF persisted or was still inducible detailed analysis of the left atrium, inter-atrial septum in right atrium was performed to identify electrical activity of other areas that was then ablated. This process was considered as completed when sinus rhythm was restored and no residual CFAE or torsade like sites could be identified. Only split and blunt low amplitude potentials representing rather far potentials were left. Laser application inside the pulmonary veins, the atrial appendages, and the coronary sinus was avoided. After an observation time of 15-20 minutes final rapid burst stimulation was performed via the pinelectrodes of the ELMA catheter.

If other arrhythmogenic substrates were present these were also abolished. When the patient was in sinus rhythm 20-30 min after burst atrial stimulation the catheter was removed and the patient

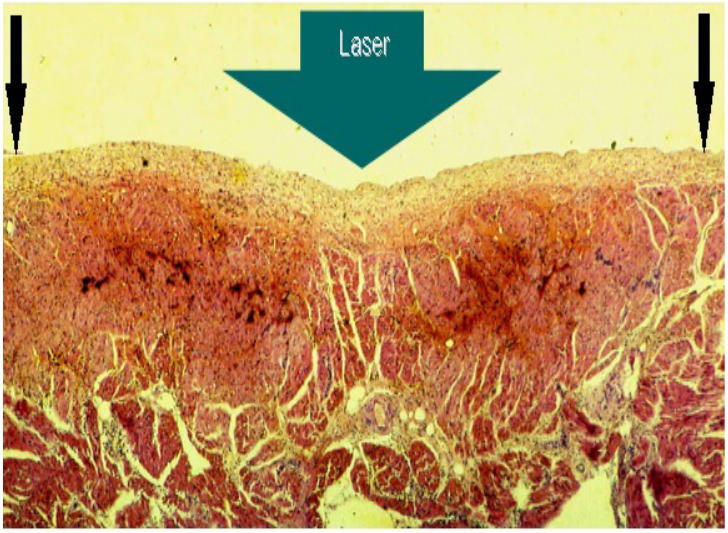

Figure 1: Cross-sectional view of a 3h old HE stained lesion produced by laser application aimed at the endocardial side of the right atrial lateral wall of a dog, showing clear cut transmural coagulation necrosis with intramural hemorrhage and vacuolization. There is a slight dip in the central region of the lesion (thick arrow). Note: the endocardial layers are morphologically intact; there is no tissue vaporization with crater formation.

referred to the ward with Holter-monitor.

Acute Results and clinical outcome

The very first l-lpAF laser ablation procedure was performed in April 13th, 1988 in the EP laboratory of the Cardiac Department of the Hospital Bogenhausen, Teaching hospital of the Technical University of Munich. The patient suffered from frequent attacks of palpitations and weekly syncope. Prior to l-lpAF ablation, an

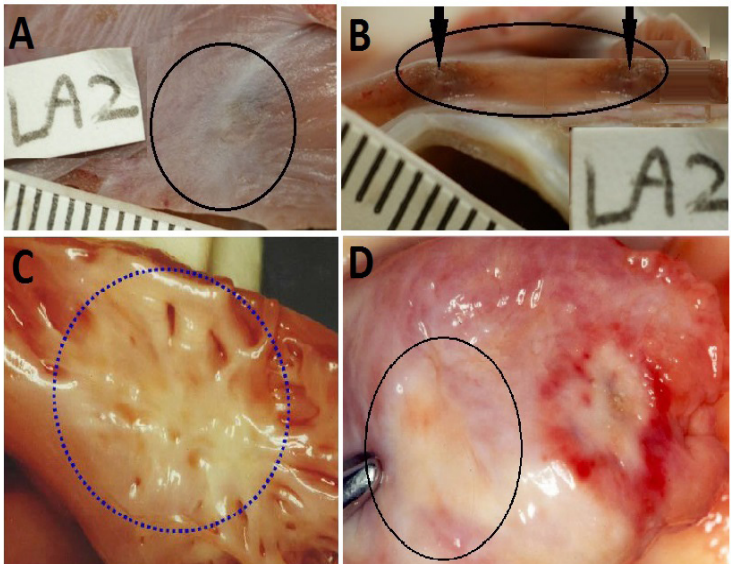

Figure 2: Gross pathology showing subacute 6 hours old atrial lesions produced by laser catheter applications at 15W/15s aimed at the endocardial surface of the posterior left atrial wall (LA_2) A endocardial view: showing coagulation necrosis achieved without tissue vaporization with crater formation (black circle), the anatomic integrity of the atrial wall is preserved, and B Section through that transmural lesion (black oval), showing, a slight intramural hemorrhage at the margins of the lesion (black arrows), and, C and D showing two chronic, three months old transmural fibrous scars in the right atrial free wall, endocardial and epicardial view respectively (circles), and an acute, three hours old, transmural lesion of coagulation necrosis surrounded by a ring of hemorrhage.

accessory atrioventricular pathway with bidirectional conduction properties was localized in left atrial lateral wall and was laser ablated March 3d, 1988 [Figure 5].

All of the patients were in AF at the beginning of the ablation procedure. During catheter exploration of the atrial cavities various types of local electrical potentials including rapid relative regular high frequency sharp demarcated potentials, various types of CAFE and even torsade de point like electrograms were displayed in the focused LEG. In 5 of the 48 patients all these types of LEGs were found during catheter exploration in different sites of the atria. Torsades like tracings were seen in 5 patients in the right atrial LEGs [Figure 6]. During laser applications aimed at the areas with rapid firing as shown in LEG1 in [Figure 4], the potential amplitudes dwindled gradually and eventually were abolished permanently [Figure 7].

Initially in all of the patients the entire left atrial posterior wall was coagulated by creating an extensive contiguous lesion that rendered the area around the pulmonary veins electrically inactive. A series of 11 to 16 consecutive adjacent laser applications were needed to achieve that goal. Sixteen patients (33%) converted to sinus rhythm after LA posterior wall ablation alone. In 32 (67%) patients additional applications were needed for the abolishment of local potentials in the area of the left atrial isthmus and roof, and

Table 3: Left atrial dimensions at baseline and after laser ablation of atrial fibrillation

Left Atrial dimensions	Baseline 48 Patients	Post Ablation 5-11 days	P-values 46 patients	Post ablation 11-14 months	P-values 44 patients
Diameter (mm)	44 – 59 51.73 ± 3.28	45-56 50.92 ± 2.93	P = 0.2037 NS	40 – 50 44.73	P <0.0001 ES
Major axis (mm)	66 – 83 75.92 ± 4.41	65 – 82 74.52 ± 4.15	P = 0.1139 NS	62 – 75 67.18 ± 1.17	P<0.0001 ES
Area (cm^2)	25 – 46 37.71 ± 5.32	25 – 42 35.92 ± 4.84	P = 0.0877 NQS	19 – 31 26.48 ± 5.18	P<0.0001 ES
Volume (ml)	71 – 86 78.90 ± 4.00	70 – 81 76.69 ± 2.81	P = 0.0023 VS	68 – 77 73.48 ± 3.02	P<0.0001 ES

NS = not statistically significant; NQS = not quite statistically significant
VS = very statistically significant; ES = extremely statistically significant

around the basis of the atrial appendage. In 12 (25%) patients sinus rhythm was achieved after additional 7-11 laser applications aimed at the right atrial posterior and/or lateral walls, or interatrial septum. In two of the patients 26 bi-atrial laser applications, the maximum of laser impacts per patient in this study, were needed to achieve sinus rhythm [Figure 8].

All of the patients were in sinus rhythm at the end of study. In the 4 patients with an implanted permanent pacemaker laser applications did not alter pacemaker functions but pacemaker probes hindered in some degree catheter exploration of the right atria. Laser ablation and transseptal laser puncture procedures were painless and without complications, except one bleeding of the venous puncture in the left groin. Total time of ablation procedure was 82-175 (118±72) min, and number of lesions produced per patient ranged from 14 - 26 (19 ± 4) [Table 2].

Follow-up

Holter monitoring for 24-48 hours was performed immediately following, before released from the hospital, and, on a regular basis after a month, after 6 months for two years, and every year after ablation, and, whenever patients complained and AF recurrences were suspected. DC-cardioversion was needed in 3 of the 48 patients 2-5 days after ablation. Before leaving the hospital patients were learned to reduce/avoid increase in weight, nicotine abuse, to have regular moderate physical exercise, were learned to feel and control their peripheral radial or carotid pulse and in case of palpitations to consult medical services for ECG recordings; perhaps take Propafenon ("pill-in-the-pocket") until recurrence of AF is ECG confirmed or is ruled out. After the final clinical checkup control of 2D-Doppler echo was carried out, that was repeated after 11-14 month of follow-up [Table 3].

All the patients were in sinus rhythm and off antiarrhythmic medication when leaving the hospital but anticoagulation with Warfarin with INR target of 2-3 was continued for three-6 months in all of the patients but was discontinued when stable sinus rhythm persisted. Follow-up clinical controls and 12 lead ECG at rest were performed in an outpatient clinic or by house doctors. Continuous event monitoring was performed by means of a Wrist Recorder Plus, RalinMedical irregularly in case of suspected recurrences of AF.

Thirty three patients (69%) were arrhythmia free after a single study as described including ablation of accompanying arrhythmogenic substrates such as left accessory atrioventricular pathway (n = 3) and atrioventricular nodal reentrant tachycardia (n = 2). Patients were in sinus rhythm, off antiarrhythmic drugs and had a substantially improved exercise capacity [Table 4]. Sixteen patients needed continuous medication with diuretics, angiotensin converting enzymes, and beta- blocker (Carvedilol) because of hypertension, coronary artery disease and/or congestive heart failure NYHA I-II. In 5 patients Propafenon was used intermittently ("pill in-the-pocket") for the control of transient episodes of palpitations suspected by the patient but not documented as arrhythmia recurrences.

During Follow-up the first patient in whom AF ablation was attempted in April 1988 no syncope but palpitations recurred after 6 months. She died in the ICU in another hospital after a MAZE operation she underwent 9 months after the attempted laser catheter ablation of l-lpAF. Another patient died in the ICU of another hospital after thoracic surgery because of hematothorax after a house accident 11 months, and a third patient died in hepatic coma 17 months after successful l-lpAF ablation.

Electrophysiological restudies were performed in 15 patients in whom reablation was needed for AF recurrences (n = 2) after 24 hours and 3 months respectively, and for other arrhythmias one week and up to 9 months after successful l-lpAF ablation [Table 5]. None of the patients with valvular defects had recurrences. Because of the

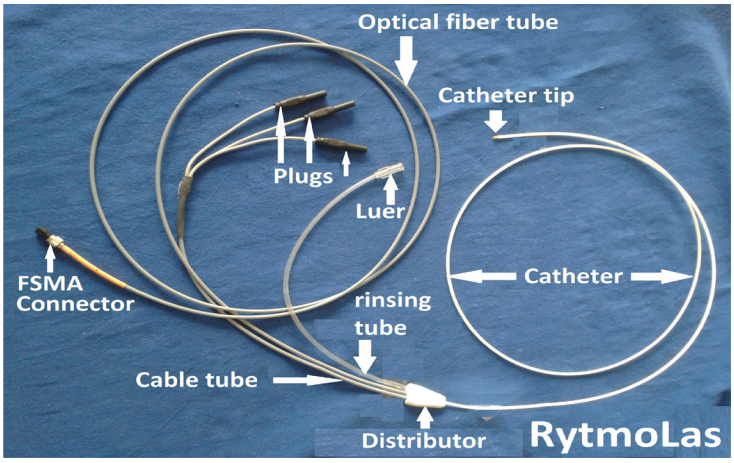

Figure 3: Overview of the open-irrigated electrode-laser mapping and ablation (ELMA) catheter RytmoLas LasCor GmbH as used in this study for laser ablation of long persistent atrial fibrillation. Total length = 300 cm, working length (catheter) = 115 cm.

mild valvular insufficiency we consider these patients also having a non-valvular AF.

All of the patients, except one, were in sinus rhythm during their last control in an outpatient clinic or by cardiologist/general practitioners, in none of them ECG controls documented recurrences of l-lpAF or other arrhythmias. After a mean of 5.2 years, patients were gradually lost and further data no longer available because of noncardiac deaths (cancer, n = 9, pneumonia = 4, liver diseases = 3, traffic accident = 1), or relocation with unknown addresses (n = 5), or could not be contacted any longer (n = 24). Two patients are still alive and under observation. One was seen in October 2016 at the age of 69, the youngest patient in our study group, with permanent AF after a redo procedure for atrial flutter in 1998. He has an irregular heart beat 65 bpm at rest and 85 bpm during exercise (moderate walking, climbing 5 stairs); has congestive heart failure NYHA II-III, is anticoagulated with Dabigatranetexelat (Pradaxa), and is under medication with diuretics, ACE inhibitors, and beta-blocker (Carvedilol). He has no neurological deficit and is able to manage his

Table 4: Quality of life after laser catheter ablation of long-persistent AF estimated with 5 points: 1 = best, 5 = worst; prior to (48 pts), after 12-14 months (45 pts), ≥ 5.2 years (39 pts)

	Not at all limited	A little	Moderate	Very strong	Extremely limited
Marks:	1	2	3	4	5
Criteria evaluated	Prior to study in 48 patients	After 3-14 mo. in 45 patients	P values	≥ 5.2 years in 39 patients	P values
Exercise / Sports	Mean = 4.48 SD ± 0.65	Mean = 2.12 SD ± 0.97	P < 0.0001	Mean = 2.04 SD ± 0.89	P = 0.7626
Palpitations	Mean = 4.24 SD ± 0.78	Mean =1.32 SD ± 0.56	P < 0.0001	Mean = 1.12 SD ± 0.33	P = 0.4507
Angina	Mean = 3.0 SD ± 0.82	Mean = 1.12 SD ± 0.33	P < 0.0001	Mean = 1.44 SD = 0.58	P = 0.0211
Breathlessness	Mean = 4.12 SD ± 0.78	Mean = 1.76 SD ± 0.38	P < 0.0001	Mean = 1.60 SD ± 0.50	P = 0.4134
Dizziness/Syncope	Mean = 3.08 SD ± 1.19	Mean = 1.20 SD ± 0.41	P = 0.0001	Mean = 1.16 SD ± 0.37	P = 0.7196

every day needs. The second patient was contacted in January 30th 2017. She is 95 years of age, in sinus rhythm after successful l-lpAF ablation and after redo procedure for common atrioventricular nodal reentrant tachycardia 21 years ago. PQ-interval is 0.20ms. She is off antiarrhythmic medication but severely handicapped by arthrosis of her leg joints and spine and she needs home help. The last control scheduled for June this year could not be performed; she died at the age of 96 years.

Discussion

This study in a small heterogeneous group of patients after life-long follow-up suggests that laser catheter ablation of l-lpAF is safe and effective. It can achieve excellent long-term results when using the open-irrigated ELMA catheter RytmoLas. A lifelong success rate of 96% is unequalled by other ablation techniques in our knowledge so far. This can be explained by several reasons.

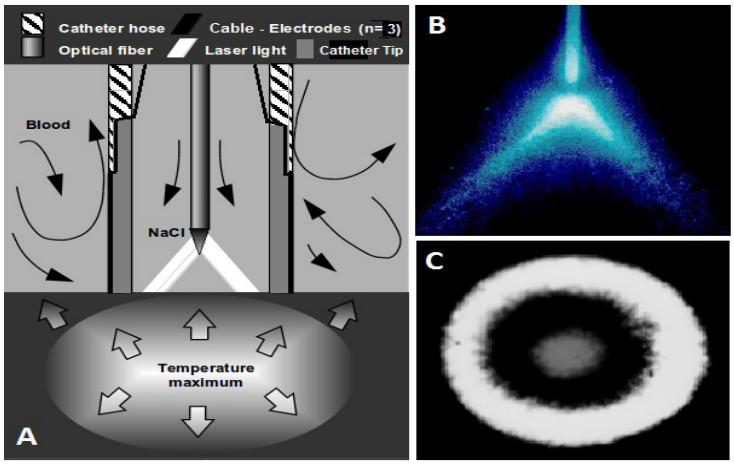

Figure 4: A Scheme, showing, the catheter tip provided with electrodes and an optical fiber mounted coaxially in its lumen at a given distance from the endhole of the catheter. Laser light is heating up the tissue with a maximum temperature intramurally 3-4 mm deep. B is showing the divergent laser beam emanated from the optical fiber tip, and C is showing the donut-like laser spot created on the targeted area in front of the catheter endhole.

The LPS of the laser: in case of inadvertent overheating in front of the ELMA catheter endhole where the "cold" laser light is emanated from and hits the target, laser application is stopped automatically by the LPS prior to the possible occurrences of thermal damage to the endocardium or catheter tip. This is a crucial safety aspect of the laser method. Other important reasons represent:

The Nd:YAG laser

The Nd:YAG laser light at a wave length of 1064nm has a very low absorption in water [16]. Radiation of photons is scattered in the myocardium and can reach deep locations before ultimately being converted into a temperature rise through absorption, with impaired temperature gradient and distribution of heat. The heat generated during photon absorption will cause a gradual rise in temperature cumulative with exposure time and rate of absorption as a function of location [17],[18]. Heat is spreading concentrically in the myocardial wall and, besides of photon absorption is further distributed by heat convection. Continuous wave 1064nm Nd:YAG laser application

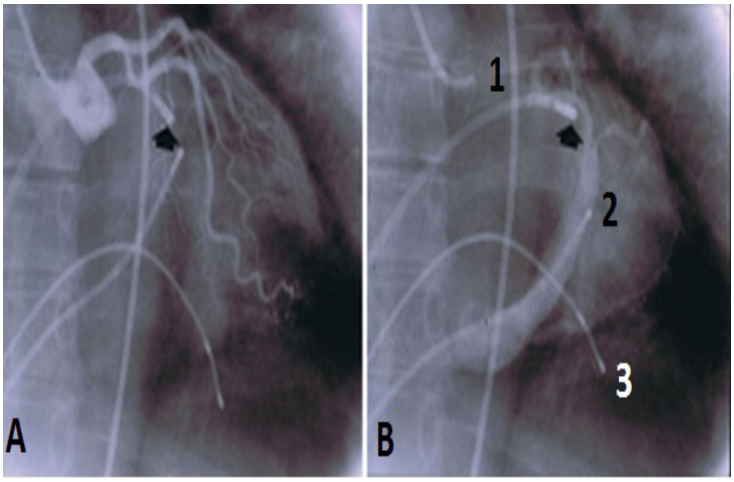

Figure 5: A shows RAO projection of a left coronary artery angiogram performed prior to the laser ablation attempt and B the coronary sinus filling with dye. The thick arrow shows the orientation of the catheter towards the location of a left sided accessory atrioventricular pathway. 1 = angiographic catheter positioned in the aortic root, 2 = 4polar electrode catheter in the coronary sinus, 3 = bipolar electrode catheter in the right ventricle.

can produce deep lesions of coagulation necrosis without thrombus or steam pop when using an open-irrigated ELMA laser catheter [19]. However, for safe laser application without collateral damages to adjacent structures of the heart, energy settings adapted to the thickness of the myocardial wall are the prerequisite [20].

The laser lesions

Laser application aimed at the thin structured atrial walls does not result in tissue vaporization with crater formation. There is no risk of myocardial wall perforation. Anatomic integrity of the irradiated atrial wall is always preserved. The gradually growing coagulation process intramurally results in a solid volume with well demarcated boundaries. Photons are absorbed intramurally whereas the catheter itself and the translucent endocardium are not heated up, and, in addition, are cooled by the saline flow of the catheter at room temperature (18°C). Laser lesions are clear cut areas of homogenous coagulation necrosis healing to dense fibrous scars without aneurysm formation and are not arrhythmogenic. There are no remnants of vital myocardial cells inside the scars. In contrast to that RF current often cause tissue vaporization with crater formation and carbonization [21]. Even new second-generation open irrigated RF catheters produce

pop and inhomogeneous lesions [22].

Laser lesions are not thrombogenic. As compared to RF current applications the estimation of D-dimer serum level in patients prior to and after laser application showed unhanged plasma D-dimer levels. Laser ablation is without thrombogenic effect neither immediately nor long term [23]. In contrast to that, RF ablation has a thrombogenic effect as reflected by elevated plasma D-dimer levels that persists through 48h after the procedure [24]. This effect needs to be taken into account when considering antithrombotic therapy in patients undergoing RF ablation. However, albeit under uninterrupted oral anticoagulation RF ablation is associated with a substantial risk of silent embolism [25]. This may represent a risk factor for significant cognitive decline [26], [27].

Also of importance for the success of the laser method are type and sizes of lesions achieved with the ELMA catheter. Transmural lesions at diameters of up to 10.0 mm and more can be created within seconds. Thus, extensive areas of coagulation can be achieved in the atrial walls with a relative small number of laser applications. The maximum of 26 laser applications in this study, totalized a radiation time of 310 s. Thereby, not points but spots, not lines but stripes of ≥5mm in width of the lesions were achieved. Width of lesions is of importance for the success of the laser method because conduction may occur over narrow lines even when transmural and contiguous [28].

The Catheter design

The open-irrigated ELMA catheter substantially contributes to both safety and efficacy of the laser method. It allows for non-contact laser light application because a fiber tip to endocardial surface contact is avoided and continuous saline irrigation through the catheter endhole avoids blood penetration into the catheter [29]. It creates a transparent medium for the laser light and cools the illuminated endocardial surface. The pin electrodes at the catheter tip with the interelectrode distances of ≤ 2.0 mm allow for registration of focused LEG from a very small area of the endocardial surface. Focused LEG recordings display electrical activity of a limited endocardial area that cannot be obtained by conventional electrode catheters with larger interelectrode distances [30], [31]. In contrast to the RF recordings, the coagulation process initiated by the laser light in the myocardial wall can be visualized online on the monitor by the gradual abatement of the electrical potentials amplitudes in the LEG. The gradual abatement of potentials amplitudes conspicuous in the LEG during radiation reflects the growths of the lesion, the spread of acute coagulation necrosis in the atrial wall. With the stop of laser application 2-3 second after abolishment of electrical potentials lesions are limited to the culprit tissue and collateral damages are avoided. This can be assumed by the follow-up of the patients which were all symptom free acutely and during long-term as well. Based on these experiences esophageal monitoring was not done and phrenic nerve captures was not confirmed neither during nor after the procedure in this study. More recently, we have tested successfully an esophageal light sensor that confirmed these assumptions [30].

Table 5: Long-term outcomes, 9.0 months to 29.2 (8.2 ± 6.5) years, in 48 patients after laser catheter ablation of long-lasting persistent atrial fibrillation (l-lpAF)

OUTCOME	No of PATIENTS	%
In Sinus rhythm	46	96%
off medication	17	35%
under medication	16	33%
after repeat study, for:	15	31%
- left atrial flutter	7	
- recurrent atrial fibrillation	2	
- typical atrial flutter	2	
- AT (right atrial reentry)	1	
- Inappropriate sinus tachycardia	1	
- common AV nodal reentry	1	
- non sustained right ventricular outflow tract tachycardia	1	
In permanent AF	1	2%
Death	1 after 9 months 1 after 11 months 1 after 17 months	6%

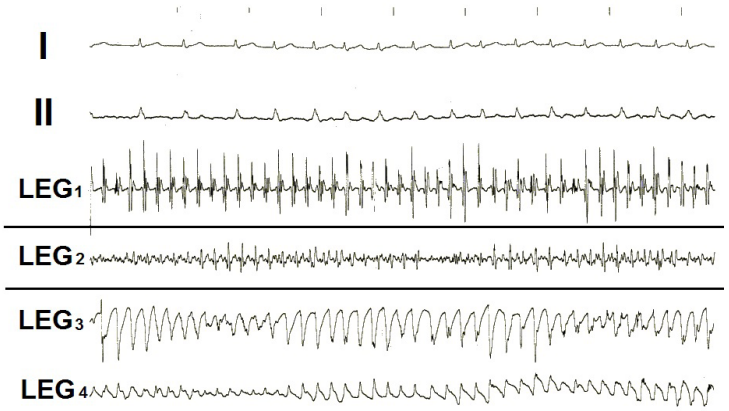

Figure 6: Examples of Intracardiac bipolar focused local electrograms (LEG) recorded from various sites of the left and right atrial walls recorded via the pin-electrodes of the open-irrigated electrode-laser mapping and ablation (ELMA) catheter RytmoLas during manual exploration of the atrial cavities in a patients with long-lasting persistent atrial fibrillation showing: LEG_1 = sharp, high amplitude, regular electrical potentials (scar related tachycardia?), $LEGT_2$ = complex atrial fragmented electrogram (CAFE potentials), and $LEG_{3,4}$ = torsade like local electrograms. I and II = surface lead electrocardiograms.

A specific advantage of laser application for treatment of tachyarrhythmias is the ability to perform treatment under normothermic conditions while avoiding interfering with electrophysiologic monitoring principles. This immediate and real-time verification of the success is extremely beneficial. Electrophysiologically guided ablation allows for a systematic approach with simultaneous validation of initial success, and, it allows for laser mapping [32]. In this study we have systematically abolished local electrical activity rather than creating anatomically guided ablation lines in isthmus areas, atrial roofs, or free walls. It was mainly an electrically but not an anatomically guided procedure. Control of immediate success in this study was carried out by monitoring of the local electrical potentials amplitude in the LEGs displayed on the monitor. Catheter manipulation was performed also under short intermittent X-ray control. With a recently developed laser balloon catheter for PVI visual control of the laser beam inside of the heart is feasible during laser application [33]. As compared to the open-irrigated ELMA catheter the balloon technique show what you do, but you don't see what you get. Efficacy similar to RF ablation is reported. It is of concern, that laser application into the stagnant blood that inevitably occurs in the occluded pulmonary veins in front of the inflated balloon bears a considerable risk for thrombus

formation. In addition, it is a sophisticated and relative expensive approach. As compared to the other routinely used ablation methods manual laser catheter application with the open-irrigated ELMA catheter has short procedure duration times, shorter X-ray exposure and energy application times regardless of catheter technique used manual, robotic Hansen or Stereotaxis [34].

Further considerations

In patients with l-lpAF atrial myocardium is found to be predominantly fibrous. Extend of atrial wall fibrosis and ablation related scarring are major predictors of success in rhythm control of AF. Circumferential PV antral scarring predicts ablation success in mild left atrial fibrosis, while additional left atrial posterior wall and septal ablation is needed for moderate fibrosis [35]. Scarred tissue is insulating the viable myocardial fibers involved in the perpetuation of AF. The 1064nm laser light is penetrating through scarred tissue [36]. In the scar 1064nm laser light is mainly scattered and eventually absorbed in the darker atrial myocardium heating and coagulating the potentially arrhythmogenic still viable myocardial fibers contained and scattered as small or larger islets within the scars.

By manipulating the flexible and resilient ELMA catheter all over the endocardial areas in the atrial cavities stable positioning over the targeted sites could be achieved without pressure control. Pressure of the ELMA catheter tip on the endocardial surface with

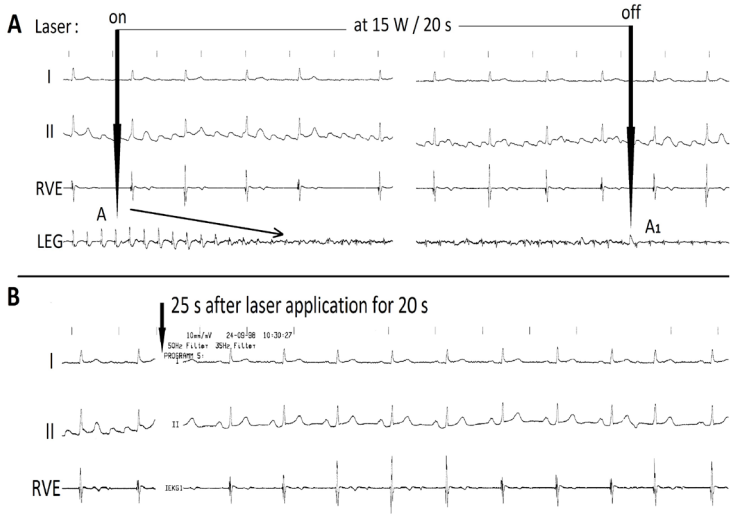

Figure 7: **Bipolar focused local electrogram (LEG) recorded during redo laser ablation for atrial flutter in a patient 6 weeks after successful ablation of long-lasting persistent atrial fibrillation showing: A gradual abatement of local electrical potential amplitudes (oblique arrow) after the onset of laser application from A, last amplitude prior to, and A1 first potential amplitude after the laser impact, and B Sinus rhythm 55 bpm achieved 25s after laser application (vertical arrows). RVE = right ventricular electrogram, I and II = surface lead electrograms.**

contact force measurement is not needed for lesion formation. Laser lesions can be achieved even without intimate endocardial catheter contact. Catheter contact force and catheter orientation towards the endocardial surface are not major determinants for laser lesion formation [29], [37], [38]. Albeit PVI is still considered the cornerstone for a successful AF ablation we did not target the pulmonary vein specifically, well-directed. Extensive coagulation of the posterior LA walls around the PV ostia was aimed at in our study by creating contiguous lesions by adjacent electrically guided laser applications. With the abolishment of potential amplitudes transmural scars around the pulmonary veins were produced, thereby inevitably resulting in effective PVI. After RF applications AF recurrences were observed despite isolated pulmonary veins [39]. In our study coronary sinus and atrial appendages were not targeted. Thereby avoiding mechanical damages to the appendages walls with the loss of their pumping function, and avoiding thrombus formation inside the appendages [40]; whereas ablation of substrates located around the basis of atrial appendages may have contributed to the success of the method [41].

As reflected by left atrial dimensions and improvements in QoL in our patients there was no indication for compromised left atrial blood transport attributable to the extensive laser induced scarring of the atrial walls. Left atrial dimensions decreased significantly in all the patients after AF ablation. Preserved pumping function of the atrial appendages might have been sufficient for a pulsatile blood flow to the ventricles, and, before all to avoid thrombus formation in the stagnant blood inside their lumen, a considerable risk of stroke. Shrinking of the atrial walls may have maintained unchanged or may have even reduced the volumes of atrial cavities. Possible laser effects on the ganglion plexi located behind the atrial posterior wall on the outcome of AF ablation cannot be ruled out but also not defined. Some decline in physical performance in this group of patients is attributed rather to their age. Metabolic effects, from diabetes, gout, obstructive sleep apnea or adiposity did not substantially influence outcome in this study group. Especially fibro-fatty infiltration of the subepicardium can contribute to the functional disorganization of the atrial myocardium [42]. Thus, maintenance of normal body weight may have substantially contributed to the success of l-lpAF ablation in this study population. Atrial metabolism and tissue perfusion are also determinants of electrical and structural remodeling in AF because rapid rates of electrical activity and contraction are enormous challenge to the energy balance of atrial myocytes [43].

Assessment of ablation-induced scarring in AF showed that catheter ablation of AF targeting PVs rarely achieves permanent encircling scar in the intended areas what is associated with recurrent arrhythmia [44]. In addition, it has been reported that PV reconnection is frequent in patients with heart failure, and, of great importance, patients presented arrhythmic recurrences even in the absence of PV reconnection, highlighting the importance of the underlying atrial substrate [45]. These facts are of special importance for evaluation of this study because all of the study patients were in heart failure NYHA II-III. Furthermore, the role of localized electrical rotors and focal impulse sources have been recognized in sustaining of AF, as well as the role of CAFE at the right atrium, where additional ablation provides an increment in efficacy when energy application addresses moving targets that changes frequently [46],[47]. All the above mentioned emphasizes that human l-lpAF is characterized by heterogeneous and unstable patterns of activation including wave fronts, transient rotational circuits, and disorganized activity [48]. Thus, PVI is far from being a cornerstone alone for successful ablation of l-lpAF.

Recently, first evidence was provided for asynchronous activation of the endo-epicardial wall during AF in humans. Endo-epicardial asynchrony as a major role in pathophysiology of AF may explain why in some patients therapy fails [49]. Rotating spiral waves have been observed also in a wide variety of nonlinear spatially distributed systems in physics, chemistry, and biology, called excitable media. In medicine, they are associated with cardiac arrhythmias. Based on these

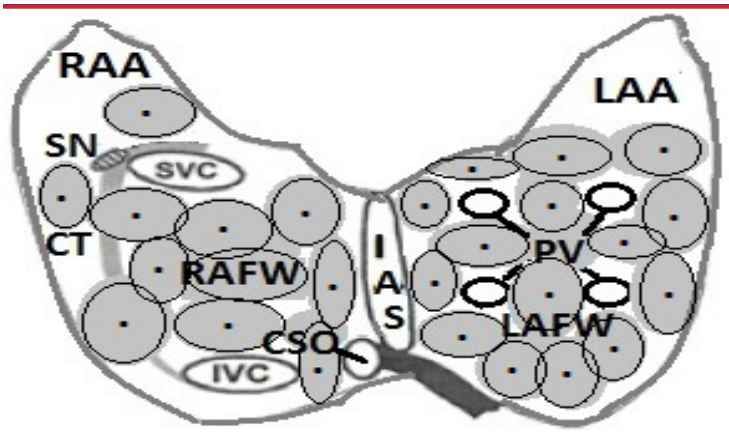

Figure 8: **Scheme showing: approximate distribution of laser spots in the atrial cavities as stepwise applied during this study for electrically guided transmural coagulation of the atrial walls, beginning in the left atrial posterior wall around the pulmonary veins, and, if needed stepwise applications aimed at the region of the left atrial isthmus, around the left atrial appendage, and eventually the right atrial walls, until sinus rhythm was achieved. RAA and LAA = right and left atrial appendages, SN = sinus nodal area, CT = crista terminalis, RAFW and LAFW = right and left atrial free walls, IAS = interatrial septum, SVC= superior vena cava, IVC = inferior vena cava, CSO = coronary sinus ostium.**

new insights, an ablation procedure has been clinically introduced that stops atrial fibrillation of the heart by destroying the electrical activity at the spiral core [50]. Some limitations and cause for concern during the follow-up of our patients are the patient compliance and feedback from surveillance centers. However, in an effort to cope with these limitations we have tried to keep close contact with patients and the surveilling physicians in order to minimize losses of information and to obtain valid results. Helpful in this regard would be an enhanced and prolonged Holter-electrocardiogram-monitoring for increased detection of atrial fibrillation [51].

Conclusions

This is the first study that qualifies the laser method as an intriguing technique superior for ablation of l-lpAF as compared to the hitherto routinely used AF ablation techniques, when using the open-irrigated ELMA catheter RytmoLas. With the laser very long-term excellent results can be achieved by including a preemptive strategy of taking out the electrical milieu substrate. The method has a low risk, a short procedure time, and reduces redo procedures. It comes down to a single catheter technique without the need for sophisticated mapping equipment. Manual exploration with the ELMA catheter under monitoring of local electrical potential amplitudes in the focused LEG are the essentials of the method, that is cost-effective and patient centered, and has the potential for becoming an all pervasive procedure. To achieve that goal further investigation, preferably multicenter study trials are warranted.

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Conflict Of Interests

None.

Disclosures

None.

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Ablation of "Background Tachycardia" in Long Standing Atrial Fibrillation: Improving the Outcomes by Unmasking a Residual Atrial Fibrillation Perpetuator

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Institutional review board statement: The study was reviewed and approved by theinstitutional review boards of Sao Paulo Cardiology Institute (IDPC) and Sao Paulo University (USP).

Abstract

Background: Catheter ablation of long-standing persistent AF (LSAF) remains challenging. Since AF-Nest (AFN) description, we have observed that a stable, protected, fast source firing, namely "Background Tachycardia"(BT), could be hidden beneath the chaotic AF. Following pulmonary vein isolation (PVI)+AFN ablation one or more BT may arise or be induced in 30-40% of patients, which could be the culprit forAF maintenance and ablation recurrences.

Methods and Results: We studied 114 patients, from 322 sequential LSAF regular ablations, having spontaneous or induced residual BT after EGM-guided PVI+AFN ablation of LSAF; 55.6±11y/o, 97males (85.1%), EF=65.5±8%, LA=42.8±6.7mm. Macroreentrant tachycardias were excluded. Pre-ablationAF 12-leads ECG Digital processing(DP) and spectral analysis(SA) was performed searching for BT before AF ablation and its correlation with BT during ablation.After PVI, 38.1±9 AFN sites/patient and 135 sustained BTs (1-3, 1.2±0.5/patient) were ablated. BT cycle length(CL) was 246.3±37.3ms. In 79 patients presenting suitable DP for SA, the BT-CL was 241.6±34.3ms with intra procedure BT-CL correlation r=0.83/p<0.01. Following BT ablation, AF could not be induced. During FU of 13→60 months(22.8±12m), AF freedom for BT RF(+) vs. BT RF(-) groups were 77.9% vs. 56.4% (p=0.009), respectively. There was no significant complication.

Conclusions: BT ablation following PVI and AFN ablation improved long-term outcomes ofLSAF ablation. BT is likely due to sustained microreentry, protected during AF by entry block. BT can be suspected by spectral analysis of the pre-ablation ECG and is likely one important AF perpetuator by causing electrical resonance of the AFN. This ablation strategy warrants randomized, multicenter investigation.

Background

Despite great progress, the long-term outcomes of catheter ablation for long standing atrial fibrillation (LSAF) remain suboptimal [1],[2]. Pulmonary vein isolation (PVI) [3],[4] is recognized as the cornerstone for paroxysmal atrial fibrillation (AF) ablation [5],[6],[7] but insufficient as a stand-alone ablation approach for LSAF [8],[9].The adjunct of linear ablation lesion sets [10],[11],[12]; ablation of complex fractionated atrial electrograms (CFAE) [13],[14]; extensive ablation including the left atrial (LA) posterior wall [15], superior vena cava (SVC) [16], coronary sinus and LA appendage or even vagal denervation [17],[18] may improve outcomes slightly but compromises procedural complexity and safety [19],[20],[21].

We have found that the AF Nests (AFN) ablation had a favorable impact on the long-term outcome after a single procedure [22],[23]. It decreased overall recurrences as compared to our conventional PV antral isolation plus CFAE ablation [24]. Interestingly, following PVI and AFN ablation,most recurrences are caused by an organized, typically fast atrial tachycardia. This residual tachycardia often appears as a transitional rhythm during AF ablation upon its organization or termination,[Figure 1]

By using spectral analysis with Fast Fourier Transform (FFT) we have found that this tachycardia is present during AF, before ablation,[25] which we have named "Background Tachycardia" (BT) [22],[26],[27]. Rapid atrial pacing following PVI and AFN ablation can also commonly induce one or more of these organized atrial tachycardias. By studying this tachycardia with spectral mapping we have found that it commonly arises from an AFN exhibiting a specific case of focal microreentry, (fractal microreentry[25]), characterized by entry block, which ensures its maintenance during AF without overdrive reversion by the AF itself. In this study, we evaluated the long-term outcome of BT ablation as an adjunct to PVI plus substrate modification by AFN ablation in patients with LSAF. In addition, we assessed the feasibility of identifying the BT by digital processing and spectral analysis of the AF on the surface electrocardiogram (ECG) prior to the ablation procedure.

Patients and methods

Study Population

In this prospective study were enrolled 114 consecutive patients with

Key Words

Arrhythmia, Atrial fibrillation, Ablation, Spectral Analysis, Rotors, AF-Nest.

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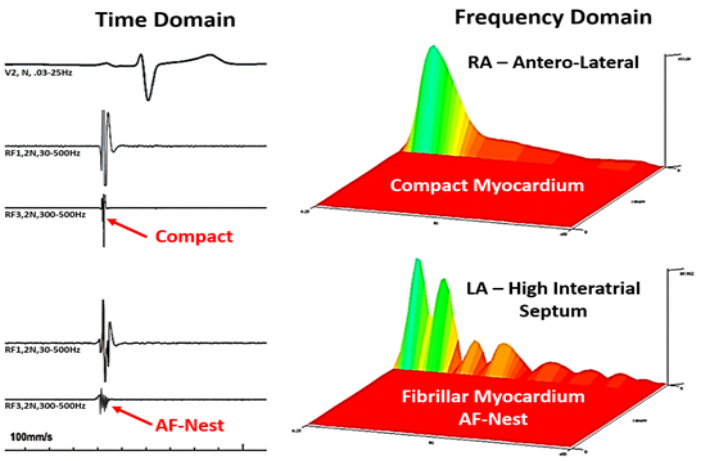

Figure 1: **Features of the compact (above) and fibrillar myocardium (below: AF-Nest 22,27,30) in the time domain (left) and in the frequency domain – spectral analysis by FFT (right). In this study, both methods were used after PVI.**

symptomatic persistent (AF that lasts longer than 7 days, including episodes that are terminated by cardioversion, either with drugs or by DC cardioversion, after 7 days or more) or LSAF (continuous AF lasting for ≥1 year when it was decided to adopt a rhythm control strategy), refractory to conventional medical treatment, in whom it was possible to induce at least one BT following PVI plus AFN ablation. The group encompasses patients with persistent and long-standing persistent AF with a mean history duration of 13.5±14.3 months, ranging from 2 to 62 months.Written informed consent was obtained from all patients prior to the procedure.

Mapping and Ablation Protocol

The procedures were performed under general anesthesia. A duodecapolar catheter was placed in the CS. Transeptal access was guided by transesophageal echocardiography. 3-D Electroanatomic mapping system (EnSiteNavX - St. Jude Medical) and a circular multi-electrode catheter were used for EGM-guided PVI. An open irrigation ablation catheter(Thermo-cool, Biosense Webster or Biotronik; 30W/45oC/17ml/minute) was used for radiofrequency (RF) delivery. Subsequently, if required, electrical cardioversion was performed to restore sinus rhythm.Following PVI, AFN sites were ablated being identified in sinus rhythm either by, conventional recording with filter settings of 100 and 300 to 500Hz pass-band to bipolar EGMs or by using a computerized spectrometer[22],[27],[28], [Figure 2].

Background Tachycardia (BT)

Following PVI plus AFN ablation, at least one BT was induced by decremental atrial pacing down to cycle length (CL) of 200ms from the distal coronary sinus (CS) or right atrium (RA). Macroreentrant atrial tachycardias were excluded. Only microreentry with a confirmed entry block was considered as BT,according to the following criteria:

1. Presence of entry block (unresponsive to overdrive suppression);
2. Radial distribution reproduced by pace-mapping;
3. Presence of significant isoelectric line in all ECG leads and;
4. Focal ablation.

Table 1: **BT ablation outcome. AA: antiarrhythmic drugs; *Kaplan-Meier Cumulative Survival.**

BT Ablation Outcome	N	%	Success without AA (60 months*)	P
RF Termination, RF(+) group	62	54.4	77.9%	
Non-RF Termination, RF(-) group	52	45.6	56.4%	
Spontaneous Reversion	22	19.2		p=0.009
External Cardioversion	15	13.2		
Mechanical Reversion	15	13.2		

Ablation Endpoint

Our stepwise ablation strategy is presented in [Figure 3]. The procedure was terminated due to:

Inability to re-induce sustained tachyarrhythmia;Successful BT ablation orUnsuccessful BT ablation requiring electrical cardioversion.

Post-Procedure Follow-up

All patients were followed in our AF clinics as well as via telephone and Internet. Strict rhythm monitoring was obtained, including ECG and 24h-Holter at 1, 3, 6 months and then yearly or whenever there was AF/AT recurrences and/or symptoms. The follow-up (FU) ranged from 13 to 60 months with a mean of 22.8 ± 12 months.

Spectral Analysis of ECG Prior to Ablation

Seventy-nine of 114 patients (69.3%) had a suitable ECG for digital QRS-T wave subtraction(≥5 minutes of 12-lead noise-free ECG in AF without aberrancy, ventricular ectopic beats and significant pauses), [Figure 5]. A customized system was used for QRS-T averaging, digital subtraction and spectral analysis of the isolated atrial activity. The fundamental frequency achieved by integrating the FFT of each 12-leads was compared with the BT frequency obtained after PVI plus AFN ablation.

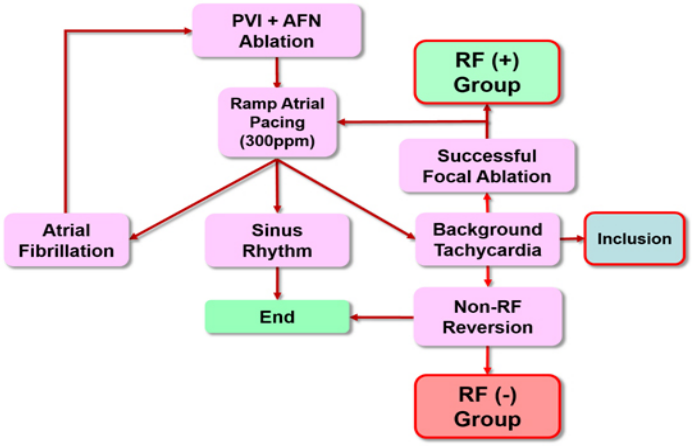

Figure 2: **Study design. Only patients in whom it was possible to induce and characterize at least one BT following PVI and AFN in the same session were included. The cases were followed and compared according to RF reversion, RF(+) group or non-RF reversion, RF(-) group.**

Statistical Analysis

Quantitative data are shown as the mean value ± standard deviation.Normality was evaluated by the Kolmogorov-Smirnov test. Paired-samples two-tailed t-test was applied to establish comparisons between continuous data before and after BT ablation.Survival analysis was obtained with Kaplan-Meier. A Pearson's correlation was applied to test the real BT frequency with the suspected BT frequency obtained by spectral analysis of the ECG before ablation. Statistical analysis was performed using IBM SPSS StatisticsVersion 19 software. All values were considered statistically significant at two-tailed value less than 0.05.

Results

From a cohort of 322 consecutive persistent and long standing

Table 2: Location of the focus of the last BT defined by RF BT interruption and sinus rhythm recovery. Typically, they were found in the AFN areas. ND: not defined / not mapped (cases with spontaneous or mechanical reversionby the mapping catheter or who were cardioverted due to prolonged procedure). See Figure 5 for more details (the cells' colors show the BT lication in the map) . IA: interatrial.

Atrium	Site	N	%
RA41 (35.9)	RA wall	26	22.8
	RA AV node	3	2.6
	RA IA septum	12	10.5
LA 40 (35.1)	LA wall	7	6.1
	LA IA septum	13	11.4
	LA PV	17	14.9
	CS ostium	3	2.6
Not Defined		33	28.9
Total		114	100.0

atrial fibrillation ablation, after isolation of the pulmonary veins and AF-Nests ablation, it was possible to induce a tachycardia compatible with BT in 114(35.4%) subjects, 97 males (85.1%).The mean age was 55.6±11 (24-77) years. The mean left atrial (LA) diameter was 42.3±7 (27-67) mm, and the mean left ventricle (LV) ejection fraction by transthoracic anteroposterior echocardiographyview was 65.5±8 (47-76%). The AF-Nests were most frequent in the PV antrum, at the interatrial septum, in the left posterior septal space, in the cristaterminalis, at the superior vena cava insertion and close to the coronary sinus ostium.

PVI and AFN ablation

EGM-guided PVI was achieved in all patients. Subsequently, filtered conventional or spectral mapping was applied to guide AFN ablation (mean of 38.1±9 AFN per patient). Following PVI and AFN ablation, 135 BT were induced, 1.2±0.5 per patient, ranging from one to three, one in 92 patients (80.7%), two in 14 patients (12.3%) and three in 8 patients (7%).The ablation BT outcomes are presented in [Table 1].

BT Ablation

BT was successfully ablated in 62 patients (54.4%), RF(+)group. On the other hand, BT ablation could not be completed in 52 patients (45.6%), RF(-)group due to spontaneous reversion while mapping (22); mechanical reversion by the catheter (15) or electrical cardioversion due to prolonged procedure time (15), [Table 1].

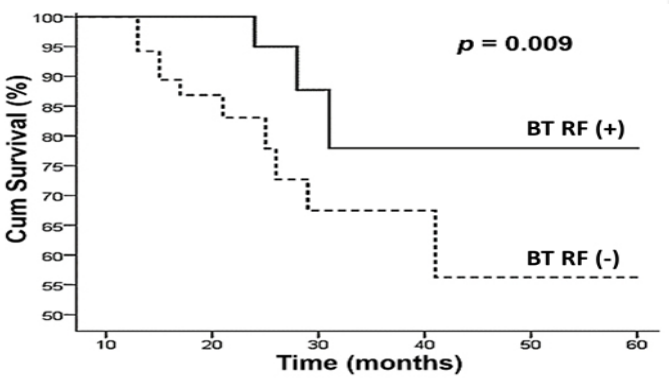

Figure 3: Cumulative Kaplan-Meier survival curves comparing the outcome (up to 60 months) of group RF(+) (reverted by RF) with group RF(-) (non-RF reversion).

The mean fluoroscopy time was 49.4±18 minutes and the average total procedure time was 4.3±1.4 hours. There were no significant major complications. Two patients exhibited BT in the atrioventricular (AV) node region successfully ablated but leading to transient 2nd degree, type I AV block in one and transient complete AV block in the other. Groin hematomas occurred in three patients and arterial-venous fistula, treated by ultrasound transducer compression, occurred in one patient.

After a mean follow-up of 22.8±12 months (13-60 months) AF free survival, defined as no AF or BT without antiarrhythmic drugs was 77.9% in RF(+) Group and 56.4% in the RF(–) Group (p=0.009), [Figure 4].

Researching for the BT before Ablation by Spectral Analysis of the ECG

The BT frequency obtained by digital processing and spectral analysis of the extracted atrial activity on a pre-ablation ECG was compared with the actual spontaneous or induced BT frequency

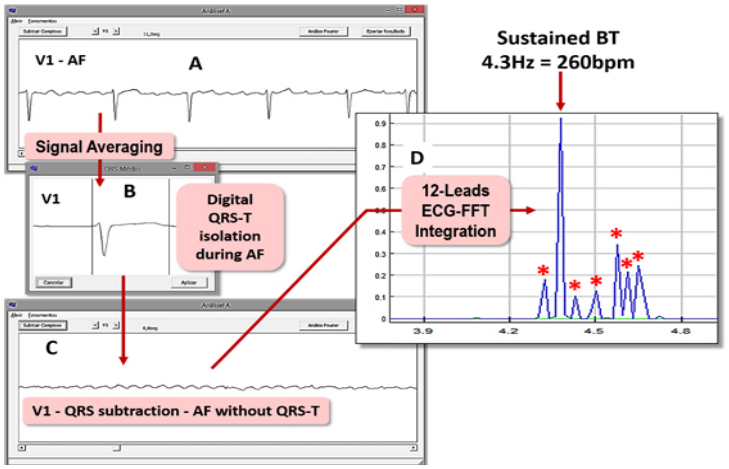

Figure 4: Methodology to search the BT in the ECG before ablation. At the end, it allows the spectral analysis of isolated atrial activity from the conventional ECG. A: standard ECG; B: pure QRS-T without AF, obtained by digital signal averaging of the whole ECG; C: QRS-T subtraction from the tracing A obtaining a clean and continuous AF without ventricular activity; D: the spectrum of "isolated AF" is obtained by applying Fourier in C and integration of the 12-ECG leads. In this example, there is a clearly dominant peak that matches a tachycardia with a frequency of 4.3Hz (231ms/260bpm) and six other non-sustained (*). The main one is likely one AF perpetuator in this case, keeping the AFN resonating under high frequency stress.

by endocardial mapping during ablation, [Figure 5]. Only stable ECG,suitable for digital processing (lasting five minutes or more, free of noise, significant pauses, ventricular ectopic beatsand aberrancy),obtained in 79 patients (69.2%), were included in this analysis.There was a high positive correlation in predicting BT CL from the surface ECG (2-tailed Pearson positive correlation coefficient r = 0.83, p<0.01), [Figure 6].

Discussion

In this prospective study, we describe an ablation strategy for patients with LSAF. In addition to PVI, it includes the adjunctive ablation of AFN and spontaneous or inducible specific residual atrial tachycardia, namely BT.

In this study BT was considered when stable rapid atrial tachycardia was obtained under the following conditions:

1. During AF ablation the atrial rhythm often evolved to a rapid

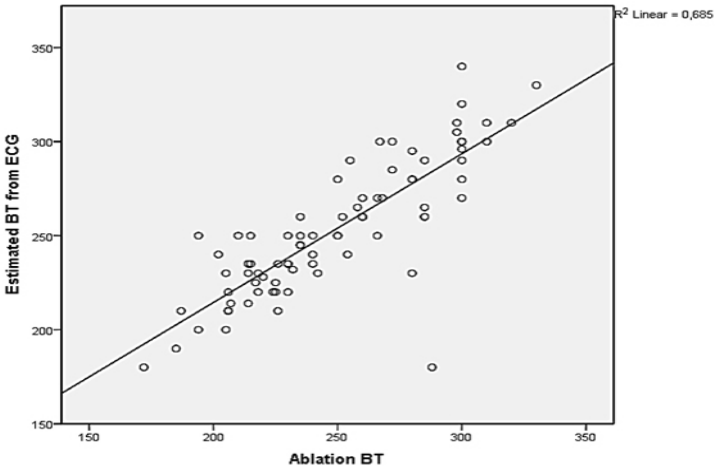

Figure 5: The mean BT frequency by ECG analysis before AF ablation was 253.3±35.6bpm (CL=241.6±34.6ms) and the mean BT frequency after AF ablation was 249.1±37.3bpm (CL=246.3±37.3ms) with a high Pearson 2-tailed positive correlation coefficient r = 0.83, p<0.01).

and regular tachycardia. From that moment on, although we no longer had FA, we still had a sustained atrial tachycardia;

2. In many cases, at the end of ablation, having the sinus rhythm recovered, the rapid atrial stimulation (up to 300ppm) even no longer inducing AF, it was able to reproduce a fast and sustained regular atrial tachycardia.

From this moment onwards, having excluded atrial flutter and gross atrial macroreentry tachycardias, we compared this tachycardia with the dominant frequency obtained by spectral analysis using FFT applied to the pure AF signal (after QRS-T subtraction) before ablation. This spectral analysis, prior to AF ablation, clearly indicates that there is at least one organized dominant tachycardia under in the AF environment. The most interesting is that the frequency of this tachycardia had a high positive correlation with the residual tachycardia found after ablation and considered BT in this study. This suggests that this tachycardia probably exists before ablation, hereafter being called "Background Tachycardia". Even more interesting is the fact observed in this study that the attempt to ablate this BT seems to greatly increase the long-term success rate of the long-lasting AF ablation.

In this study, we found that these tachycardias usually present the following features:

1. High frequency,
2. Entry block characterized by the absence of "reset" and the impossibility of interference or overdrive reversion. This property shows that this tachycardia is protected by an entry block which allows the tachycardia to exist even during AF, preventing it to be reverted by the large number of stimuli under the AF electrical storm,
3. Focal origin suggested by electroanatomical mapping, by means of entrainment and punctual elimination, without the need of blocking lines;
4. Surface ECG with isoelectric line suggestive of focal tachycardia rather than macroreentry [Figure 7],
5. The origin of focal microreentry protected with entry block is also suggested by the impossibility of reversion by overdrive, but by the immediate stopping with cardioversion, suggesting that it is not originated by hyperautomatism.

Tachycardias with BT features were induced only in 114 (35.4%) of 322 LSAF cases. This means that PV isolation and AF-Nests ablation was probably sufficient to eliminate a great number of non-discovered BTs. Interestingly, BT with similar rates could be suspected on surface ECG during AF, prior to ablation, by spectral analysis of the surface AF recording without the QRS-ST complex. Successful BT ablation had a significant impact on long-term procedural efficacy with a 2-year AF freedom. The lack of statistical significance between the two groups (RF+ versus RF-) in the variables known to influence the clinical outcome reinforces this hypothesis, [Table 2].

Additionally, it is conceivable that AF-Nests ablation contributed to the favorable outcomes as even patients in whom we could not eliminate the BTs, experienced no recurrences in 82% at 2 years post ablation. As the study suggests, those atrial sites exhibiting AF-Nests may also harbor BTs. This could reflect at least a transient modification or elimination of the critical substrate responsible for initiation and maintenance of AF, even without complete PVI or even with PV reconnection. Undeniably, further substrate and/or modulators may emerge over time leading to AF and/or BTs recurrences.

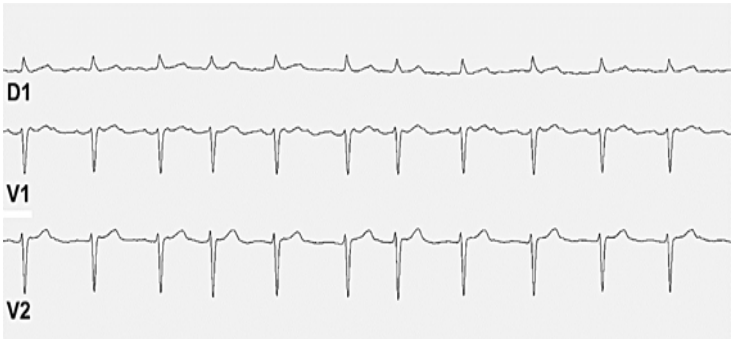

Figure 6: Recurrence three months after ablation. Usually the complaint of palpitation with rapid and irregular pulse leads to the diagnosis of AF. Indeed, D1 and V2 leads can be confused with AF. However, careful analysis of V1 suggests a regular fast atrial tachycardia instead of AF (typical of BT). This diagnosis is fundamental, as the treatment must target BT focal ablation rather than a new conventional AF ablation.

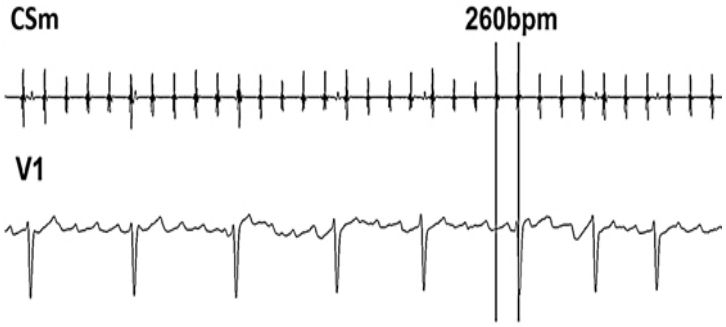

Figure 7: Regular tachycardia induced after PVI and AFN ablation in the same patient of the Figure 4. Instead of AF, it was induced a very rapid atrial tachycardia matching the frequency predicted by the ECG spectral analysis, before ablation. It suggests that this tachycardia existed before ablation and is likely responsible for the maintenance of AF (BT). Prior the ablation, the noise caused by the AFN resonance precludes the visualization and mapping of this tachycardia. CSm: recording of atrial activity within the coronary sinus.

Our concepts of AFN and BT are summarized below since they may contribute to explain or have pathophysiologic implications for the mechanisms of LSAF[22],[29]. Ongoing and future investigations may further solidify these findings in that the AFN and BT are

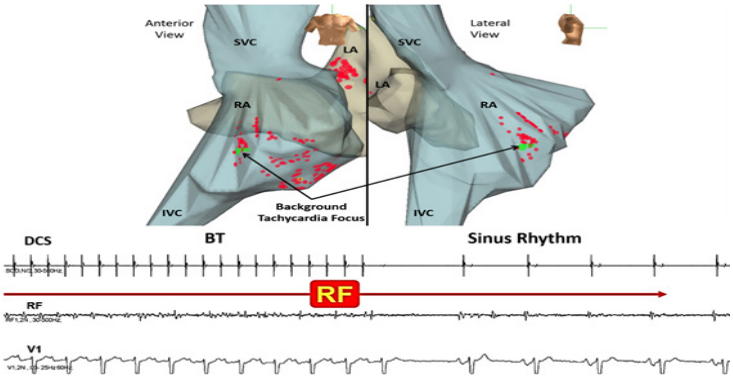

Figure 8: **Upper: 3-D geometric endocardial reconstruction of the left and right atria by electro-anatomic mapping. The red dots represent AFNs ablated with RF. There is an AFN group in the anterior-inferior wall of the RA nesting the BT focus reverted by RF ablation in a very small area (focal ablation). Lower: BT reversion during RF application in the RA lower anterior region as shownon the electroanatomic mapping(upper).**

important players inthe LSAF physiopathology.

Background Tachycardia (BT)

The assessment of BT electrophysiological properties and its structural correlates is challenging and was not the purpose of this study. However, typically a BT [Figure 7] consists of a fast (249.1±37.3bpm, CL=246.3±37.3ms), focal microreentrant tachycardia exhibiting entrance block due to lack of resetting and overdrive suppression. Rarely, by using high pacing output (20 mA/1.5ms) directly over a BT site, we could revert it. This seems to work as an AFN micro-cardioversion. Nevertheless, this was not evaluated systematically ever since our purpose was to revert the BT by ablation.BT spectral analysis suggests that it is formed by a specific type of microreentry (fractal microreentry)explaining its main feature, the entry block.

It is likely that one or more unrecognized BTs coexist during AF and may even play a "clock" role, protected by entry block, perpetuating AF. Interestingly, there was a significant distribution of BTs in RA 35.9% vs. 35.1% in LA. However, since PVI and AFN ablation in the LA were performed prior BT induction, it is probable that some LA BTs were unintentionally eliminated underestimating the actual number of BTs in the LA. However, the presence of BTs in RA suggests that this chamber should be systematically treated in LSAF ablation, [Figure 9].

AFNests Ablation

The AFNwere described in the nineties, even in the normal heart, by scanning the atrial endocardium with on-line spectral analysis in sinus rhythm[22],[27],[30],[31],[32].Recently, their relationship with the neuro-myocardial interface was confirmed[33] as suggested by the original study[22].This technique revealed that AFN are atrial clusters of fibrillar myocardium, which main feature is cell-to-cell electrical disconnection.AFN are different from CFAEs[28]. They exhibit a heterogeneous, multi-peak frequency spectra in sinus rhythm. The AFN favor anisotropic conduction[34],are possible sources for microreentry and electrical resonance[35] and may give us some insight on why AF can occur in apparently normal hearts without fibrosis, in which are clearly related to the insertion of the veins (pulmonary veins, coronary sinus and cava veins) and to the neuro-endocardial interface[27],[33],[36],[37]. In all these areas, a significant intersection and blending of different conductive and non-conductive tissues gives rise to the very distinct AFN spectral properties.Despite potentially anisotropic, there is normal conduction through the AFN during sinus rhythm; where as at faster rates they trigger repetitive responses (electrical resonance[35]) likely due to progressive micro-reentries(fractal microreentry) creating a self-limited but an essential AF substrate even in the absence of disease[27].The spectral analysis has endorsed that the AFN electrical resonance is the main responsible for the irregular and intense electrical noise visible on the baseline AF ECG[22],[35].Nevertheless, as the resonance is a self-limited decremental oscillatory phenomenon, it may account for paroxysmal AF, however long-standing and permanent AF require one or more continuous, uninterrupted driver such as BT, suspected on pre-procedure ECG during AF and showed after, during ablation, [Figure 5]. The electrical noise caused by AFN resonance precludes the BT visualization, but with progressive AFN ablation,the noise decreases or disappears allowing the BT visualization.Extensive AFN ablation makes the AF reinduction very difficult. Following PVI and unintentional AFN ablation during AF, the rhythm may be progressively organized and may convert into a fast, regular residual atrial tachycardia, here described as "Background tachycardia", [Figure 1].

Uncovering the BT in the ECG before Ablation

Based on earlier observations of BT behavior as a potentialAF sustainer, we postulated that it could be extracted from the previous conventional ECG with AF. This was achieved by using spectral analysis of the isolated atrial activity extracted from the AF ECG before ablation. With a specific methodology and software[25], [Figure 5], we found that the anticipated BT frequency had a strong positive correlation with the frequency of actual BT induced after ablation with 2-tailed Pearson correlation coefficient equal to 0.83 ($p<0.01$) having the normality confirmed with Kolmogorov-Smirnov test, [Figure 6]. This is a significant indication that BT actually coexists during AF, protected by entry block, and probably plays a role like a "clock" perpetuating the AF. These findings show that, under the apparent chaotic LSAF atrial activity, there is at least one organized fast tachycardia, [Figure 5], in which the spectral analysis shows more six ancillary and non-sustained BTs contributing to the complex

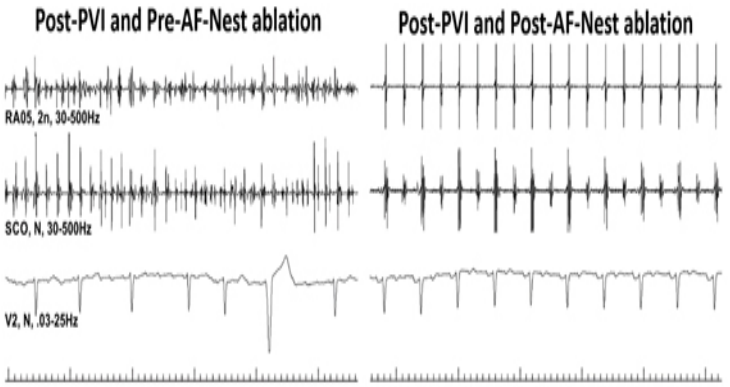

Figure 9: **Tracings of the same patient before and after AFN ablation. Instead of reverting the AF, the ablation resulted in a progressive rhythm organization, exposing BT after eliminating the resonance noise. The observation of this group of patients suggests that this type of tachycardia exists during AF before ablation, protected by an entry block. It works as one AF maintainer or clock. SCO: sinus coronary ostium.**

AF electrical activity. The interaction of these very fast tachycardias with the dynamic changes of the atrial refractory period may cause intermittent spiral activation, possibly given rise to"rotors" and "spiral waves".

AF Physiopathology Based on Spectral Study and Background Tachycardia

The [Figure 10] shows a model of the possible participation of at least one BT in the AF physiopathology.

Insights About the Futur of AF Ablation

BT facilitates the understanding of the physiopathology of AF using spectral analysis concepts. In addition, we are exhaustively seeking for a way to identify the BTs prior to AF ablation, during AF. When this became possible, it is likely that we will be able to revert a long-lasting AF with focal ablation and only then, in sinus rhythm, to perform the PVs isolation, simplifying the procedure of persistent and long-lasting AF. Our expectation is that the evolution of the technology around this concept could improve the understanding of the AF physiopathology, simplify the ablation of refractory AF cases, improve the outcome for the patient and reduce the effort of the electrophysiologist.

Relationship with BT to Rotors and Microreentryduring AF

Although beyond the scope of this study, it isplausible that the BT isone driving source for LSAF as described by Jalife[38],[39], and Narayan[40], expressed as rotors with AF termination by ablating these stable presumed sources. The ability of AF re-induction following rotor ablation is not yet well established clinically. In our study, following AFN and BT ablation, AF is typically not inducible. We have observed that some BT, especially the ones with high frequency, may show a behavior compatible with rotors. It may be due to the perifocal atrial refractory period dynamics, promoting constant, rapid and progressive changes in the perifocal activation leading to "spiral activations".

Our approach precludes mapping and ablation of BT before PVI and AFN ablation whereas a computerized system allows mapping-guided rotor ablation as utilized in the CONFIRM trial[40]. However,

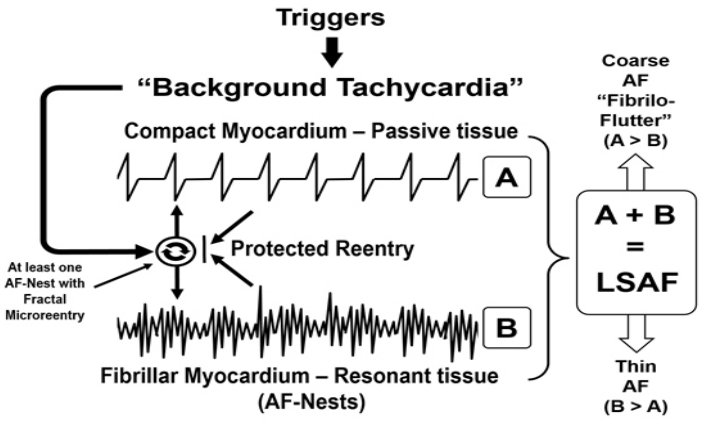

Figure 10: AF physiopathology based on the BT and AF-Nests. A fast BT keeps the "Fibrillar Myocardium" (AF-Nests) resonating with very fast and disorganized electrical activity (B) while the "Compact Myocardium" shows a regular and organized response (A). LSAF results from the sum of all these electrical activities (A+B). A "coarse AF" may appear if A>B and "thin AF" may arise case B>A and/or by the presence of more than one BT. The BT survival is assured by the entrance block and the LSAF and even the permanent one may be reinforced by the presence of more than one BT.

it brings new mechanistic insight in AF physiopathology.Another very likely association may exist between BT and focal sources or microre entry recently described by Haissaguerre and colleagues by utilizing a high resolution, 3-D body surface mapping system "ECGI" integrated with a pre acquired cardiac CT scan[41]. As we have described, the numbers and distribution of BT are similar to their findings using ECGI during AF.

Even though both computerized mapping systems may allow ablation during AF, our approach includes ablation of other critical tissue / substrate such as the AFN sites in addition to BT as driving sources, accounting for our satisfactory long-term outcomes.

Study Limitations

The incidence of BT following ablation of LSAF may be greatly dependent on the actual ablation strategy and stimulation protocol. Since we performed PVI and extensive AFN ablation, BT could only be observed in 35.4% of 322 patients. The incidence of BT could have been higher without AFN ablation (note that BT was apparently present on pre-ablation ECG in all patients with suitable ECG, 69.3%) or lower incidence with a less aggressive stimulation protocol. We were fairly aggressive by including rapid atrial pacing up to 300 ppm. The lack of a standard protocol for AF induction post AF ablation is a limitation of this and others AF ablation studies.

Future software versions of the ECG spectral analysis will overcome current limitations requiring long, stable and low noise recording, without ventricular ectopic beats, aberrancy or major oscillations of RR, QT intervals and baseline, which precluded ECG analysis in 30.7% of patients in this initial trial.

In addition, the adjunct of AFN ablation to PVI may have accounted to a fairly satisfactory ablation outcome even in the RF(-) group with incomplete BT mapping and ablation. The AFN mapping without spectroscopy may be less accurate, however, as it was a complement to PVI and under specific filter settings, we believe that this presumed limitation has been irrelevant.

An implantable loop recorder was not used to assess the outcome of our ablation strategy. All patients were followed up by the conventional resources utilized in most studies, irrespective of BT ablation results.

Even though the BT concept here described may be the critical driving source for LSAF, our mapping and ablation strategy lack the ability to target BT during AF.

Unfortunately, we still cannot accurately identify the BT during AF, however it was possible to find that the spectral analysis of pure AF signal (without QRS-T) prior to ablation, has a dominant frequency with a high positive correlation with the BT frequency obtained after ablation, suggesting that they could be the same tachycardia. At this moment, we are working deeply on this issue, because when to be possible to identify the BT during AF, we could start the long-standing AF ablation by a focal ablation, reverting the AF and isolating the PVs subsequently.

Additionally, this study did not have the merit of analyzing the pathological characteristics of the foci-related tissues as well as the voltage mapping. These questions will be extremely important in the next studies.

Conclusions

The adjunct of Background Tachycardia ablation to PVI and AF-Nests ablation was safe and improved long-term results of long-standing AF ablation. Background Tachycardia is likely due to sustained microreentry, protected during AF by entry block. It

can be revealed during AF by ECG spectral analysis and is likely one important driver that perpetuates AF by causing resonance of specific tissues, namely the AF-Nests. Our findings may bring new insight into the physiopathology of long-standing AF. This ablation strategy warrants randomized, controlled, multicenter investigation.

Conflict Of Interests

None.

Disclosures

None.

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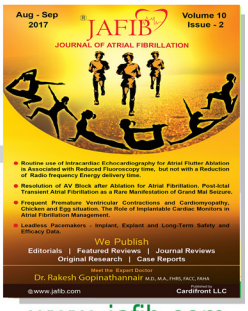

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Is CHA_2DS_2-VASc Score Different in Patients with Non-valvular Atrial Fibrillation Suffering from Cerebral and Non-cerebral Thromboembolism?CHA_2DS_2-VASc Score in Thromboembolism

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Abstract

Background: Thromboembolic complication is directly related to CHA_2DS_2-VASc score in patients with non-valvular atrial fibrillation (NVAF). In this study we compared the CHA_2DS_2-VASc score and in-hospital mortality between NVAF patients with non-cerebral thromboembolism and those with stroke.

Methods: We retrospectively reviewed medical records of 213 patients with NVAF who experienced stroke and 115 patients with NVAF who experienced non-cerebral thromboembolism between 2010 and 2015. In all patients, CHA_2DS_2-VASc score before the event was calculated.

Results: The mean CHA_2DS_2-VASc score was similar in patients with stroke (4.52±1.66) and those with non-cerebral thromboembolism (4.29±2.02) (p=0.196). In-hospital mortality rate was similar between the groups (19% vs. 17%, p=0.756). The rates of coronary artery disease (52% vs. 38%, p=0.014), prior transient ischemic attack (16% vs. 5%, p=0.001), and prior non-cerebral thromboembolism (18% vs. 3%, p<0.001) were higher in patients with non-cerebral thromboembolism. Warfarin (55% vs. 14% p<0.001) and antiplatelet use (56% vs. 40%, p=0.004) was more common in the non-cerebral embolism group, while non-vitamin K antagonist oral anticoagulant (NOAC) use was more common in the stroke group (15% vs. 7% p=0.026).

Conclusions: The patients with stroke had similar CHA_2DS_2-VASc score and in-hospital mortality compared to patients with non-cerebral thromboembolism.

Introduction

Atrial fibrillation (AF) is the most common type of cardiac arrhythmia encountered in clinical practice [1]. Atrial fibrillation can result in complications such as heart failure and decrease in the quality of life that are associated with morbidity and mortality. Apart from these complications arterial thromboembolism is another important complication of AF [2]. Prevention and treatment of thromboembolic complications is one of the main goals of AF management [3]. Stroke is the most feared and well-known thromboembolic event associated with AF [4],[5]. However, non-cerebral peripheral embolism is another important cause of morbidity and mortality in AF [2]. Besides, AF is the most important risk factor for non-cerebral embolism and an important prognostic marker [6]-[9].

The CHA_2DS_2-VASc score [congestive heart failure / left ventricular dysfunction, hypertension, age≥75 years (double), diabetes, stroke (doubled) – vascular disease, 65–74 years of age, and sex category (female)] is the most commonly used method to evaluate the risk stratification of thromboembolism in AF. Although the use of CHA_2DS_2-VASc score has been recommended to estimate thromboembolic events in patients with AF, observational and randomized clinical studies have mostly focused on the prevention of stroke [10]. Also in clinical practice, CHA_2DS_2-VASc score is used with particular focus on the prevention of stroke in patients with non-valvular AF (NVAF). The risk level for thromboembolic events based on the CHA_2DS_2-VASc score is not sufficiently known in

Key Words

CHA_2DS_2-VASc score, stroke, non-cerebral embolism, non-valvular atrial fibrillation.

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patients with non-cerebral arterial thromboembolism. As a result, it is not known whether patients with cerebral or non-cerebral thromboembolism have different levels of thromboembolic risk as assessed by the CHA_2DS_2-VASc score.

In this study we compared the thromboembolic risk level based on CHA_2DS_2-VASc score and in hospital mortality between NVAF patients with stroke and those with non-cerebral thromboembolism.

Methods

The present study retrospectively reviewed medical records of the patients, who experienced stroke or non-cerebral embolism due to NVAF between 2010 and 2015. The diagnosis of stroke was established by demonstration of the infarcted brain area using cranial computed tomography or cranial diffusion magnetic resonance imaging in patients developing sudden onset of weakness and loss of sensation, speaking and understanding disorder, impaired consciousness, and confusion. If clinical symptoms of stroke have resolved within the first 24 hours, patients with or without a demonstrable infarct area were regarded as transient ischemic attack [11].

The diagnosis of non-cerebral peripheral arterial embolism was confirmed by the presence of the symptoms and findings of acute ischemia with an onset five days before hospital admission, observation of a short occlusion in arterial bifurcation and trifurcation line consistent with a thrombus formation using Doppler ultrasonography and angiographic methods (intraarterial digital subtraction angiography, computed tomography (CT), magnetic resonance (MR) angiography), and detection of an embolus with defined margins during surgery. Acute embolism affecting visceral organs was diagnosed by the presence of acute onset of symptoms and demonstration of embolic occlusion using imaging methods such as CT and MRI.

Patients with valvular AF, intraventricular thrombus, infective endocarditis, pulmonary embolism and deep vein thrombosis, patients with a prosthetic valve, patients with a history of critical leg ischemia, graft occlusion, and patients with a vascular aneurysm were excluded. Accordingly, 213 patients with stroke and 115 patients with non-cerebral embolism were included in the study. The two groups were compared with respect to age, demographic risk factors, previous use of antiplatelet and anticoagulant drugs, CHA_2DS_2-VASc score [congestive heart failure / left ventricular dysfunction, hypertension, age≥75 years (doubled), diabetes, stroke (doubled) – vascular disease, 65–74 years of age, and sex category (female)] and mortality. CHA_2DS_2-VASc score, antiplatelet and anticoagulant use, hospitalization procedure and mortality rate were compared between the patients according to the localization of non-cerebral embolism.

Statistical analysis

Statistical analysis was performed using the SPSS (version 15.0, SPSS Inc., Chicago, Illinois) software package. Continuous variables were expressed as mean ± standard deviation (mean ± SD), and categorical variables were expressed as percentage (%). The Kolmogorov-Smirnov test was performed to test whether variables were normally distributed. Inter-group differences were evaluated using Student's t-test for normally distributed continuous variables and using Mann-Whitney U-test for variables that did not show normal distribution. ANOVA was used to compare continuous variables between more than two groups. Chi-square test was used for the comparison of categorical variables. A two-tailed p value of <0.05 was considered statistically significant.

Table 1: Baseline characteristics of patients with stroke and non-cerebral thromboembolism

	Stroke N:213	Non-cerebral thromboembolism N:115	p value
Age, years mean±sd	75,7±10	73,4±12,8	0,073
Gender, Female, n(%)	135 (63%)	61 (53%)	0,069
Hypertension n(%)	156 (73%)	91 (79%)	0,238
Diabetes Mellitus n(%)	71 (33%)	50 (43%)	0,069
Coronary artery disease n(%)	81 (38%)	60 (52%)	0,014
Peripheral artery disease n(%)	13 (6%)	12 (10%)	0,158
Chronic renal failure n(%)	21 (10%)	18 (16%)	0,122
Heart Failure n(%)	64 (30%)	29 (25%)	0,354
Hyperlipidemia n(%)	43 (20%)	41 (36%)	<0.001
Prior stroke n(%)	37 (17%)	13 (11%)	0,145
Prior transient ischemic attack n(%)	11 (5%)	18 (16%)	0,001
Prior non-cerebral embolic event n(%)	6 (3%)	21 (18%)	<0,001
Warfain use n(%)	30 (14%)	63 (55%)	<0.001
INR>2	4 (13%)	13(21%)	0,394
NOAC use n(%)	33 (15%)	8 (7%)	0,026
Antiagregan use n(%)	85 (40%)	65(56%)	0,004
CHA_2DS_2-VASc score median (IQR), mean±sd	5 (0-9) 4,52±1,66	5 (0-9) 4,29±2,02	0,196
CHAD-VASc Score, n(%)			
0	3 (1,4%)	1(0,9%)	0,671
1-3	53 (25%)	39 (34%)	0,082
4-6	131 (61%)	58 (50%)	0,053
7 and more	26 (12%)	17 (15%)	0,510
Hospital mortality n(%)	40 (19%)	20 (17%)	0,756

CHA_2DS_2-VASc : [congestive heart failure / left ventricular dysfunction, hypertension, age≥75 years (doubled), diabetes, stroke (doubled) – vascular disease, 65–74 years of age, and sex category (female)] INR: International normalization ratio, NOAC: Non-vitamin K antagonist oral anticoagulants N: number,Sd:standart deviation

Results

Demographic and clinical features of the patients are presented in [Table 1]. The mean age (75.7±10 years vs. 73.4±12.8 years, p=0.073) and gender distribution (females, 63% vs. 53%, p=0.069) were similar in the stroke and non-cerebral embolism groups. The rates of hypertension, diabetes mellitus, chronic renal failure, peripheral arterial disease, heart failure, and in-hospital mortality were comparable between the groups (p<0.05). However, the rates of coronary artery disease and hyperlipidemia were higher in the non-cerebral embolism group (p<0.05).

Although the rate of prior stroke was comparable between the stroke and non-cerebral embolism groups, the rates of prior transient ischemic attack and prior non-cerebral embolism before the last incident were higher in the non-cerebral embolism group (p<0.05). Prior NOAC use was higher in the stroke group, whereas antiplatelet and warfarin use was more common in the non-cerebral embolism group (p<0.05). International normalization ratio (INR) value was above 2 in 13% of patients that received warfarin therapy before the index event in the stroke group, and this rate was 21% in the non-cerebral embolism group. The difference between the groups was not statistically significant (p=0.394).

The median and mean CHA_2DS_2-VASc score was similar between

stroke and non-cerebral embolism group (median(min-max): 5(0-9), mean±sd: 4.52±1.66 vs. 4.29±2.02, p=0.013). When grouping the patients according to the CHA_2DS_2-VASc score, the number of patients with a score of 1 to 3 points, number of patients with a score of 4 to 6 points and number of patients with a score of 7 points and above were comparable between the stroke and non-cerebral embolism groups (p>0.05).

In the non-cerebral embolism group, 63% had lower extremity embolism, 29% had upper extremity embolism, 5% had mesenteric embolism, 2% had both right and left lower extremity embolism, and 2% had both upper and lower extremity embolism [Figure 1]. The mean CHA_2DS_2-VASc score, rates of medical and surgical therapy, and prior antiplatelet and anticoagulant use were comparable when grouping the patients according to anatomic localization of non-cerebral embolism. However, there was a significant difference between all groups with respect to mortality according to the anatomic localization of embolism (p<0.05).

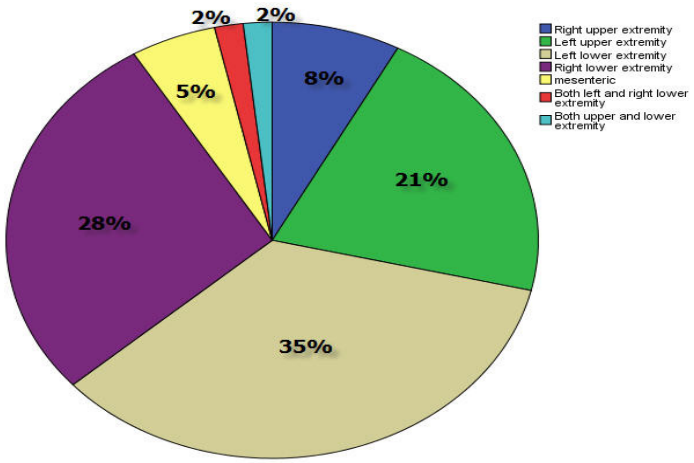

Figure 1: Anatomic distribution of non-serebral embolic events

Discussion

This study compared the thromboembolic risk level based on CHA_2DS_2-VASc score before the index event and in hospital mortality between NVAF patients suffering stroke and non-cerebral arterial thromboembolism. CHA_2DS_2-VASc score and in hospital mortality was not different between NVAF patients with stroke and non-cerebral thromboembolism.

Thromboembolic events associated with AF have been one of the most important factors determining prognosis [5]. The studies have therefore aimed at developing a risk-stratification method and $CHADS_2$ score [cardiac failure, hypertension, age, diabetes, stroke (doubled)] has been the first scoring system developed for this purpose [10]. Yamamato et al. has been the first to evaluate the value of $CHADS_2$ score in predicting non-cerebral embolic events. $CHADS_2$ score was found to be unreliable in predicting non-cerebral embolic events. The most important limitation of their study was that the data of stroke patients were obtained from other studies [13].

CHA^2DS^2-VASc score has been proposed with the addition of certain risk factors for thromboembolism such as female gender, vascular disease, and age at or above 65 years to the $CHADS^2$ score, and this extended scoring system has been introduced into the practice in many countries [14]. Bekwelem et al. performed a meta-analysis of studies on patients with NVAF receiving anticoagulant and antiplatelet drugs, and they reported the incidence, risk factors and consequences of extracranial embolism. The analysis of these data showed comparable CHA_2DS_2-VASc scores in patients with stroke and those sustaining extracranial embolism [15]. However, all patients in this analysis set had received antiplatelet or oral anticoagulant drugs as this meta-analysis reviewed previous phase 3 and phase 4 studies. Therefore, their data do not reflect real world situation. The present study directly compared CHA_2DS_2-VASc scores between NVAF patients with stroke and non-cerebral embolism. CHA_2DS_2-VASc score was similar between two groups. Another remarkable finding was that factors constituting the CHA_2DS_2-VASc score were not identical in the two groups. For instance, history of coronary artery disease was more common in patients with non-cerebral embolism. Actual cause of this finding is unknown; however, higher prevalence of certain risk factors such as hypertension, hyperlipidemia, diabetes, and chronic renal failure in patients with non-cerebral embolism might have contributed to this finding.

Another remarkable finding of the present study was higher prevalence of transient ischemic attack and previous non-cerebral embolism in patients with non-cerebral thromboembolism. Although actual cause has not been clearly identified, some factors have been associated with this finding. One of these factors is high caliber of peripheral arteries, and thus, size of the embolus must be large enough to produce clinical symptoms of acute embolism. It was considered that due to large size of embolus in patients with non-cerebral embolism, detection rates of clinical stroke and non-cerebral embolism were higher in these patients. Prospective clinical studies are required to confirm this theory.

The second factor is that the mechanism of thrombus formation can be different in stroke patients and patients with non-cerebral embolism. Stroke and transient ischemic attack can be associated with non-thromboembolic factors such as thrombosis or plaque embolization in the intracranial arteries. Other atrial factors in addition to AF such as endothelial dysfunction, fibrosis, impaired myocyte function, chamber dilatation and mechanical dysfunction in the left atrial appendage even may cause stroke independently[16].

Although we meticulously selected the patients with non-cerebral thromboembolism embolism as defined in methods section. Peripheral arterial occlusion might be resulted from aterothrombosis instead of thromboembolism due to higher rate of coronary artery disease and hyperlipidemia in the non-cerebral thromboembolism group.

It is not known as how this factor varies in the two groups. It is however clearly known that oral anticoagulation is indicated in NVAF patients with transient ischemic attack or stroke independent of the pathophysiology . The third factor is that the use of oral anticoagulant therapy is less satisfactory in patients with non-cerebral embolism. Although the use of antiplatelet drugs is more common in patients experiencing non-cerebral embolic events, anti-platelet therapy is known to be less protective against thromboembolism. Warfarin use is more common in patients with non-cerebral embolism; however, number of patients achieving therapeutic targets is lower. More common NOAC use in stroke patients might have protected these patients against extracranial embolism. Beklewen et al. reported that NOAC use was associated with a 30% further decrease in the risk of extracranial embolism compared with the risk of stroke [15]. This finding is supports the finding of the current study.

In the present study, the majority of the patients (95%) experienced

Table 2: Characteristics of patients according to location of embolism

	Upper extremityα N:33	Lower extremityα* N:74	Mesenteric N:6	p
CHA_2DS_2-VASc score mean±sd	3,90±2,02	4,5±1,97	4,83±2,14	0,306
Surgical or endovascular procedure during hospitalization n(%)	24 (73%)	48 (65%)	6 (%100)	0,173
Hospitalization without surgical or endovascular procedure n(%)	9 (27%)	26 (35%)	0 (0%)	0,173
Prior oral anticoagulation use n(%)	19 (58%)	49 (66%)	2 (33%)	0,232
Prior antiaggregan use n(%)	20 (61%)	40 (54%)	4 (67%)	0,719
Hospital mortality n(%)	4 (12%)	12 (16%)	4 (67%)	0,005

αtwo patients had both upper and lower extremity embolism who are not included
*Two patients have bilateral lower extremity embolism included in lower extremity group.
CHAD-VASc : [congestive heart failure / left ventricular dysfunction, hypertension, age≥75 years (doubled), diabetes, stroke (doubled) – vascular disease, 65–74 years of age, and sex category (female)]
N:number

extremity embolization while a small portion (5%) experienced mesenteric embolization. These data are close to those reported by Abbott et al. [17] in a series of cases from the US (83% vs. 8%), while these data were different than reported in the study by Frost et al. (60% vs. 40%) [18]. The prevalence of mesenteric embolism might have been underestimated for being difficult to remember this condition in the diagnosis, frequently remaining overlooked or misdiagnosed [19]. On the other hand, it was suggested that splenic embolisms result in insignificant clinical consequences and renal embolisms become symptomatic and manifest clinical signs in late periods, and this explains why such visceral embolisms are underreported [20]. Mortality rate was comparable in the stroke (19%) and non-cerebral embolism (17%) groups. Mortality rate in patients with upper and lower extremity embolism was lower than stroke patients; however, mortality rate in patients with mesenteric embolism was higher than in stroke patients, despite CHA_2DS_2-VASc score in mesenteric embolism group was not different than the score of stroke patients. According to our findings, the differences in mortality in patients with stroke and non-cerebral embolism were due to the localization of embolism rather than thromboembolic risk level. Durability to ischemia and clinical consequences are different between affected organs. Extremites are more durable to ischemia and clinical outcomes are more tolerable comparing to stroke. In patients with mesenteric embolism, operational procedure more complex and clinical risk level (late admission, difficult to diagnose) is higher than the patients with upper and lower extremity embolism.

Study Limitations

Since the data of the present study are based on retrospective review of hospital records, some data may be missing or inaccurately recorded. Low rate of visceral embolism due to misdiagnosed or undiagnosed patients associated with difficulties in diagnosing mesenteric, renal and splenic embolism might have biased the study findings. On the other hand, some patients with non-cerebral embolism may have remained asymptomatic due to small size of the embolism, and this may have caused that some patients with non-cerebral embolism may have not examined objectively.

Conclusions

Among patients with NVAF CHA_2DS_2-VASc score was similar between stroke and non-cerebral thromboembolism. In addition mortality rate was comparable between the two groups. However the parameters constituting the CHA_2DS_2-VASc score were not identical for stroke and non-cerebral embolism groups. The prevalence of non-cerebral embolism was higher in patients with a previous history of transient ischemic attack and non-cerebral embolism. For this reason, predicting non-cerebral embolism requires development of a different scoring system to predict thromboembolism.

Conflict Of Interests

None.

Disclosures

None.

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Routine Use of Intracardiac Echocardiography for Atrial Flutter Ablation is Associated with Reduced Fluoroscopy Time, But Not with a Reduction of Radiofrequency Energy Delivery Time

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Abstract

Background: The ablation of cavotricuspid-isthmus (CTI) atrial flutter (AFL) dependent atrial flutter could be difficult in patients with complex anatomy of the CTI.The aim of the study was to assess whether the use of intracardiac echocardiography (ICE) was associated with less fluoroscopy time and faster ablations of cavotricuspid isthmus dependent atrial flutter (CTI-AFL).

Methods: Patients with an indication for an ablation of a CTI-AFL were enrolled. Patients in which ablation of a CTI-AFLas part of an atrial fibrillation ablation were not included. Randomization was done using the envelope method. Standard techniques (i.e., coronary sinus, 20-polar halo catheter, and an ablation catheter), and criteria of success (bidirectional block through the CTI) were used. In patients randomized to the ablation with ICE, a 10F AcuNav ICE probe (Siemens, Germany)was used.

Results: Seventy-nine patients were enrolled; 40 were randomized to ablation with ICE and 39 without ICE. The X-ray exposure was shorter (3.29±2.6 vs. 5.94±3.43 min, p<0.001) and total X-ray dose was reduced (3.30±1.98 vs. 6.68±5.25 Gy.cm2, p<0.001) in the ICE group. However, the total RF energy ablation time was not different between groups (ICE group: 604.56±380.46sec vs. 585.82±373.39 sec, p=0.8). The procedure duration was slightly longer in the ICE group (82.0±20.8 vs. 72.1±19.0 min, p=0.03). Procedural success was 100% (40/40) in the ICE group and 95% (37/39) in the control group. Two control patients required crossover to ICE at a prespecified point to achieve bidirectional block. There were two femoral hematomas in the ICE group and one in the control group.

Conclusion: The use of ICE for atrial flutter ablation is associated with less fluoroscopy time and improved ability to achieve bidirectional block compared to traditional conventional flutter ablation methods. However, it is not asoociated with reduced ablation time or overall procedure duration.

Introduction

Pharmacological treatment of typical atrial flutter (AFL, i.e. cavotricuspid isthmus dependent atrial flutter) is rarely effective and often insufficient to control the high ventricular rate during ongoing AFL. [1] Catheter ablation of AFL has been shown superior compared to pharmacological treatment and utilizes routine catheter ablations. [2] The goal of the procedure is the creation of bidirectional block across the cavotricuspid isthmus (CTI). The single-procedure success rate is more than 90% in treated patients.

Catheter ablation of AFL has a 1-10% clinical recurrence rate, that is related to inability to create durable bidirectional block. [3]Failure of CTI ablation in many patients is largely due to the anatomy of the CTI isthmus, including: 1) a steep angle at the onset of the CTI; 2) concave shape of the isthmus; 3) unexpected pouches, and;4)a prominent Eustachian ridges.[4]

To overcome these anatomical difficulties and to increase the procedural success rate, several techniques and tools have been developed to facilitate ablation of the CTI. As shown recently, the ablation of the CTI can be made easier using 3D mapping systems [5] or steerable sheaths. [6]

Intracardiac echocardiography presents a valuable tool for coupling to electrophysiology procedures. The method was first reported for use in AFL ablationsby Chu et al. [7] The use of ICE during AFL ablation can visualize pouches, the presence of the right coronary artery, and reveal prominent Eustachian ridges. Whether the routine use of ICE is associated with a shortening of the total procedure time, and reduced fluoroscopy and radiofrequency delivery times remains unclear, and was the aim of the present study.

Material and methods

Patients

Patients with documented or ongoing typical AFL were eligible for the study. Patients indicated for more complex ablation procedures (e.g., concomitant pulmonary vein isolation), and patients undergoing a redo procedure for AFL were excluded. Ablations took place during ongoing arrhythmia or while the patient was in sinus

Key Words

Atrial flutter, Ablation, Intracardiac echocardiography, Fluoroscopy.

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rhythm. The study was approved by the local ethics committee, and all patients provided informed consent before enrollment. Patients were randomly assigned to undergo CTI ablation with ICE (ICE group), or without ICE, using a conventional fluoroscopic approach (non-ICE group). 3D electroanatomic mapping system was not used during ablations. The randomization was done using the envelope method. All procedures were performed by two surgeons who were familiar with ICE during all kind of ablations since 2010.

Catheter ablation

The electrophysiological study and catheter ablation were performed during the fasting state. Continuous ECG monitoring was performed using surface (low pass filter 0,1 Hz, high pass filter 25 Hz, and notch filter 50 Hz) and endocardial electrocardiography (low pass filter 30 Hz, high pass filter 250 Hz, and notch filter 50 Hz) at a sweep speed of 200 mm/s. Data were stored on a digital amplifier and recorder system (LabSystem PRO v2,6a EP Recording System, C. R. BARD, Lowell, MA, USA).

The duration of the procedure was defined as lasting from the initial connection of the patient to ECG monitoring in the EP lab until the withdrawal of the sheaths and final assessment of hemostasis (achieved through manual compression). In patients randomized to the ICE group, two sheaths (F6, F11) were inserted. From the left femoral vein, a 10-F phased-array ICE probe (AcuNav, Siemens,Erlangen, Germeny) was inserted into the right atrium and connected to echocardiography (Vivid Q, GE Healthcare, Wauwatosa, USA), and a 6-F decapolar catheter was inserted into the coronary sinus (Dynamic XT Catheter, Boston Scientific, Marlborough, MA, SA or ViaCath, Biotronik SE &Co.KG, Berlin Germany). The right femoral vein was used to introduce a7-F duodecapolar (halo) catheter into the right atrium (Map-iT™ TF 4/3.3F Duo-Decapolar,Access Point Technologies, Rogers, MN, USA or ViaCath, Biotronik SE &Co.KG, Berlin Germany) and a 3.5 mm irrigated-tip ablation catheter (AlCath Flux Black or Blue eXtra Gold, Biotronik SE &Co.KG, Berlin Germany) was placed in close proximity to the right atrial cavotricuspid isthmus using an 8F long sheath (Fast-Cath™ SR0™, St. Jude Medical, Plymouth, MN, USA). In patients randomized to the non-ICE group, the same decapolar, duodecapolar, and ablation catheters were inserted, however, all were inserted via the right femoral vein.

In the beginning of the ablation, the ablation catheter was positioned at the ventricular aspect of the CTI. Ablation was carried out using the power-control mode with the energy output set at 25–35 W (30–35 Watts close to the tricuspid valve, and 25 Watts close to the inferior caval vein), temperature was limited to 43 ˚C and the irrigation rate was 15–30mL/min, under anatomic (ICE or fluoroscopy) and electrographic guidance using the point-by-point technique, which means that the ablation catheter was not withdrawn during individual applications of energy, unless necessary (due to an increase in impedance or temperature, or catheter instability). The duration of RF energy pulses, on one location, was 40 sec. After which, the ablation catheter was slightly withdrawn, the next position was checked using ICE (if available), fluoroscopy, and local electrocardiogram.Ablationswere performed either during ongoing AFL or during sinus rhythm (pacing from the proximal CS or distal poles on duodecapolar catheter) with the procedural endpoint being a complete bidirectional isthmus block. Bidirectional block was assessed by activation sequence on duodecapolar catheter and proximal pole of CS catheter during stimulation from distal pole of duodecapolar catheter and proximal pole of CS catheter. In difficult cases,differential pacing was performed to distinguish complete from incomplete blocks. If a complete conduction block of the CTI was not present after the firstablation line, individual conduction gaps were sought out and ablated. If the block was not achieved in the non-ICE group after 10 min of X-ray,it was recommended that the ICE should be added (without a change in surgeons. In such cases, the ICE probe was added from the left femoral vein. After block completeness, a 15-min waiting period was started, after which the block was reassessed. If the bidirectional block was maintained, the procedure was finished and all catheters and sheaths were withdrawn. If conduction remained, gaps were once again sought out andablated, and a new 15-minwaiting period was started.

Table 1: Basic clinical characteristics of studied patients in both groups

	ICE (n=40)	No-ICE (n=39)	p
Age	68.6 + 8.8	67.4 + 9.3	0.55
Gender (male)	29 (73%)	27 (69%)	0.75
LV EF (%)	51.6 + 13.2	54.2 + 11.5	0.36
LA size (mm)	44.8 + 5.4	44.1 + 4.5	0.53
Tri gradient (mmHg)	25.9 + 6.4	28.8 + 7.3	0.15
Mi regurgitation (moderate, severe)	4 (10%)	5 (13%)	0.69
History of atrial fibrillation	14 (35%)	13 (33%)	0.88
History of AFL (months)	15.4 + 26.0	8.9 + 14.8	0.28
History of heart failure	22 (55%)	17 (44%)	0.31
NYHA class (in HF pts.)	1.7 + 0.8	1.6 + 0.8	0.89
History of hypertension	29 (73%)	23 (59%)	0.33
Amiodarone	7 (18%)	4 (10%)	0.35
Propafenone	4 (10%)	3 (8%)	0.72
Beta-blocker	21 (53%)	27 (69%)	0.13
Ongoing Warfarin	23 (58%)	21 (54%)	0.74
LMWH	4 (10%)	4 (10%)	0.97
NOAC	9 (23%)	9 (23%)	0.95
Aspirin	4 (10%)	5 (13%)	0.69

Data are shown as mean+SD or absolute number and frequencies. Statistical analysis was done using t-test or chi-square test.
LV EF – left ventricular ejection fraction, LA size – left atrial size, Tri gradient – gradient on tricuspid valve, LMWH – low molecular weight heparin, NOAC – novel anticoagulants

Statistical analysis

Continuous variables are shown as mean ± SD. Comparisons between groups were performed using the Student's-test, or the Mann-Whitney U-test, as appropriate. Categorical variables are shown as absolute numbers and frequencies, and were compared using the Fisher´s exact test. Statistical significance was defined as a $p<0.05$ using a 2-tailed comparison. Statistical analyses were done using Sigma STAT software (Systat Software, Inc., San Jose, CA, USA).

Results

Eighty were initially enrolled in the study. Bidirectional block across the CTI was achieved in 79 (98.7%) of patients: in one patient, atrial fibrillation occurred during the procedure, and reoccurred despite IV anti-arrhythmics and electrical cardioversions; thus, in this patient, the presence of a block through the CTI could not be verified. Therefore, this patient was excluded from the analysis due to inability to test the endpoint. It means, 79 patients were included in the analysis. There were 56 (71%) men (mean age 67.7 ± 12.9 years). Ongoing AFL at the start of the ablation was present in 45(57%) of

Table 2: Procedure and ablation variables

	ICE (n=40)	No ICE (n=39)	p
Ongoing AFL at the start	24	21	0.58
Total procedure time (min)	82.0 + 20.8	72.1 + 19.0	0.03
X-ray time (min)	3.29 + 2.60	5.94 + 3.43	<0.001
X-ray dose (Gy.cm^2)	3.30 + 1.98	6.68 + 5.25	<0.001
Nr of RF pulses	18.6 + 12.9	19.1 + 13.7	0.85
Energy duration (sec)	604.6 + 380.5	585.8 + 373.4	0.73 ± 0.42
Length of the CTI (mm)	28.6 + 12.4		
Reconduction	6 (15%)	6 (15%)	1.0

patients (mean CL 238.9 ± 25.8 ms). Forty patients were randomized to the ICE group and 39 patients to the non-ICE group. Basic clinical characteristics of both groups are shown in [Table 1]. There were no significant differences in terms of baseline characteristics between the two groups. The ablation catheter, as seen during the ICE guided ablation in one patient from the ICE group is shown in [Figure 1].

All procedures and ablation variables are shown in [Table 2]. In the non-ICE group, eight patients (20.5 %) received more than 10 min of X-ray exposure; however, in only two of them (5%), ICE probe was added (these patients were analyzed in the non-ICE group). The addition of ICE was only recommended, not mandatory after achievement of 10 min fluoroscopy, and the final decision was left on the operator. In the two patients, in whom the ICE probe was added, not only X-ray exposure, but also the number of RF energy applications was very high (more than 1000 sec in both of them). In both patients, a CTI block was finally achieved. A concaved CTI with a prominent Eustachian ridge was observed by means of ICE. In the ICE group, the X-ray exposure longer than 10 min was present in 2 patients. Reconduction across the CTI, during the 15 min waiting period, occurred in 12 patients (6 patients in the ICE group and 6 patients in the non-ICE group, in the majority of them this occurred shortly after the first ablation line and block), however, a bidirectional block was ultimately achieved in all of these patients.

Regarding complications, there were three small hematomas, two in the ICE group (5%) and one in the non-ICE group (2.5%). However, none required a transfusion of blood products or prolongation of hospitalization. Additionally, one steam pop occurred in each group without complications.

In the ICE group, the X-ray time was significantly shorter compared to the non-ICE group (3.29 ± 2.60 min vs. 5.94 ± 3.43, p=0.0003). Similarly, the radiation dose was significantly lower in the ICE group (3.30 + 1.98 Gy.cm^2 vs. 6.68 + 5.25 Gy.cm^2). However, the number of RF energy pulses (18.5 ± 12.9 vs. 19.1 ± 13.7) and the total RF energy duration (604.6 ± 380.5 sec vs. 585.8 ± 373.4 sec) were similar in both groups. The total procedure time was non-significantly longer in the ICE group. The total procedure time was longer in the ICE group than in the non-ICE group (82.0 + 20.8 min vs. 72.1 + 19.0 min); however, the prolongation was due to one more venous access in the ICE group.

Discussion

Our main findingswere that the use of ICE significantly shortens X-ray exposure, but not the number of RF energy applicationsor the RF time. The use of ICE was 100% effective in terms ofcreation of a bidirectional block (compared to 95% effectiveness without ICE). In difficult cases that originally started without the use of ICE, the addition of ICE enabled a bidirectional block across the CTI to be achieved.

Several tools and techniques have been developed to facilitate CTI ablation. Matsuo et al. reported a reduction in time and amount of RF energy needed in a randomized study comparing steerable vs. non-steerable long sheaths for CTI ablations without different X-ray exposure. [6]Reduced ablation times and amounts of energy delivery was only seen in patients with a non-straight CTI anatomy (concave and pouch-like, determined by cardiac CT) but not in patients with "easier" straight CTI anatomy. It means, in patients with difficult CTI anatomy, steerable sheaths, due to better stability and contact, could significantly enhance CTI ablations. The use of a 3D mapping system for CTI ablation was reported by Kottkamp et al. [8] 3D mapping of CTI ablations was associated with a substantial reduction in X-ray exposure (22 min vs. 3.9 min), however, it did not lower the number of RF pulses needed to achieve a complete bidirectional block. 3D mapping systems are also not able to directly show CTI anatomy.

Because the main issue in CTI ablations has to do with difficult

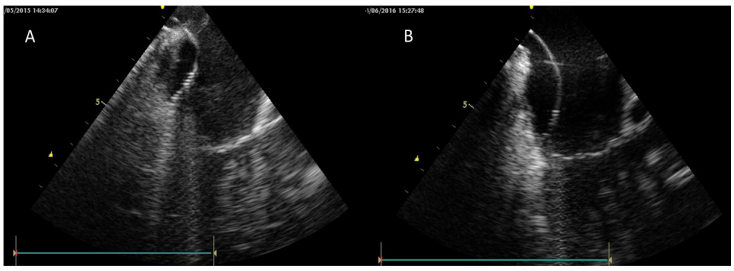

Figure 1: An example of the visualization of cavotricuspid isthmus using ICE during the ablation. A – cavotricuspid isthmus with prominent Eustachian ridge B – cavotricuspid isthmus with flat Eustachian ridge

CTI anatomy, attention needs to be focused on methods that allow visualization of the CTI. CTI anatomy can be visualized using cardiac CT, angiography, or echocardiography.

As shown by Kajihara et al., visualization of the CTI prior to ablation, using cardiac CT, is capable of predicting difficult CTI ablations and can facilitate the formation of an ablation strategy. [4] In their study, the most difficult CTI anatomies were concaved CTI (present in 26% of patients) and pouch-like CTI (present in 16% of patients). In the second part of the abovementioned study, patients with difficult CTI anatomy, which were identified prior the ablation, were randomized to the modulation ablation technique (catheter inversion technique) or conventional technique. Modulation of the catheter shape, based on the knowledge of CTI anatomy, was associated with shortened RF application duration and lower total amounts of RF energy, as well as reduced X-ray time (14 min vs. 6.8 min). It emphasizes the importance of the knowledge of CTI anatomy for the ablation. However, cardiac CT has its own level of radiation exposure, and cannot be used in real-time during the ablation.

Another way to visualize CTI anatomy involves angiography, in which a contrast dye injection is applied via a pigtail catheter into the inferior vena cava at its junction with the right atrium (isthmogram). Unlike a cardiac CT, an isthmogram can be done directly in the EP lab. Da Costa et al. showed that isthmus characteristics, such as a concave shape or prominent Eustachian ridge, are factors that significantly increase procedure duration, X-ray exposure and the

duration of required RF applications.[9]

Because of the absence of radiation exposure and real-time visualization during ablation, ICE represents an optimal tool for CTI visualization during ablations. The use of ICE during CTI ablation was reported for the first time by Chu et al. in 1994.[7]ICE, especially in patients with complicated CTI anatomy, can make ablations feasible, even in patients with a history of unsuccessful ablations. [10]Recently, Bencsik et al. reported a randomized study similarly designed as ours. [11] In contrast to our results, they found not only lower X-ray exposure, but lower RF energy application in patients ablated with ICE.In contrast to our study, Bencsik et al. reported higher overall X-ray times (18.6min in the conventional group, and 5.5min in the ICE group). In our patients ablated without ICE, the X-ray time of 5.9 ± 3.4 min was closer to the X-ray time of patients ablated with ICE in Bencsik´s study. In this context, thesignificant reduction of X-ray exposure seen in our study, i.e., 3.29 ± 2.6 min in our ICE group, is of importance and could be achieved only by a new tool added to conventional setting. The RF duration time in our study (604.6 ± 380.5 sec, or 585.8 ± 373.40 sec, resp.) varried between the values reported by Bencsik for their ICE and conventional groups (i.e., 482.8 ± 534.1 in the ICE group and 779.7 ± 620.8 sec in the conventional group). The explanation of lower X-ray exposure, but unchanged RF energy application between ICE and non-ICE groups in our study, could have been due to the ablation technique used in our lab (point-by-point approach). With the point-by-point technique, ICE is used for catheter visualization (i.e. instead of X-rays), however, it is not used to assess the formation of the RF lesion.

Thirteen percent of the conventionally ablated patients in the Bencsik´study, and 5% of our patients had to be switched to the ICE approach in order to complete the bidirectional block. In our study, the efficacy of CTI flutter ablation was 100% in the ICE group, and 95% in the non-ICE group (up to switch to the ICE approach). We can´t conclude that the ablation in those patients would have been unsuccessful without the switch to ICE; however, the addition of ICE facilitated a successful ablation result.

The total procedure time was longer with ICE than without using it. However, in the ICE group, there was one more vein puncture, and because the total procedure time was calculated until successful hemostasis, the prolongation of the procedure was caused by additional vein puncture and adequate hemostasis. Importantly, in the ICE group, no more major vascular complications were observed, despite having one more 11F vein puncture in patients on anticoagulation.

Over the last year, the awareness of the risk related to the use of ionizing radiation in medicine has progressively increased. According to a survey undertaken in Italy, interventional cardiologist and electrophysiologist represent more than 60% of the medical staff receiving the highest annual radiation exposure, with no statistical difference between physicians, nurses and technicians. [12] Due to both the stochastic and deterministic effect of radiation, there is no magnitude of radiation exposure that is known to be completely safe and, the use of radiation exposure should be As Low As Reasonably Achievable (ALARA principle). This principle confers to physicians the responsibility for reducing as much as possible the dose of radiation during cardiovascular procedure, in order to minimize the radiation injury of the patients as well as of the medical staff. ICE represent an excellent tool for on-line visualization of the anatomy of the area of interest, ablation and other catheters without any exposue of radiation, and so could be considered even for conventional ablation in any patient.

Conclusions

The use of ICE for atrial flutter ablation was associated with less X-ray exposure and reduced total X-ray dose, but did not reduce the total radiofrequency energy ablation time. The use of ICE for atrial flutter ablation was 100% effective in terms ofcreation of a bidirectional block. Moreover, in difficult cases (in patients with an unsuccessful ablation using fluoroscopy), the addition of ICE was effective in creating a bidirectional block across the cavotricuspid isthmus.

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Conflict Of Interests

None.

Disclosures

None.

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Resolution of AV Block After Ablation for Atrial Fibrillation

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Abstract

We report a case with complete atrioventricular block (AVB) present both during sinus rhythm and with atrial fibrillation (AF). He had declined pacemaker placement and opted for ablation for the symptomatic AF. He underwent staged hybrid approach with video-assisted thoracoscopic surgical maze (VATS) followed by endocardial ablation. VATS included ganglionic plexi cauterization. One month after the endocardial procedure, he had complete resolution of AF and AVB and remains so at 18 months follow up. We discuss possible abolition of vagal input for this improvement in AV conduction.

Introduction

Association of sick sinus syndrome(SSS) and atrial fibrillation (AF) is well known. Additionally, vagal stimulation evokes bradycardia, and predisposes to atrial fibrillation by the effect on the I kach,ado channels, and a reduction in atrial refractory period respectively. [1]Paroxysmal AF episodes also cause sinus node dysfunction through electrical remodeling.[2]Ablation of AF has been shown to significantly reduce sinus pause and avert pacemaker requirement, [3] however the effect of AF ablation on atrioventricular node (AVN) function is unknown. We report case with resolution of complete atrioventricular block (AVB) after AF ablation.

Case Report

A 64-year-old athletic male presented with exertional fatigue and dyspnea. He has a known history of cavo-tricuspid isthmus dependent atrial flutter with 4: 1 AV block [Figure 1A], which was ablated in 2006 without recurrence. Thereafter he had chronic asymptomatic bradycardia with a prolonged PR interval [Figure 1B] and Wenckebach AV block attributed to high vagal tone, with appropriate increase in heart rate on the treadmill. In June 2011, he reported symptoms of exertional fatigue and palpitations, electrocardiogram (ECG) revealed AF with slow ventricular rate, [Figure 1C] with 60% burden of AF on a 24 hour monitor. When in sinus rhythm, he also had complete AVB with good escape rate. [Figure 1D] Medical management was limited by low heart rate and the pauses noted on the monitor. He declined pacemaker and opted for ABL for AF after 40 months of having paroxysmal episodes. After multiple consultations, opinions and considering various options, he chose to have hybrid ablation with video-assisted thoracoscopic surgical maze (VATS) followed by endocardial ablation. VATS included epicardial pulmonary vein (PV) isolation, ablation of ganglionic plexi, roof and floor of left atrium (LA), right atrial line from SVC to IVC, ligament of Marshall (LOM) disconnection and left atrial appendage ligation. On post-operative day one, electrocardiogram (ECG) revealed transient resolution of AVB [Figure 2A], with subsequent paroxysmal atypical atrial flutter and complete AVB [Figure 2B][Figure 2C]. Nine weeks later, he underwent endocardial mapping (CARTO 3 system, Pentarray Nav Eco mapping catheter) and ablation (Navistar RMT 3.5 mm). He required isolation of one anterior connection in left superior pulmonary vein. The atypical flutter involved mitral isthmus, which terminated during ablation into sinus rhythm with transient Wenckebach AV block it was confirmed to be at the level of AV node. The gap in roof line was reinforced and septal line to mitral annulus completed to eliminate fractionated signals. [Figure 3] During the first week he remained in Wenckebach AV block, however AV conduction normalized at one month follow up. He has remained in sinus rhythm with normal PR interval without recurrence of AF or atrial flutter after 18 months. [Figure 2D] Exercise stress test on the treadmill revealed an appropriate increase in heart rate with normal PR and Wenckebach AVB with longest PR 200 msec at peak exercise. [Figure 4] He continues to exercise without any limitations.

Discussion

We have described a case of resolution of high-degree AVB after sequential epicardial and endocardial ablations for AF.He is known to have reduced AVN function as observed by 4: 1 block with atrial flutter and baseline complete AVB, in the absence of rate controlling agents.

Clinical AVN is richly innervated with cholinergic nerve terminals, with higher density compared to surrounding structures; on the other hand sympathetic innervation at AVN is similar to that of other locations.[4]The parasympathetic nerve terminals at the AVN

Key Words

Vagal denervation,Atrial fibrillation,AV block,Resolution

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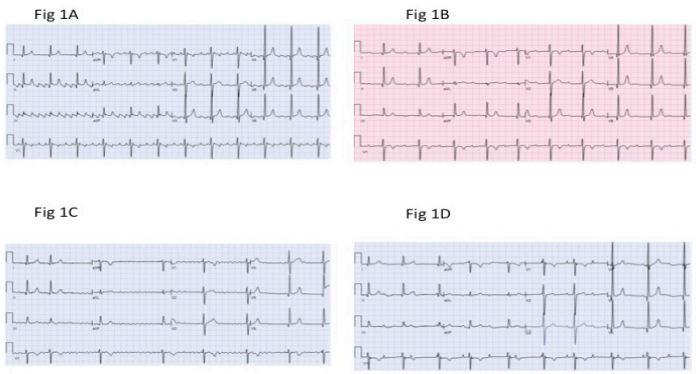

Figure 1: Preoperative electrocardiograms.A-Atrial flutter with 4: 1 block; B-Sinus Bradycardia with prolonged PR interval; C – Atrial fibrillation with bradycardia; D- Normal sinus rhythm with complete heart block and AV dissociation.

receive input from the vagi through ganglionic plexi located in the epicardial fat pads.In the canine heart, AV node obtains signals from right and left vagi via ganglionic projections around right and left superior pulmonary veins respectively.[5]In a study among surgical patients, the stimulation of fat pad around right inferior pulmonary vein was found to cause block in the AV node and refractoriness of the surrounding atrial myocardium suggesting a pathway from right vagus.[6]

In patients undergoing epicardial ablation for AF, Xhaet et al showed that ablation of posterior epicardial fat pads leads to a loss of vagal effect at the AVN demonstrated by lack of ventricular slowing

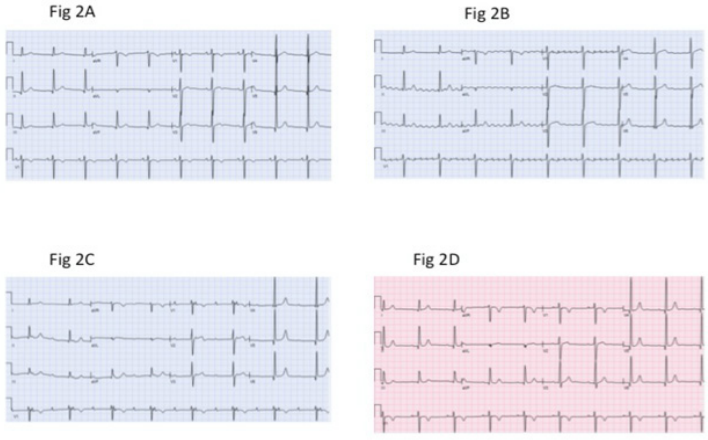

Figure 2: Post operative electrocardiograms.A-Normal sinus rhythm on post operative day one; B- Atypical flutter with complete heart block; C- Normal sinus rhythm with complete heart block and AV dissociation; D- Normal sinus rhythm with normal PR interval post endocardial ablation.

with high frequency stimulation.[7]While ablation of the anterior right ganglionic plexus (ARGP) located near the sinus node has been shown to attenuate the vagally mediated slowing of ventricular rate, the combined ablation of ARGP and left inferior ganglionic plexus (LIGP)is needed to eliminate the ventricular slowing caused by vagal stimulation, thus emphasizing the significance of left sided parasympathetic terminals.[8] In addition, the LOM ablation attenuated the ventricular slowing response caused by stimulation of the left superior ganglionic plexus (LSGP). LIGP and LSGP are

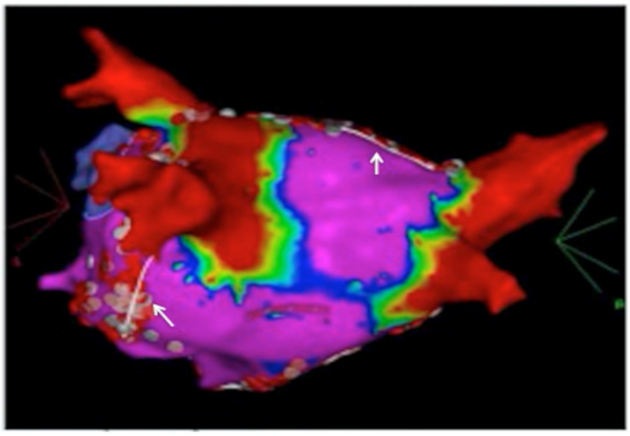

Figure 3: Electroanatomical map (CARTO, Biosense Webster Inc) of left atrium PA view. Red color represents low voltage areas in sinus rhythm. Superior and inferior white arrows represent roof and mitral isthmus lines during endocardial ablation.

located near the atrial junction of the left inferior PV and left superior PV respectively, which along with LOM complete the epicardial portion of the mitral isthmus and its extension to the upper ridge. Thus these endocardial areas are likely important conduits for the parasympathetic inputs from left vagus.

In our patient ganglionic plexi around the pulmonary veins and LOM were ablated epicardially and absence of aystole or bradycardia on high frequency stimulation post ablation was confirmed during surgery. After epicardial ablation, on post operative day one, there was a transient resolution of AV block, which recurred later through the hospital stay. During endocardial ablation, besides reinforcement of roof and left superior PV isolation and septal fractionated areas, mitral isthmus was ablated for the atrial flutter. Though there was a transient resolution of AVB after epicardial ablation, the complete resolution subacutely after endocardial ablation could represent a need for both endocardial and epicardial approaches to cause transmural elimination of nerve terminals at the mitral isthmus from the left vagus.

After eighteen months, he has normal AV conduction at rest with an excellent exercise capacity, and a mild degree of Wenckebach AVB at heart rate > 100/min. To our knowledge this is the first case to show significant improvement in AVN function of AF ablation. The effect on AVN function in AF ablation, mediated by elimination of

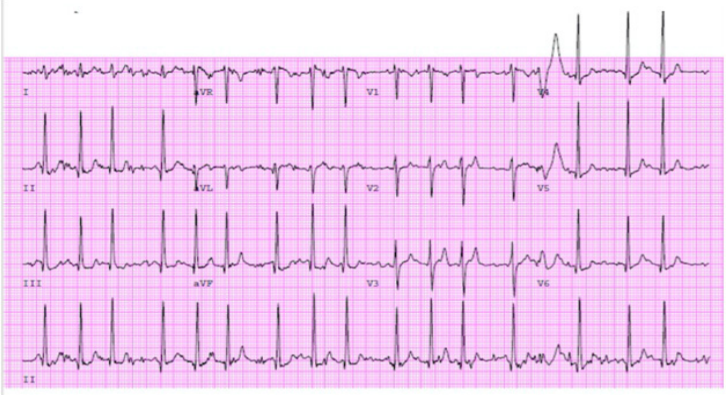

Figure 4: ECG recorded during exercise treadmill test - sinus tachycardia with normal PR interval with 3: 1 Wenckebach AV block.

parasympathetic terminals needs to be further investigated.

Conflict Of Interests

None.

Disclosures

None.

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Post-Ictal Transient Atrial Fibrillation As A Rare Manifestation Of Grand Mal Seizure

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Abstract

Atrial fibrillation (AF) most frequently occurs as a consequence of multiple etiologies including valvular disease, coronary artery disease, hyperthyroidism, alcohol ingestion, and pulmonary embolism. However, on rare occasion transient AF may be a result of generalized tonic-clonic seizures (GTCS). A 33-year-old-man presented to the emergency department following GTCS in AF with rapid ventricular response. He had no previous documented history. Diagnostic evaluation including electrolytes, thyroid function, cardiac enzymes, serum and urine drug screen, and two-dimensional echocardiogram were unremarkable. Diltiazem was initiated for rate control with spontaneous conversion to sinus rhythm with no recurrence. AF post-seizure is a rare phenomenon but should be considered in epileptic patients. Anticoagulation must be considered in AF due to the risk of cardioembolic stroke but should be weighed against the potential risk of head injury and subsequent intracranial bleed in patients with grand mal seizures.

Introduction

A wide range of autonomic imbalances may result following seizures and can cause various cardiac arrhythmias and repolarization abnormalities.[1] Increased vagal discharges may cause bradycardia and asystole, while increased sympathetic activity results in sinus tachyarrhythmias. Dangerous neurogenic cardiac arrhythmias, such as Atrial Fibrillation (AF) during the peri-ictal period are rare but should be considered in an epileptic patient. We present a case of atrial fibrillation following a generalized tonic-clonic seizure with spontaneous conversion to sinus rhythm with no recurrences.

Case

A 33-year-old obese man (body mass index: 46.18 kg/m^2) with a history of depression, and epilepsy maintained on lacosamide (200 mg twice daily) and carbamazepine (200 mg twice daily)presented initially to the emergency department (ED) following a complex partial seizure. He was a former smoker and had never used any alcohol or recreational drugs. On arrival to the ED, he was awake and alert.His heart rate (HR) was 74 beats/min, blood pressure (BP) 119/67 mm Hg, temperature (Temp) 98.1˚F and respiratory rate (RR) 18 breaths/min. His oxygen saturation (SpO_2) on room air was 99%. His serum electrolytes were within normal ranges. A 12 lead electrocardiogram (ECG) revealed normal sinus rhythm [Figure 1]. No further investigations were obtained,and he was subsequently discharged home.

Approximately three hours post-discharge, he was transported back to the ED with witnessed tonic-clonic seizure accompanied by fecal incontinence. On presentation, he was in a postictal state. A computed tomography scan of the head was obtainedand did not reveal any pathological abnormalities.His BP was 107/59 mm Hg, temperature was 98.4˚F, RR 16 breaths/min, and SpO_2 on room air was 93%. His pulse was irregularly irregular, and telemetry demonstrated AF with rapid ventricular response. A 12 lead ECG showed AF with a ventricular rate of 160 beats/min [Figure 2].Laboratory values revealed electrolytes within normal ranges; thyroid stimulating hormone (TSH) of 1.14 IU/ml (normal range: 0.27–4.2 IU/ml); negative urine drug screen; and negative cardiac enzymes. Two-dimensional echocardiogram demonstrated left ventricular ejection fraction of 55% with no evidence of cardiac chamber dilatation, pulmonary hypertension, or valvular abnormalities.

A bolus dose of diltiazem (10 mg) followed by a diltiazem drip at a rate of 5 mg/hrwas initiated for rate control, and approximately 3 hours following the presentation,the patient's rhythm spontaneously converted to sinus rhythm. His seizures remained controlled withanti-epileptics, and after monitoring for 48 hours, he was discharged home without anticoagulation based on a CHA_2DS_2VASc score of zero. Since the time of discharge, he has not required any admissions for either seizures or episodes of AF.

Discussion

The most common peri-ictal arrhythmia is sinus tachycardia, which accompanies 90% of all seizures.Bradycardia and asystole are uncommon and occur in only about 0.5% of seizures.[1]Peri-ictal AF is a rare phenomenon, with only 14 cases reported in the literature to

Key Words
Atrial fibrillation, Seizures, Anticoagulation.

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Table 1: Literature review of the cases of seizure-induced atrial fibrillation

Case	Year	Age/Sex	Type of seizure	Atrial fibrillation duration	Recurrence of atrial fibrillation	Treatment given	References
1	1998	74/F	GTCS	2 hours	Not reported	spontaneous conversion	Tigaran et al[2]
2	1998	47/M	GTCS	Not reported	Not reported	IV digoxin and verapamil, spontaneous conversion	Tigaran et al[2]
3	2000	Not reported	GTCS	Not reported	Not reported	Spontaneous conversion	Nei et al[3]
4	2004	Not reported	GTCS	>110 sec	Not reported	Spontaneous conversion	Nei et al[4]
5	2004	Not reported	Complex partial seizure	55 sec	Not reported	Spontaneous conversion	Nei et al[4]
6	2006	Not reported	Not reported	Not reported	Not reported	Not reported	Britton et al[5]
7	2012	45/M	GTCS	90 min	Yes, 1 month later following GTCS	Propafenone (70 mg in 100 cm3 of saline infusion	Vedovello et al[6]
8	2012	41/ M	GTCS	2 hours	None	spontaneous conversion	Herskovitz et al[7]
9	2012	37/M	Focal seizure with secondary generalization	2 hours	Yes, same hospitalization following seizure	Amiodarone after 2ndAF following a seizure. Patient discontinued medication.	Herskovitz et al[7]
10	2012	24/M	GTCS	<6 hours	No	spontaneous conversion	Herskovitz et al[7]
11	2012	21/M	GTCS	<6 hours	No	spontaneous conversion	Herskovitz et al[7]
12	2012	23/M	GTCS	~ 25 hours	Not reported	spontaneous conversion	Surges et al[8]
13	2012	25/M	GTCS	>3 hours	Not reported	spontaneous conversion	Surges et al[8]
14	2014	18/M	GTCS	~6 hours	No	Synchronized cardioversion	Singh et al[9]
15	2017	33/M	GTCS	~3 hours	No	Diltiazem, spontaneous cardioversion	Dangol et al (Current case)

date [Table 1].[2]-[9] Most of the casesin the series were20 - 40 years of age;the majority were males. Nearly all of the patients suffered GTCS;complex partial seizure was seen in one patient, and seizure type was not reported in one. In most cases, AF was transient with spontaneous conversion to sinus rhythm.One case received digoxin and verapamil for rate control. In two of the cases (case 7 and 9 in the table series), propafenone and amiodarone were used respectively for rhythm control after the second episode of peri-ictal AF. In these two cases, no inter-ictal arrhythmias were reported. Anticoagulation for stroke prevention was not reported in any of the cases and thus CHA_2DS_2VASc scores were not obtained.

Atrial Fibrillation can be clinically silent in one-third of the cases, and asymptomatic AF preceding the seizure is always a possibility. However, our patient was in sinus rhythm on initial presentation and also denied previous history of AF. Triggering factors, such as valvular disorders, hyperthyroidism, drug or alcohol intoxication, and other medical conditions known to cause AF were absent in our patient. The only identifiable risk was lacosamide. Even though the incidence of lacosamide triggered AF is < 0.5% (typically with a dose of 600mg per day),[10] our patient was not taking the prescribed lacosamide(200 mg twice daily). Thus, given the absence of obvious cardiac diseases and medical conditions associated with AF, and the association of massive catecholamine release following GTCS,[11] seizure-induced AF is a strong possibility in this case. Moreover, the observation of transient AF following GTCS in ten of the fourteen cases (in the table series) supports the pathophysiological relationship between AF and GTCS.

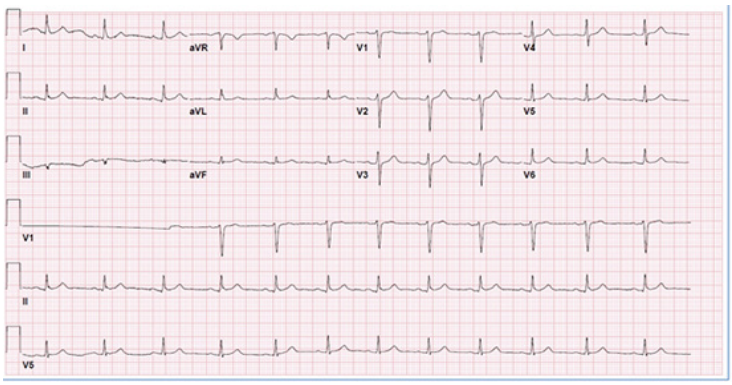

Figure 1: ECG of the patient during initial presentation demonstrating normal sinus rhythm

AF is a prothrombotic state and tends to increase the risk of cardioembolic stroke in susceptible individuals. Given the risk for stroke and the potential impairment of cardiac function, AF demands immediate treatment. In hemodynamically unstable patients, synchronized cardioversion is the treatment of choice. Stable patients are managed medically with rate andrhythm control.Anticoagulation for stroke preventionisbased on the individual's CHA_2DS_2VASc score. The American Heart Association/American College of Cardiology/ European Society of Cardiology (AHA/ACC/ESC) recommends oral anticoagulation, either with a vitamin K antagonist (warfarin, to an international normalized ratio (INR) of 2-3) or any of the novel oral anticoagulants (e.g. apixaban, rivaroxaban or dabigatran), in individuals with a CHA_2DS_2VASc score of ≥ 2. However, this score is weighed against the risk of bleeding.In patients with a high HASBLED score ≥ 3, caution should be applied while prescribing anticoagulation.[12],[13]

This prompts the question of whether individuals with seizure-induced AFand aCHA_2DS_2VASc score of ≥2 should be chronically anticoagulated.It should be emphasized that peri-ictal AF is typically transient, and given the potential risk for fall with subsequent head injury and intracranial hemorrhage, anticoagulation in an epileptic patient should be used with caution. In our opinion, the best approach to such rhythm disturbance is adequate treatment and control of seizures. In cases of recurrent seizures secondary to drug refractoriness or medication noncompliance, the long-term use of

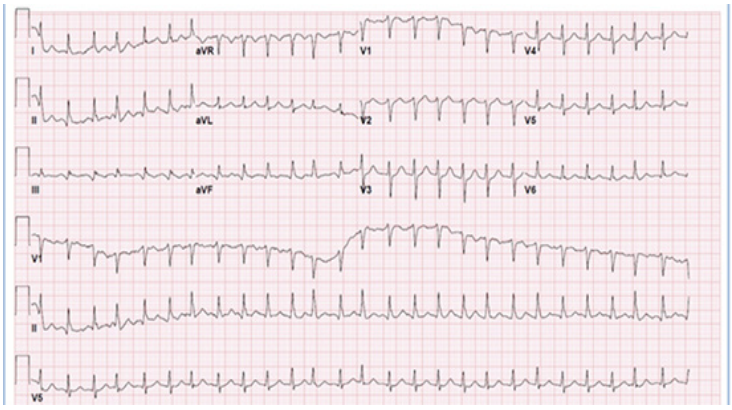

Figure 2: ECG of the patient during second presentation demonstrating atrial fibrillation with rapid ventricular response

appropriate antiarrhythmics to prevent the development of AF may be considered.

Conclusions

AF is a rare consequence of GTCS and is generally transient. The best approach to the management of peri-ictal AF is prevention with adequate seizure control.Given the transient nature of peri-ictal AF and the potential for head injury with subsequent intracranial bleed, anticoagulation for stroke prevention should be cautiously used. Long term use of appropriate antiarrhythmicsmay be an alternative in refractory cases in order to remediate the long term useof anticoagulation.

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Conflict Of Interests

None.

Disclosures

None.

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Frequent Premature Ventricular Contractions and Cardiomyopathy, Chicken and Egg situation

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Abstract

Premature ventricular contractions (PVCs) are usually regarded as benign in the absence of structural heart disease. However, frequent PVCs can lead to depressed LV function, called PVC-induced cardiomyopathy and can be reversible after suppression of PVCs. On the other hand, PVCs can be a part of underlying structural heart disease and may be linked to increased risk of sudden death. In this work, we reviewed the current literature on PVC-induced cardiomyopathy based on a case presentation.

Introduction

Premature ventricular contractions (PVCs) are usually regarded as benign in the absence of structural heart disease. However, frequent PVCs can lead to depressed LV function, called PVC-induced cardiomyopathy (PVC CMP) and can be reversible after suppression of PVCs. On the other hand, PVCs can be a part of underlying structural heart disease and may be linked to increased risk of sudden death [1]-[6].

Differentiation of these two entities can be challenging. Late gadolinium enhancement (LGE) cardiac magnetic resonance (CMR) is the gold standard imaging modality for myocardial tissue characterization [7]. In patients with enlarged cardiac chambers, LGE CMR may have a role in the differentiation of PVC CMP from primary cardiomyopathies and in predicting the improvement of left ventricular function [8].

LGE CMR can facilitate VT ablations by providing detail about myocardial scar location and geometry. Here, we present the case of a patient with hemodynamically unstable sustained VT and frequent VPCs with left bundle branch block (LBBB) - inferior axis morphology, and review current methods used for differentiation of two entities.

Case

A 52-year-old man with a history of hypertension, frequent VPCs (34% in previous Holter) was referred to our hospital with hemodynamically unstable sustained VT (230 bpm). 12-lead ECG demonstrated LBBB and inferior axis morphology with early precordial transition. After electrical cardioversion, he had multiple episodes of nonsustained VT with the same morphology. His sinus ECG was unremarkable. Echocardiogram showed enlarged cardiac chambers, global hypokinesia with a LVEF of 30%. Coronary angiography revealed normal coronaries. Due to frequent VPCs, VPC CMP was suspected. For discrimination of VPC CMP from primary CMP a CMR study was planned.

CMR with a 1.5-T scanner (Siemens Essenza, Forchheim, Germany) was performed in multiple anatomic planes using T1-weighted and cine steady-state free precision sequences. Contrast-enhanced sequences to evaluate early myocardial perfusion and delayed myocardial enhancement were also performed, using 0.1 mL/kg gadobenate dimeglumine. LGE CMR demonstrated basal septal scar in the left ventricular outflow tract (%6 of LV myocardium), which raised the possibility of a substrate-mediated VT.

Programmed electrical stimulation performed at RV apex induced the clinical VT. Conventional activation mapping demonstrated earliest activation in the septal part of LVOT. The voltage during sinus rhythm at this site was <1.5 mV, suggesting scar consistent with delayed enhanced CMR image. Ablation at the superior border of the septal scar (30–50 W) resulted in noninducibility of the VT with programmed electrical stimulation of up to triple extrastimuli. Two days after the VT ablation, due to presence of septal scar the patient had an implantable cardioverter- defibrillator (ICD) implanted for secondary prevention. During a 12-month follow-up period despite the patient remained symptom free with no ventricular arrhythmia on Holter monitor and ICD interrogation, he had no reversal of depressed systolic function.

Discussion

Premature ventricular contractions occur frequently in the general population. Although in patients with structurally normal hearts, PVCs have previously been found to be benign, there is conflicting

Key Words

Ventricular premature contraction, PVC-induced cardiomyopathy, Tachycardia induced cardiomyopathy, Cardiac magnetic resonance.

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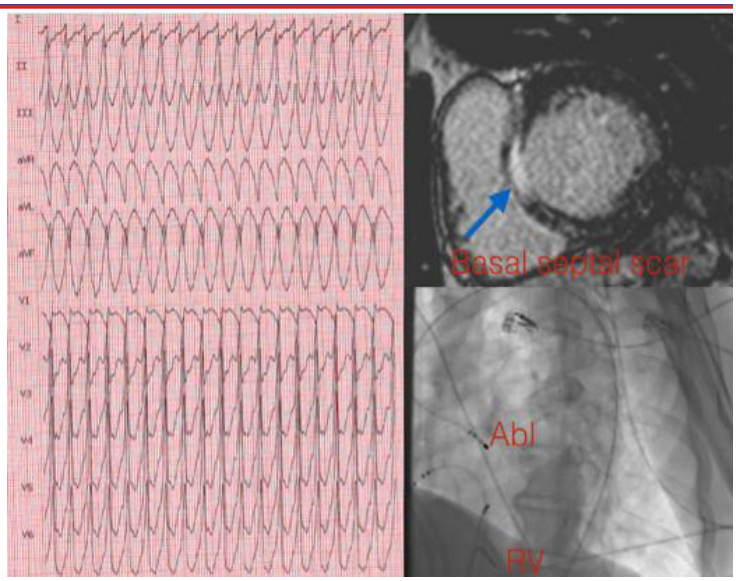
data suggesting that the presence of more than 30 PVCs per hour, PVC couplet, or the presence of R on T have been associated with a small absolute but statistically significant two-fold increase in mortality [9]. As frequent VPCs can be a part of a structural heart disease, and therefore frequent VPCs are a cause of cardiomyopathy. Discrimination of these two pathology is important, because their association with sudden cardiac death, and therapeutic options may be different. Primary LV cardiomyopathy in which LV scar is generally present, is associated with increased risk of sudden death and an ICD should be inserted, on the other hand systolic dysfunction caused by frequent PVCs may be reversible with catheter ablation.

Real prevalence of PVC CMP is unknown, due to challenges in the diagnosis of PVC CMP, which typically requires demonstration of the reversibility of the cardiomyopathy with suppression of PVCs. Among all patients with cardiomyopathy, those with PVC CMP likely constitute only a small percentage. In a community-based prospective study, 0.3% developed abnormal left ventricular ejection fraction (LVEF) over 5 years and the attributable risk of PVCs for congestive heart failure was estimated to be 8.1% [10]. High PVC burden increases the risk of PVC CMP. Baman et al. found that a PVC burden of ≥24% to have a sensitivity of 79% and a specificity of 78% for identifying patients with PVC CMP [11]. Other studies have found statistically discriminatory PVC burden thresholds of 16% (3) and 26% [12]. The clinical value of these proposed thresholds has not been further clarified, and a lower threshold may be desired to achieve a higher sensitivity when used to evaluate patients for potential treatment. A PVC burden of 10% or a PVC frequency of 10,000 PVCs/24h has been used as an inclusion criterion in a number of recent studies [12]-[14]. Besides frequency, there are several risk factors associated with PVC CMP development. The duration of the presence of frequent PVCs are linked to PVC CMP. The initial onset may occur sooner as PVC CMP in an experimental animal study was found after only 8 weeks of induced frequent PVCs [15]. Lack of palpitations, an epicardial origin of PVCs [16] and a longer PVC QRS duration [14] have been found to be predictors for the presence of PVC CMP. The PVC burden required to develop PVC CMP has been found to be lower in patients with QRS duration ≥ 150 ms [17].

Pathophysiology of PVC CMP is not fully described. PVC may be associated with increased wall stress, which may lead to LV remodeling and dysfunction. The increased wall stress may come from two different features associated with PVCs. Firstly, the propagation of the depolarization wave occurs independently of the conduction system and leads to a slower and dyssynchronous activation of the individual wall segments. Secondly, the abnormal coupling interval of PVCs may be followed by a compensatory pause, which leads to increased filling pressure from the long diastolic period. At the cellular level, in a canine model of PVC CMP, the calcium current, ICaL, the rapid component of delayed rectifier potassium current, IKr, and the inward rectifier potassium current, IK1, have been found to be decreased [18],[19]. Histological studies in PVC CMP model of canine myocardium showed no histopathologic abnormalities such as inflammation, fibrosis, increased apoptosis, or abnormal mitochondrial oxidative phosphorylation [20]. Fibrosis and scar deposition represents irreversible myocardial damage and generally consistent with underlying cardiomyopathic process. Imaging of fibrotic tissue may be key diagnostic modality to identify reversibility of systolic dysfunction after suppression of PVCs.



CMR imaging is able to visualize myocardial pathologies. LGE-MRI can identify scar in the LV. In this technique the signal of normal tissue is nulled and represented with black color. Due to delayed contrast enhancement scar tissue becomes bright. Scar size measurements typically based on signal intensity distribution, and the ratio of white to black regions. Therefore, delayed enhancement is only able to visualize localized scar not diffuse fibrosis.

Myocardial scar identified by CMR is associated with irreversible injury. Hasdemir et al [8]. investigated the prevalence of scar in patients with PVC CMP. They studied 298 consecutive patients with frequent PVCs and VT. Twenty-seven (9.1%) patients found to have LVEF ≤50% and diagnosed as presumptive PVC CMP. Improvement in LVEF after effective treatment of index ventricular arrhythmia was observed in 22 of 27 patients (PVC CMP group; mean PVC burden of 30.8 ± 9.9%). LVEF did not improve in five of 27 patients (primary cardiomyopathy group; mean PVC burden of 28.8 ± 10.1%). LGE-cardiac magnetic resonance (CMR) imaging was performed in 19 of 22 patients with PVC CMP and one patient (5%) had LGE. All five patients with primary cardiomyopathy underwent LGE-CMR imaging and four patients (80%) had LGE. Different studies have demonstrated that the prevalence of LGE range from 30% to 70%, in patients with different types of cardiomyopathy. For nonischemic cardiomyopathies, the type of LGE patterns are varied, including midwall patchy hyperenhancement, epicardial involvement, or global subendocardial enhancement aids in the diagnosis. They concluded that the presence of localized scar in those patients affects prognosis and can be used as a predictor of increased cardiac events. In patients with presumptive PVC CMP absence of LGE is a rule, and LGE CMR may have a role in the differentiation of PVC CMP from primary cardiomyopathies and in predicting the improvement of left ventricular function. In our case presence of basal septal located scar was considered as arrhythmic substrate of primary nonischemic cardiomyopathy.

Main goal of the treatment of PVC CMP is of suppression of PVCs pharmacologically or by catheter ablation. The initial treatment of frequent PVC, particularly with concurrent cardiomyopathy, is frequently beta-blockers, which is also part of guideline therapy for cardiomyopathies [21]. In patients with no more than mild LV dysfunction and absence of clinical heart failure, a non-dihydropyridine calcium channel blocker is a reasonable

alternative that traditionally has been associated with good response to arrhythmias of outflow tract arrhythmia. Efficacy of beta-blockers and calcium channel blockers in suppression of PVCs are 10% and 15% respectively [22]. Class I and III antiarrhythmic drugs are more effective than beta-blockers and calcium-channel blockers. Among class I antiarrhythmics, flecainide and propafenone reduced PVC counts by 83% and 73%, respectively. The class III antiarrhythmic sotalol reduced PVC count by 70%. Highest efficacy was found for amiodarone with a reduction of PVC count by 84%. Despite the higher efficacy, use of antiarrhythmics are restricted due to potential side effects. Catheter ablation has emerged as an efficacious treatment option in the elimination of frequent PVCs. In a number of case series, acute success rate has been greater than 80-90% and long-term success has been greater than 80%. Reversal of LV dysfunction has been reported in more than 70% of patients in selected patient populations [18].

Although studies with catheter ablation have shown higher proportion of patients with PVC suppression and improvement of LV systolic function compared to studies with antiarrhythmic therapy, there are only very limited number of studies comparing the two treatment modalities directly. Two large studies have compared catheter ablation with antiarrhythmic drug therapy directly. In a randomized study, catheter ablation was associated with a significantly lower rate of PVC recurrence compared to antiarrhythmic therapy with either propafenone or metoprolol (19.4% vs. 88.6%) in patients with frequent PVCs from the RVOT [23]. The study was not designed to conclude whether there was a difference in the effect on patients with PVC CMP. The other study was non-randomized and catheter ablation was associated with a two-fold higher proportion of patients achieving normalization of LV systolic function compared with antiarrhythmic therapy only (47% vs. 21%) in patients with frequent PVCs [24]. After catheter ablation, LVEF improved by 13% in patients who achieved normalization of LV systolic function. Also, catheter ablation was associated with greater reduction in PVC frequency than antiarrhythmic therapy (94% vs. 49%). However, the patients in the antiarrhythmic group received a wide-variety of antiarrhythmic drugs. Also, relatively more patients with outflow tract PVCs were treated with ablation, confounding the results. The effect of the best available antiarrhythmic therapy may have been underestimated.

Although underlying pathology of PVC CMP is unclear, short-term animal experiments do not support a role for fibrosis [20], the study on PVC CMP by using electroanatomical mapping system showed a leftward shift in the unipolar voltage, but not in bipolar voltage distribution [25]. Bipolar voltage shows local events, where as unipolar mapping has wider field of view [26]. In the study of Tanaka and co-workers associated leftward shift in unipolar voltage distribution with diffuse interstitial fibrosis. CMR quantitation of global and regional interstitial fibrosis has recently become possible with the development of novel contrast-enhanced T1 mapping techniques. In this study, CMR data with T1 mapping was not available. Identification of diffuse fibrosis by T1 mapping in patients with PVC CMP has not been investigated yet. Diffuse fibrosis may be a reason for inadequate reversal of LV function after VPC ablation in some patients. Prevalence of diffuse fibrosis identified by T1 mapping and its relationship between reversibility after ablation should be an interest of future studies.

Although improvement in LVEF after PVC ablation was initially described in patients with suspected PVC-induced cardiomyopathy, a recent study showed a comparable benefit in patients with previously diagnosed cardiomyopathy and therefore considered to have a "PVC-worsened" cardiomyopathy [27]. El Kadiri M et al. investigated the impact of frequent VPCs on nonischemic cardiomyopathy. In this study all patients who underwent CMR imaging were found to have LGE suggesting a disease process other than PVC CMP. Successful ablation was found to improve LV function, but did not always normalize the EF [28].

Penela D, et al. assessed whether ablation might remove primary prevention implantable cardioverter-defibrillator (PP-ICD) indication in patients with frequent PVC. Sixty-six consecutive patients with PP-ICD indication and frequent PVC (17% ischemic heart disease) underwent PVC ablation. ICD was withheld and indication was re-evaluated at 6 and 12 months. LVEF progressively improved from 28±4% at baseline to 42±12% at 12 months ($p<0.001$). NYHA class improved from 2 (3%) patients with NYHA-1 at baseline to 35 (53%) at 12 months ($p<0.001$). The PP-ICD indication was removed from 42 (64%) patients during follow-up, 38 (92%) of them at 6 months, showing an independent association with baseline PVC burden and successful sustained ablation (SSA). In patients with SSA, a cut-off value of 13% PVC burden had 100% sensitivity and 93% specificity (AUC 99%) for removing ICD indication post-ablation. No sudden cardiac deaths or malignant ventricular arrhythmias were observed in this study. They concluded that in patients with frequent PVC and PP-ICD indication, ablation improves LVEF and in most cases allows removal of the indication [29]. CMR data of these patients is not available, CMR would be beneficial in selecting candidates in whom ICD indication would be removed. In addition to this, removal of ICD indication in two thirds of the patients seems to be high. Removal of the indication of ICD decision should be evaluated carefully, it should be kept in mind that late sudden cardiac death has been reported after apparent regression of tachycardia induced cardiomyopathy [30]. Larger randomized studies with CMR imaging are needed to identify patients whose ICD indication could be removed.

In our case, presence of localized basal septal scar and detection of earliest activation during VT on concomitant low voltage area supported the diagnosis of substrate related VT and primary LV cardiomyopathy. Despite ICD implantation for primary prevention in patients is seriously questioned in NICM after DANISH trial [31], we considered our patient as a high risk individual with more than 5% scar in LV myocardium [32]. Present case highlights the importance of scar imaging by CMR, a potentially useful technique for discrimination of these two entities.

Primary LV cardiomyopathy in which LV scar is generally present, is associated with increased risk of sudden death and an ICD should be inserted » this assumtion is no more valid since primary prevention ICD implantation is seriously questioned in non ischemic CM (see DANISH trial) and is only debatable in case of EF < 35%.

Conclusions

VPCs are commonly seen in general population. Identification of individuals who are at high risk of cardiomyopathy development is important. Furthermore, suppression of VPCs can improve LV ejection fraction in patients with depressed systolic function after catheter ablation. Presence of myocardial scar seen by CMR may identify patients who have irreversible primary cardiomyopathy and may not benefit from ablation therapy.

Conflict Of Interests

None.

Disclosures

None.

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The Role of Implantable Cardiac Monitors in Atrial Fibrillation Management

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Abstract

Continuous heart rhythm monitoring using implantable cardiac monitors (ICMs) for atrial fibrillation (AF) management is steadily increasing in current clinical practice, even in the absence of an established indication provided by international guidelines. The increasing use of such devices is mainly associated with recent technological improvements including miniaturization, easier implant procedures, and remote monitoring, all of which make this strategy continuously more appealing and promising. For these and other reasons, ICMs have been proven to be a safe and highly effective tool for detecting AF episodes. However, ICMs are not the best option for every patient, as limitations exist. Therefore, it is imperative to weigh the possible benefits against the potential limitations of using these devices when deciding individualized patient care.

Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia, and it is associated with a reduced quality of life and an increased number of adverse outcomes such as stroke, heart failure, increased number of hospitalizations, and mortality[1]-[4]. Therefore, an early diagnosis of this arrhythmia is crucial in order to adopt the most appropriate treatment strategy. Cardiac implantable electronic devices (CIEDs) and implantable cardiac monitors (ICMs) seem to be a very effective tool to achieve this objective, rather than intermittent monitoring[5]-[9]. In fact, the use of ICMs is continuously growing in everyday clinical practice, together with recent technological improvements including miniaturization, easier implant procedures, and remote monitoring. However, due to the lack of sufficient trial-based evidence[6], AF is currently not considered an established indication for ICM adoption.

The aim of this review is first to evaluate and potentially expand the contemporary role of ICMs in clinical AF management and then to describe the technical issues eventually affecting the efficacy of this monitoring system.

Rhythm monitoring in AF patients

The rate control therapy for AF management does not require any sophisticated tools to monitor its efficacy. In contrast, ECG monitoring is needed when "rhythm control" approach is applied. However, an accurate detection and quantification of AF episodes might be very challenging. It is well established that there is a poor correlation between symptoms and arrhythmic events in AF patients[6]. Also, silent AF frequently occurs, as a high incidence of episodes without any symptoms has been detected using CIEDs[7],[8]. The TRENDS trial was a prospective, multicenter observational study that enrolled 2486 patients after CIED implantation (pacemakers or defibrillators with an implanted atrial lead). Subclinical (asymptomatic) atrial tachyarrhythmias (TAs) were diagnosed in 45% of 1988 patients without a documented history of prior AF[7].

In the ASSERT trial there was a substantial incidence of subclinical AFs in a cohort of 2580 patients without previous evidence of AF and in whom there was implanted a pacemaker or implantable cardioverter defibrillator (ICD) containing an atrial lead. These arrhythmias were detected in 10.1% of the patients within the first 3 months after implantation and at least once in 34.7% of the patients during a mean follow-up period of 2.5 years[8].

While the prevalence of AF can be underestimated, especially in asymptomatic patients, its incidence can also be overestimated as some patients may incorrectly attribute extra beats or sinus tachycardia to AF. In patients with permanent pacemakers for brady-tachy syndrome, the sensitivity and positive predictive value of symptoms to detect AF were 19% and 21%, respectively[9]. Other confounding variables may be antiarrhythmic drugs and catheter ablation. Although catheter ablation may affect the progression of the disease by reducing the rate of relapses[10], it can also change the perception of arrhythmia recurrences. In particular, asymptomatic episodes may occur and significantly increase after catheter ablation[11],[12].

Heart rhythm monitoring can be performed with continuous or intermittent strategies. The continuous approach is essentially based on implantable devices (pacemakers, ICD, ICM), whereas the

Key Words

Atrial fibrillation, Continuous monitoring, Implantable Cardiac Monitor, Loop recorder, Subcutaneous electrocardiogram.

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Table 1: Recommendations, advantages and limitations for the use of ICM in atrial fibrillation management

Indications for ICM use in AF management
Determination of the efficacy of rhythm control therapy
Assessment of freedom from AF after catheter ablation
Detection of AF in patients with cryptogenetic stroke
Advantages
Avoidance of unreliable subjective evaluation of the effect of any therapy
Overcoming the limits of intermittent AF monitoring system
Shortening of the time needed to obtain relevant information
Limitations
Lack of clinical evidence of the benefits of ICM to guide medical and device therapy
Presence of false positive arrhythmic episodes
Invasive procedure and risk of local complications

intermittent approach includes ECG, Holter (24h to 7 days) and event recorders. It is not surprising that studies have demonstrated that arrhythmia detection improves with increasing intensity of monitoring[13]. When compared with CIEDs, intermittent ECG monitoring demonstrated a significantly lower sensitivity (31–71%) and negative predictive value (21–39%) for identification of patients with any atrial TAs[13]. Charitos et al. reported similar results, using the rhythm histories from 647 patients with implanted devices[14]. For this reason, intermittent rhythm monitoring techniques are unreliable estimators of the true AF burden as well as subjective evaluation based upon putative symptoms. In this scenario, where the CIEDs are considered as the gold standard for AF monitoring, the ICM offers a valuable tool of continuous rhythm monitoring in patients without indication for permanent pacemaker or ICD.

Clinical Indications for ICM

AF detection for the Assessment of Arrhythmic Burden

According to current guidelines, one of the primary indications of AF catheter ablation is to reduce arrhythmia-related symptoms and to improve quality of life[5]. However, arrhythmia monitoring is an essential component of clinical trials aimed at assessing the outcomes of ablation procedures. In fact, silent AF was found to be associated with morbidity and mortality. Therefore, there is general agreement that continuous arrhythmia monitoring should be incorporated in all clinical trials designed to assess the efficacy of AF catheter ablation tools and techniques[5].

The ABACUS study compared the ICM to conventional monitoring (30-day transtelephonic monitors at discharge and after 5 months) in patients undergoing AF ablation, showing that ICM can detect more arrhythmias, despite the presence of false detections[10]. After AF ablation, 44 patients received ICMs and conventional monitoring. Over the first 6 months after ablation, conventional monitoring revealed AF in 7 patients (18%) and ICM confirmed AF in all of them. In an additional 11 patients (29%), no AF was seen by standard monitoring but was accurately detected by ICM[15]. Pedrote et al. estimated the AF burden before and after catheter ablation with an ICM, establishing the true efficacy of the technology. This study showed a complete freedom from AF after circumferential pulmonary vein isolation in 57% of patients and a significant worsening in AF burden in 17% of patients[16]. In a randomized trial by Pokushalov E. and colleagues, arrhythmia recurrences detected by ICM guided the decision for an early repeat catheter ablation, showing that patients with AF recurrences after index procedure are likely to benefit from a redo ablation, especially when AF is triggered by atrial premature contractions or atrial flutter/tachycardias (AFl, ATs)[17]. Continuous monitoring with ICM was also used in other studies after surgical AF ablation[18] and coronary artery bypass grafting (CABG)[19]. In both these studies, the ICM was considered an essential tool to correctly quantify the AF incidence. In addition, patients with typical AFl without documentation of AF episodes represent another cohort of interest. In fact, Mittal S and colleagues documented, using ICM monitoring, that 55% of AFl patients experienced AF episodes after cavo-tricuspid isthmus ablation during a mean follow-up of 382±218 days. This study proved the important role of ICM for long-term AF surveillance also in this subset population[20].

ICM-guided therapy

There is no evidence that ICM could guide the use of anticoagulant drugs, and discontinuation of oral anticoagulation (OAC) is not recommended in post-ablation patients with elevated $CHADS_2$ or CHA_2DS_2-VASc scores. However, patients undergoing AF ablation, particularly in younger cohorts, are usually highly motivated by the potential OAC interruption in case of procedural success. One possible way to minimize the risk of thromboembolism in these patients could be continuous rhythm monitoring[5]. A recent study by Zuern et al. showed that rhythm monitoring by ICM in patients

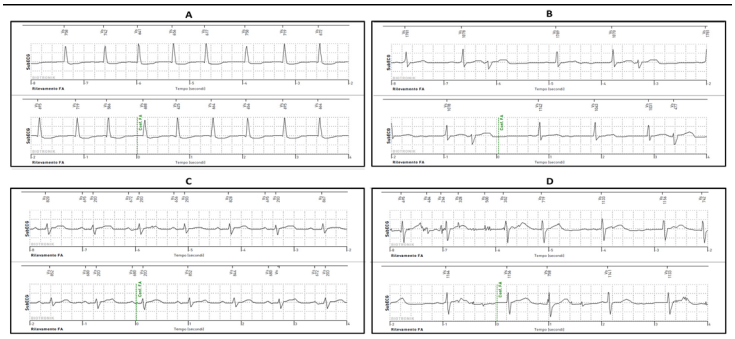

Figure 1: Examples of subcutaneous electrocardiogram (subECG) from ICMs identified as AF episodes by the automatic algorithm. 5 (A) True positive AF episode (B) False positive AF episode due to undersensing of premature ventricular contractions (C) False positive AF episode due to oversensing of P waves (D) False positive AF episode due to oversensing of noise. First-line ICM markers (black ticks); second-line ICM subECG; third-line time (seconds).

who have stopped OAC after catheter ablation of AF seems to be a safe and promising approach. The entire cohort of patients was composed by 63 individuals with a $CHADS_2$ score ranging between 1-3 undergoing ablation. At 1.3 years after ablation, about two-thirds of patients were off OAC in the absence of cerebrovascular events[21]. However, despite the promising and attractive results, the relatively small sample size and the short follow-up interval prevent one from drawing robust conclusions. Recently, the REACT.COM pilot study established the feasibility of ICM-guided intermittent anticoagulation with novel anticoagulants (NOAC) in patients with a low thromboembolic risk profile. After AF ablation, 59 patients with a mean $CHADS_2$ score of 1.3±0.5 underwent continuous rhythm assessment with ICM. Use of rapid onset novel oral anticoagulants (NOACs) allow for targeted anticoagulation only around an AF episode. Over 466±131 mean days of follow-up there were 35 AF episodes longer than 1 hour in 18 (31%) patients, resulting in a total time on NOAC of 1,472 days. This represents a 94% reduction in the time on NOAC compared to chronic anticoagulation. There

were three traumatic bleeds (all on aspirin), three potential transient ischemic attacks (all on aspirin with $CHADS_2$ score of 1), and no strokes or deaths[22]. A randomized trial of ICM-guided versus chronic NOAC (REACT-AF) is ongoing in a moderate-risk AF population with nonpermanent AF[22].

The use of ICM has class IIa indication in case of undocumented palpitations[6]. This statement is based on the results of the RUP study, in which 50 subjects with unexplained palpitations were randomly assigned to receive a ICM or a conventional monitoring strategy[23]. A diagnosis was obtained in 5 patients in the conventional strategy group, and in 19 subjects in the ICM group (21% vs. 73%, p < 0.001). Among all documented supraventricular tachycardias, AF was the most frequent finding with an incidence of 23% in the ICM group as compared to only 4% in the conventional group.

ICM in cryptogenic stroke patients

Cryptogenic stroke (CS), or brain infarction from an unknown cause, accounts for 20 to 40% of ischemic stroke[24]. AF can be the underlying cause of CSs, as recent trials have observed a significant relationship between device-detected atrial arrhythmias and stroke risk[7],[8]. Detection of silent AF is crucial, as it changes the standard of care from antiplatelet to anticoagulation therapy[25]. Two recent prospective randomized studies, CRYSTAL AF and EMBRACE, demonstrated that a marked improvement in AF detection yielded more comprehensive arrhythmia monitoring strategies compared to standard care in subjects with CS[26],[27]. In particular, the CRYSTAL AF trial used ICM in the continuous monitoring arm, detecting AF episodes in 12.4% of patients during a 12 month period of time as compared to 2% in the control group. Cumulative AF detection rates in the ICM arm increased progressively to 30% at 36 months[28]. Therefore, the benefit of an ICM strategy for the detection of AF in patients with CS is clear; the number of estimated ICMs necessary to detect a first episode of AF is 14 for 6 months of monitoring, 10 for 12 months, and 4 for 36 months[28]. In addition, a meta-analysis of three randomized controlled trials and 13 observational studies was published including 774 patients with ICM and 996 patients with wearable devices for a median duration of 365 days (range 50–569 days). Pooled odds ratio (OR) showed increased detection of AF with prolonged monitoring (OR 4.54, 95% confidence interval [CI] 2.92, 7.06; P < 0.00001) compared to not-implantable routine follow-up. There was a significantly higher AF detection with ICM (23.3%; CI: 13.83–32.29) compared to wearable devices (13.6%; CI: 7.91–19.32; P < 0.05)[29].

ICM-Related Technical Aspects

AF detection performance

The modern ICMs are equipped with an automatic algorithm for AF episodes detection. The arrhythmia detection algorithms are all based on the identification of QRS signals. The AF detection algorithm analyses the stability of the R–R interval, based on the differences in consecutive pairs of QRS cycles. If the variability shows a predefined pattern, the heart rate is classified as AF. The corresponding episode snapshots are stored in the device memory. Additionally, ICM allows the quantification of the daily AF burden, defined as the percentage of time spent in AF. These detection algorithms have been extensively validated using continuous Holter monitoring as the gold standard. Sensitivity and specificity in detecting AF patients ranged from 96% to 100% and 67% to 86%, respectively. Sensitivity was lower when considering the detection of all AF episodes, ranging from 88% to 95% with positive predictive values around 70%[30]-[32]. Complete data are reported in table 2. Despite these positive results, nowadays, the most accurate method for assessing the true AF-burden is represented by CIEDs[33].

Recently, some solutions have been implemented to increase the AF detection performance of ICMs. Among them, an improved algorithm has been developed (Reveal LINQ, Medtronic Inc.) by checking the presence of P waves once the R-R variability exceeds the AF threshold. This algorithm aims to reduce the false positive episodes triggered by runs of atrial ectopies with irregular coupling intervals or sinus arrhythmia, and it was able to reduce inappropriate episodes and duration by 46% and 55%, respectively, compared to the original system[34]. Another solution has been implemented by a different manufacturer (BIOTRONIK SE&Co) in order to reduce false positive episodes caused by the instability between adjacent cycles for ectopic beats. This improved "geminy" algorithm checks not only the immediate adjacent intervals but also every second (bigeminy), third (trigeminy) and fourth (quadrigeminy) interval for periodicity. If such a periodicity is found, AF detection is suspended.

Clinical data are lacking regarding the ICM performance focusing on P wave detection and signal. Currently available devices do not automatically report this information, but the possibility to have visual evidence of the P wave in the sub-ECG snapshot is a real adjunctive value. Improving filtering and amplification of atrial signal frequencies might be possible, as demonstrated by research analysis[35].

ICM Pitfalls

One of the main problems regarding the use of ICMs is the inability to obtain a clear and accurate signal during sub-cutaneous ECG (subECG) monitoring. Artifacts are often present and can hamper the clinical value of these devices, leading to frequent non-diagnostic interrogations. A QRS or R wave undersensing and oversensing may reflect false asystole and false high ventricular rate episodes, respectively[36],[37]. This issue can also interfere with the AF detection performance due to a false high RR variability. The most important action to avoid such a problem is based upon the implantation technique (choosing the implantation site, creating a tight subcutaneous pocket) in order to achieve a higher and more stable R wave sensing. The devices have a dynamic sensing threshold, which is automatically adjusted after each sensed R wave. Higher amplitudes of sensed R waves means higher chances to avoid oversensing of P waves, T waves and noise, while ensuring a reliable

Table 2: Atrial fibrillation detection performance of ICM

	Hindricks G. et al.[30] (Reveal XT, Medtronic)	Ciconte G. et al.[31] (BioMonitor, Biotronik SE&Co.)	Nolker G. et al.[32] (Confirm DM2102, St. Jude Medical)
Episode sensitivity	88.2%	95.4%	94.0%
Episode specificity	-	-	96.7%
Episode positive predictive value	73.5%	76.3%	59.1%
Episode negative predictive value	-	-	88.3%
Subject sensitivity	96.1%	100%	100%
Subject specificity	85.4%	67.0%	85.7%
Subject positive predictive value	79.3%	83.0%	64.0%
Subject negative predictive value	97.4%	100%	100%

sensing of the next R wave. Additionally, it can allow for faster sensing thresholds decreases to avoid R wave undersensing, as the ICM signal is usually affected by intrinsic beat-to-beat amplitude variability. Examples of true and false positive AF episodes are shown in [Figure 1].

When dealing with sub-ECG technology, one should always be aware that atrial arrhythmias with regular ventricular response would be probably missed, as they do not exceed the irregularity threshold of the AF algorithm. These episodes might be detected by lowering the threshold for high ventricular rate episodes, but this is not always possible as it may increase the number of false positive events, especially in younger patients.

Another pitfall might be the storage capacity of every ICM device, as the presence of many false episodes might reduce the diagnostic accuracy, because such events may be overwritten due to memory limitation[37]. Newer ICMs, with daily remote monitoring, can overcome this issue, providing the possibility of daily and automatic data transmission, allowing full availability of all episodes in the remote archive, even when the events number exceeds the nominal storing capacity.

Finally, even if the ICM implantation is a minimally invasive procedure, it might carry a risk of minor complications requiring extraction, such as insertion site pain, minor bleeding, and wound infection. The small size of the new devices and the lack of device fixation with sutures also make spontaneous ICM migration along the tissue plane over the chest, axilla, or abdomen plausible, leading to possible loss of signal or difficulties during the next explant procedure. The lack of device fixation is particularly a problem for patients with generous sub-cutaneous fat, in whom a potential ICM migration may lead to a lower signal quality in the follow-up as compared to the one recorded at the time of the implant. However, the incidence of such events appears to be very low, being reported in roughly 1% of the cases[38].

Implantation Considerations

The implantation procedure of injectable or insertable new generation devices has become easier and faster as compared to the implantation of older devices. All systems include an implantation kit and minimal skin opening is needed to execute the subcutaneous device insertion. The typical implant location for an ICM is the left parasternal area of the chest over the fourth-fifth intercostal space. An example is reported in [Figure 2]. There are two recommended inclinations: device parallel to the sternum and device at a 45° angle to the sternum. This second position should be parallel to both ventricular and atrial depolarization vector and, therefore, should maximize the signal of the ICM [Figure 3]. Because the surgical scar in the anterior chest region may have aesthetic implications, especially in younger patients, a transaxillary approach has also been proposed, which provides a more cosmetic implant where the wound is hidden in the left axillary region[39]. A recent study reported that injectable ICMs are usually implanted with an incision site prepared with Betadine or Chlorhexidine. Device fixation is usually not performed and periprocedural antibiotics are used in roughly half of the cases. The wound closure method is usually suture or adhesive strips[38].

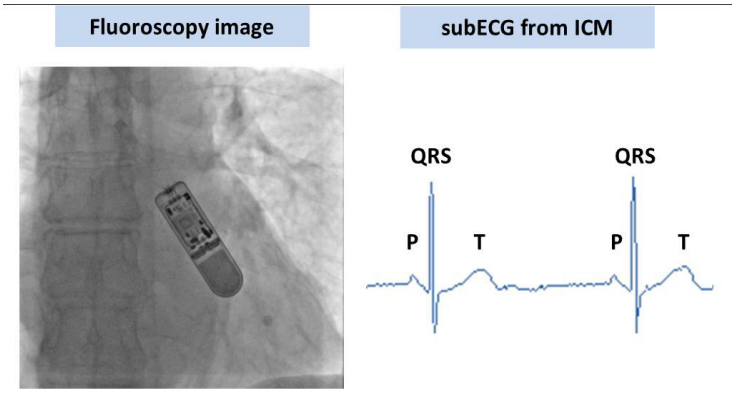

Figure 2: Example of ICM implantation with the corresponding final fluoroscopy image and the subcutaneous electrocardiogram (subECG) detected by the device.

Although the procedure is minimally invasive, the feasibility and safety of insertion outside the traditional electrophysiology laboratory has not been deeply investigated. There is only one non-randomized single-center study comparing ICM implantation between the electrophysiology laboratory and a procedure room. There were only 1.7% of overall complications without any significant difference between the two environments[40]. Moreover, an increased risk of complications with the new injectable ICM compared to its predecessor has been reported to be due to the use of the implantation kit and to the lack of suture for the incision[41]. Additionally, a recent case report described a spontaneous external device migration of the new generation device due to the slim profile and the lack of secure skin closure[42]. These data highlight that, despite the easy implant technique, the ICM procedure has to be performed rigorously in order to avoid potential complications.

Finally, one should consider complications arising from the device explant. In fact, the extraction is not always as simple as the implantation procedure, since it may have some drawbacks with the new miniaturized injectable ICMs. First, again in patients with generous subcutaneous fat tissue, it could be difficult to identify the exact device location, and a chest radiograph could become necessary to identify the correct position and avoid multiple incisions[42]. In addition, the skin wound, at the time of the extraction, may be larger as compared to the one performed for the implantation, raising an esthetic issue, particularly in women.

Remote Monitoring

The new-generation ICMs are equipped with remote monitoring (RM) technology. The devices are able to transmit daily diagnostic data and arrhythmic episode snapshots through a wireless receiver without any active patient or physician interaction. Therefore, these transmissions can be reviewed by the hospital staff, who are automatically advised in case of predefined clinical alerts. There are two main advantages related to this technology: (i) avoidance of frequent in-hospital visits scheduled to reduce the risk of loss of information due to device memory overflow, (ii) shortening of the time needed to obtain relevant information and to take appropriate therapeutic action. Although RM has already been proven to be effective in the follow-up of patients with pacemaker or ICD[43], there are few published data regarding ICM. Furukawa and colleagues showed that when RM was used in patients with unexplained syncope, the mean time from ICM implantation to the diagnosis was 28±49 days, which was 71+17 days less than in the clinical practice of 3-monthly in-office follow-up examinations. In addition, RM was well accepted by patients and avoided a 45% of memory saturations which would have occurred without it[44]. A significant reduction in the mean time from implant to diagnosis was also confirmed in a study of

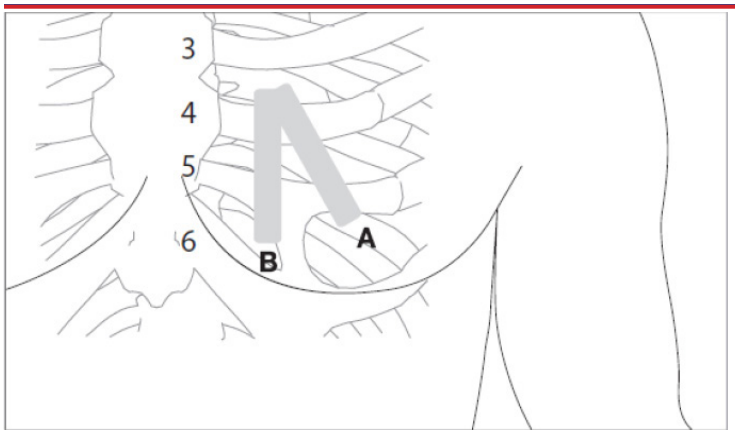

Figure 3: The typical location of an ICM is in the left parasternal area of the chest over the fourth-fifth intercostal space. There are two recommended inclinations: device parallel to the sternum (B) and device at a 45° angle to the sternum (A).

109 patients implanted with ICM for syncope using RM [260 days (range, 5-947 days) vs 56 days (range, 0-650 days)][45]. To date, to the best of our knowledge, there is only a single report regarding RM of ICM for AF reporting promising results. A single center pilot study involving 186 patients suffering from AF demonstrated that 26% of the patients had a clinical intervention triggered by remote transmissions with a mean follow-up of 6 months. All the clinical interventions were performed within 24 hours after the remote alert. The most common response was a change in therapy [46]. In addition, RM may be a useful tool for identifying patients with frequent false positive alerts, allowing immediate corrective actions (i.e. reprogramming the ICM, modifying the predefined RM alerts). However, it should be noted that the RM of ICM generates a higher number of alerts compared with other implantable devices that will need to be reviewed, resulting in a consequent higher workload for the hospital staff[47].

Conclusions

In current clinical practice, the use of ICMs is considered a safe and highly effective tool for detecting episodes of AF. Recent technological improvements, including miniaturization, easier implant procedures, and remote monitoring, make this strategy appealing and promising in the real world management of AF patients, leading to a more extensive adoption by expanding the current indications. In the future, the next-generation ICMs may be also integrated with smartphones allowing self-monitoring with a handheld electrocardiogram[48].

However, improvements regarding automatic algorithm are still required for ameliorating AT/AF detection, which may significantly reduce the misdetection rate without affecting device sensitivity. A reliable P wave detection might also be crucial to reach this objective.

There are still some „grey-zones“ in which the use of such devices could also be useful. In fact, patients with a history of non-persistent AF and intermediate to low thromboembolic risk might benefit from an ICM-guided pharmacological therapy according to the effective AF burden. This approach might prevent the adverse events risk related to both antiarrhythmic and anticoagulant therapy.

Finally, the recent technological improvements do not necessary imply a step forward, as the signal quality of a sub-ECG may be affected by patient-specific features. For this reason, this technology may not represent the best option for every patient. Therefore, it is imperative to weigh the possible benefits against the potential limitations when deciding individualized patient care and especially when dealing with a more extensive adoption of these devices.

Conflict Of Interests

None.

Disclosures

GC and CP have nothing to disclose. DG is employee of Biotronik Italia.

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Leadless Pacemakers – Implant, Explant and Long-Term Safety and Efficacy Data

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Abstract

Implantable cardiac pacemakers have seen remarkable progress in the last sixty years and remained as cornerstone therapy for symptomatic bradycardia. Despite this progress the current day traditional transvenous implanted pacemaker systems are limited by the need for a surgically created pocket for the generator, indwelling leads in the vascular system and lastly passage through the tricuspid valve. A majority of the implant and explant related complications are due to the surgical pocket and indwelling leads. Leadless pacemakers represent a major leap in technology and emerged as an alternative to traditional systems promises to eliminate lead and pocket associated complications. As with any disruptive technology, some questions remain unanswered with the leadless pacing systems, specifically longevity and end of life management for the device. Despite the unknowns, as the technology progresses, it is possible that pacing leads will become extinct and pacemakers will miniaturize even further. This review summarizes the available technology, implant and explant details, and long-term safety and efficacy data for leadless pacemakers.

Introduction

"When Henry Ford made cheap, reliable cars people said, 'Nah, what's wrong with a horse?' That was a huge bet he made, and it worked" - Elon Musk

Initial interest for cardiac pacing was reported in the 1930s with Hyman's "artificial pacemaker" (his term), in which a hand crank created an electric current that drove a DC generator directing electrical impulses to the patient's right atrium through a needle electrode placed through intercostal space. At that time, due to perceived disruptive nature of this approach Hyman faced professional skepticism, litigation, and accusations of creating "an infernal machine that interferes with the will of God".[1]

Cardiac implantable electrical devices have seen remarkable progress in the last sixty years. Since the first entirely implantable pacemaker performed in 1958, major advancements in design, complexity and battery longevity made implantable pacemaker therapy a very acceptable option and have benefited millions of patients around the world. Despite these improvements the current day traditional transvenous implanted pacemaker systems are limited by the need for a surgically created pocket for the generator, indwelling leads in the vascular system and lastly passage through the tricuspid valve.

Key Words

Leadless pacemaker, Cardiac device, Percutaneous delivery, Cardiac implant, Pacemaker.

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The pocket is associated with risk of hematoma and infection with initial implant and every generator replacement. The intravascular leads pose a risk of access site complications, venous thrombosis and occlusion, lead malfunction, and infection often necessitating entire system extraction. [2], [3] Passage of right ventricular lead through the tricuspid valve is associated with risk of valve dysfunction and regurgitation that may result in symptomatic right heart failure requiring repair.[4] The leads are inherently thrombogenic, eliciting fibrotic reactions that make removal technically challenging, with a risk of venous perforation, valve disruption, hemothorax, and death. [5] The leadless pacing system was developed to overcome these limitations, and represents a major leap in technology that allows a completely intracardiac implant. The introduction of "leadless" pacing systems as an alternative to traditional systems promises to eliminate lead and pocket associated complications.

Technology

To date, two leadless pacing systems have been introduced. The NanostimTM leadless cardiac pacemaker-LCP [Figure 1] (St. Jude Medical, Sylmar, CA, USA) (currently on voluntary hold due to a battery advisory) and the MicraTM transcatheter pacing system – TPS (Medtronic, Minneapolis, MN, USA)[Figure 1].

Both devices are completely contained single units with battery and circuit material contained in a small metallic unit with bipolar sensing and pacing electrodes. Each of these devices has a fixation mechanism mounted at the distal end and a docking mechanism to deliver and retrieve the device built at the proximal end [Figure 1]. A steroid eluting electrode is present at the distal end independent of the fixation components. Comparative details on the devices are listed in [Table 1]. LCP utilizes a screw-in helix based active fixation and a secondary fixation mechanism with tines compared

Table 1: Leadless pacemaker device comparison. [13, 14]

Parameter	Nanostim (LCP)	Micra (TPS)
Length (mm)	42	25.9
Diameter (mm)	5.99	6.7
Volume (cm3)	1	0.8
Weight (gram)	2	2
Power source	high-density lithium carbon monofluoride battery	Lithium silver vanadium oxide/carbon monofluoride
Energy capacity	248	120
Battery longevity (years)	9.8 100%/2.5 V/0.4 msec/60b.p.m.	10 100%/1.5 V/0.24 msec/60 b.p.m.
Delivery sheath size	18F	27F
Fixation	Screw-in helix and 3 nitinol tines	Four self-expanding nitinol tines
Pacing Mode	VVI/VVIR	VVI/VVIR
Rate response	Blood temperature	Programmable 3-axis Accelerometer
Communication/ Telemetry	Conductive communication	Radiofrequency
Capture management	No	Yes

to TPS which used selfexpanding nitinol tines. LCP has a high-density lithium carbon mono fluoride battery with 248 mAh energy capacity compared to TPS which uses Lithium silver vanadium oxide/carbon mono fluoride with 120 mAh energy capacity. TPS has capture management feature to support battery efficiency. Both devices operate in a single chamber mode (VVI/VVIR) and have rate response feature, LCP utilizing blood temperature and TPS using a 3 – axis accelerometer. LCP uses conductive communication through the skin leads connected to the programmer, using 250 KHz sub-threshold pulses encoded with data, delivered during the ventricular refractory period. This supports energy saving compared to a standard radiofrequency communication used in TPS system and traditional pacemakers.

Implant

Indications

Currently, available leadless devices design only allows single chamber operation with VVI/ VVIR modes. The most common indication is atrial fibrillation with the atrioventricular (AV) block. Other indications are sinus bradycardia with infrequent pauses and sinus rhythm with AV block in patients with low level of physical

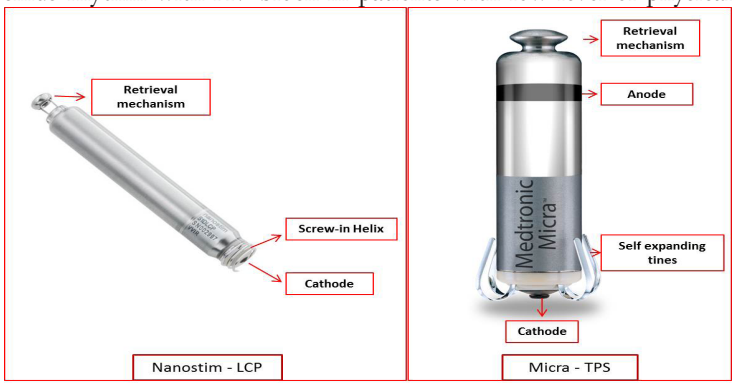

Figure 1: The Nanostim™ leadless cardiac pacemaker -LCP (St. Jude Medical, Sylmar, CA, USA) on the left image. Modified with permission from Abott/ St. Jude. Micra™ transcatheter pacing system – TPS (Medtronic, Minneapolis, MN, USA) on the right of the image. Modified with permission from Medtronic, Minneapolis, MN, USA.

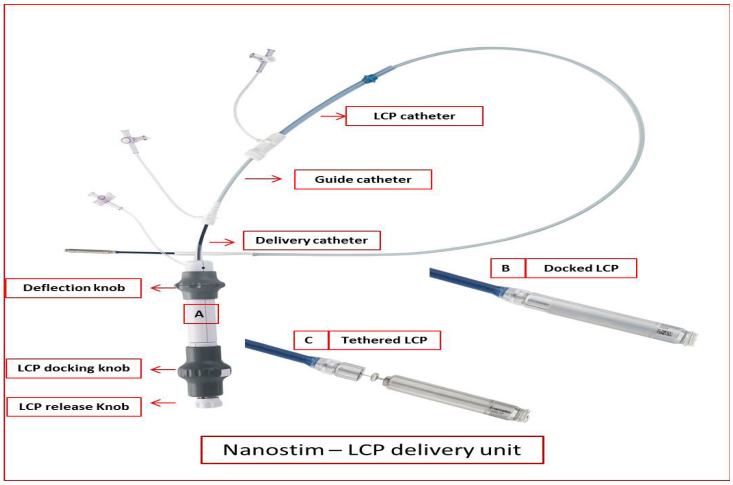

Figure 2: LCP delivery system. 3A shows delivery catheter system with the LCP at the distal end. The proximal handle has the features to adjust the deflection of the catheter and release the device after fixation. 3B shows LCP docked with the catheter. 3C shows LCP undocked, but tethered during which tug test can be performed to assess stability. Modified with permission from Abott/ St. Jude.

activity or shortened life span. In addition, for patients with a history of prior device infections and poor subclavian vascular access leadless pacing becomes attractive option compared to transvenous implantation. For young patients with and infrequent but compelling pacing indication, a leadless pacemaker may be considered, recognizing that optimal management at the time of battery depletion (extraction vs. abandonment) is not known.

Preparation prior to implantation

Prior to implantation it is important to confirm no contraindications exist for device implantation such as the presence of an interrupted IVC, IVC filter, mechanical tricuspid valve, morbidly obese that could lead to difficulty in communication with the device, intolerance to Nickel-Titanium (Nitinol) Alloy, allergy to dexamethasone acetate, another implanted device that can interfere with functioning of the

Table 2: Leadless pacemaker implantation – Efficacy outcomes [9, 11]

	Nanostim (LCP)	Micra (TPS)
Implant success (%)	95.8	99.2
Pacing capture Threshold and sensing efficacy endpoint (%)	90.0 (≤2.0 V at a pulse width of 0.24 msec and an increase of ≤1.5 V from the time of implantation)	98.3 (≤2.0 V at 0.4 msec and sensing amplitude ≥5.0 mV, or a value ≥ value at implantation)
Threshold at implant	0.82 V @ 0.4	0.63 V @ 0.24
Threshold at 6 months	0.4 V @ 0.4	0.54 V @ 0.24
Sensing at 6 months	10.6 mV	15.3 mV

device (e.g. Neurostimulator), other intracardiac implants/ leads that could interfere with the leadless system.

Pre-procedural review of anesthesia, anticoagulation strategy for the procedure, ability to use contrast, fluoroscopy or ultrasound for visualization should be considered. Implant equipment including access sheath, deflectable delivery unit, and multiple flush lines should be confirmed. The strategy for hemostasis (manual compression versus suture-based closure) should be planned and necessary tools are available in advance.

Implantation technique

Both LCP and TPS are implanted via femoral venous access and catheter-based delivery system under fluoroscopic guidance. With a deflectable delivery sheath [Figure 2]-[Figure 3] the docked unit is

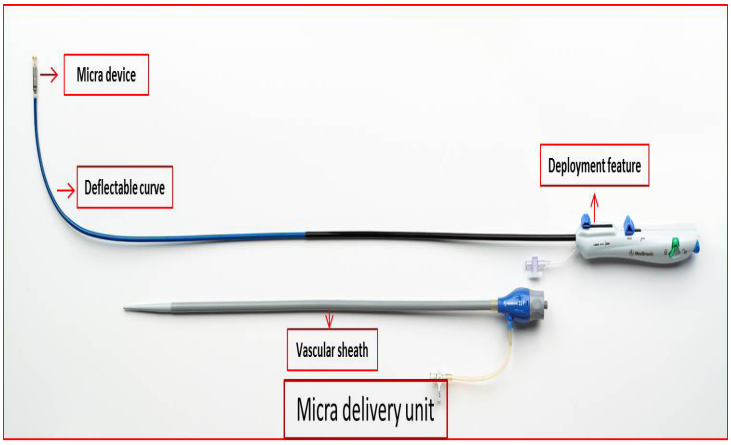

Figure 3: TPS delivery system. The lower part of the image shows the vascular access sheath. The deflectable catheter is introduced through the vascular sheath for delivery of the docked device. Modified from Medtronic, Minneapolis, MN, USA, permissions pending.

advanced from inferior vena cava to right atrium and then through the tricuspid valve into the right ventricle. Typically angiogram of the RV is performed to select the target site of implantation. LCP is implanted by the rotating the screw-in helix with the help of the chevron (marker) on the fluoroscopy for 1.25 turns. TPS has self-expanding nitinol tines that deploy after retracting the outer sheath over the device (Video 1). After fixation, the device is undocked for testing the sensitivity and capture threshold. If adequate functioning is not achieved then the device can be repositioned. After an adequate positioning, a tug test (video 2) is performed to assess the stability of the device and the released from the delivery system.

Post-implantation monitoring

Typically patients are monitored overnight for vital signs, access sites, hemostasis and telemetry monitoring. An EKG and telemetry serve for arrhythmia monitoring. Chest x-ray in two views can help confirm the stability of the device. A device interrogation post implant to confirm continued adequate functioning is appropriate. Patients will need access site care and restriction on activity until adequate healing.

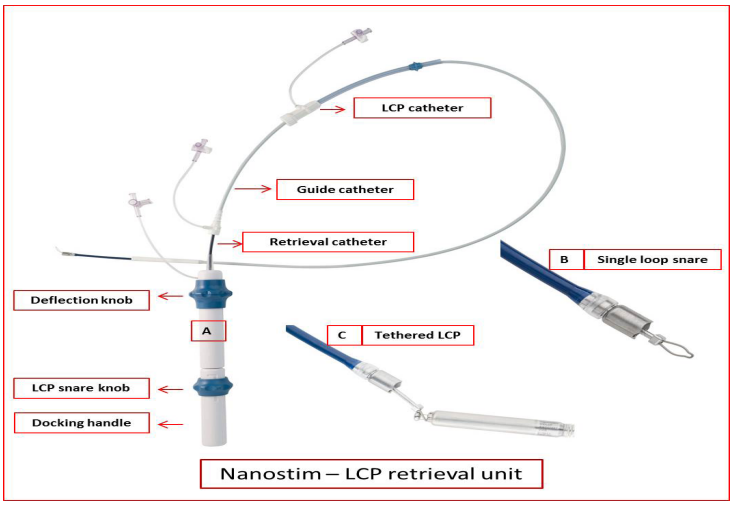

Figure 4: LCP retrieval. Figure A-D shows snare tool over the device to capture the docking knob. Figure E shows advancing the docking tool to fix with the device. Figure F shows deflectable sheath advanced over the device. Figure G shows unscrewing the device. Figure H-I show removal of the entire system for the right ventricle.

Table 3: Leadless pacemaker implantation – Safety outcomes [9, 11]

	Nanostim (N=526) (%)	Micra (n=729) (%)
Total events	6.5	4
Cardiac perforation	1.6	1.6
Vascular complication	1.2	0.7
Arrhythmia during device implantation	0.6	0
Cardiopulmonary arrest during implantation procedure	0.2	0
Device dislodgement	1.1	0
Device migration during implantation owing to inadequate fixation	0.4	0
Pacing threshold elevation with retrieval and implantation of new device	0.8	0.3
Pulmonary embolism	0.2	0.1

Explant

Indications

The benefit of explantation of leadless pacemaker should be weighed against risks associated with the procedure. Having experience with leadless pacemaker implantation and intravenous device explantation can help during the explantation of leadless system. Common reasons for removal of the device are elevated pacing threshold, change in pacing indication to a cardiac resynchronization or dual chamber pacing.[6] Other possible indications include frequent premature ventricular complexes or arrhythmia thought to be related to the device, infection and dislodgement/ migration.

A study [7] involving nine centers and 16 patients with LCP devices retrieved and showed 94% success rate in explantation without any 30-day complications. All 5/5 patients who had acute retrieval (< 6 weeks) had successful explant and 10/11 (91%) patients who had chronic retrieval (≥ 6 weeks (range, 88–1188 days) had successful explant. The indication for device removal in the acute retrieval group was an elevation in pacing threshold in 4 patients and need for an upgrade to a secondary prevention defibrillator in one patient. In chronic retrieval group, the indications included elevation in pacing threshold in 4/11 patients, right ventricular pacing-induced cardiomyopathy in 5/11, failure to pace in 1/11, and patient preference

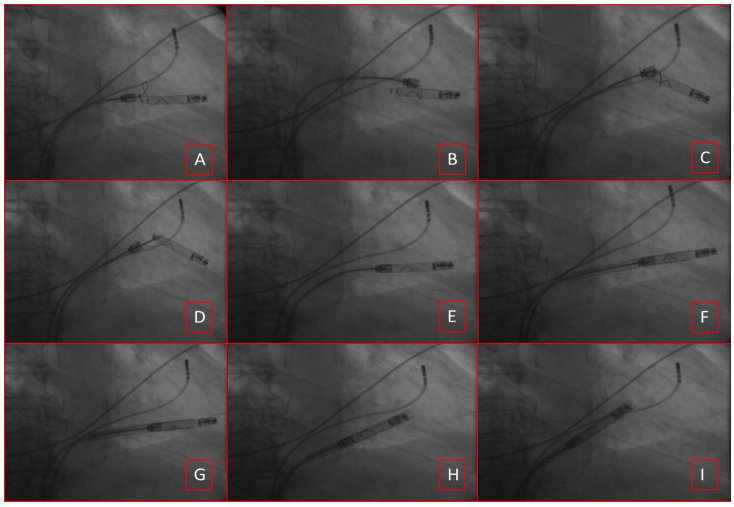

Figure 5: LCP retrieval system. 3A shows retrieval catheter system with single loop snare at the distal end. The proximal handle has the features to adjust the deflection of the catheter and snare the device and dock it. 3B shows a single loop snare. 3C shows LCP tethered with the snare. Modified with permission from Abott/ St. Jude.

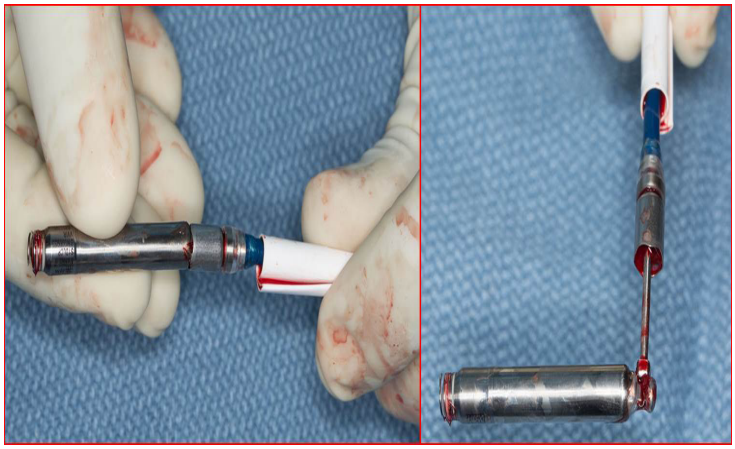

Figure 6: Explanted LCP device. Left side image shows docked explanted device. Right image shows snared device with docking tool removed.

in 1/11. Seven of the 11 patients had a new leadless device implanted. Experience with TPS retrieval is limited. After the initial day of implantation, there were six percutaneous attempts at removal listed [8]of which four were noted to be successful. A controlled report of the data on TPS retrieval is not available at this time.

Preparation prior to explanation

Prior to extraction of a leadless device, anticoagulation should be withheld and reversed if appropriate. In patients who are dependent upon pacing alternative pacing, support should be achieved either via a temporary or permanent means. Echocardiography (Intracardiac or transthoracic) can aid in retrieval process and also in the evaluation of pericardial effusion. An arterial access for adequate hemodynamic monitoring is reasonable. Retrieval of a leadless system requires femoral venous access, a deflectable retrieval sheath and snaring tools [Figure 4]. A Single- and tri loop retrieval catheters designed specifically for chronic LCP retrieval were available and can be utilized. TPS recommends standard retrieval tools (e.g. Amplatz Gooseneck® Snare Kit) that are available off the shelf. A plan to deal with pericardial effusion/tamponade should be in place prior to extraction. Depending upon the extent of injury the intervention can range from percutaneous pericardial drainage to surgical repair.

Explantation technique

A femoral venous access is obtained followed by insertion of the vascular sheath. A deflectable vascular sheath is inserted and advanced into the right atrium and then through the tricuspid valve into the right ventricle. Both devices have a knob-like structure on the proximal end that can be snared with the use of a snare. Once the LCP is docked it can then be rotated to unscrew the helix from the endocardium [Figure 5]. TPS has tine based fixation and thus once snared gentle pull in the axis of the device is performed to assess for removal. Once free the devices should be pulled back into the protective sleeve for removal from vascular space. Intracardiac imaging can be valuable in guiding extraction and assessment of effusion. Once extracted the device should be assessed for complete removal [Figure 6].

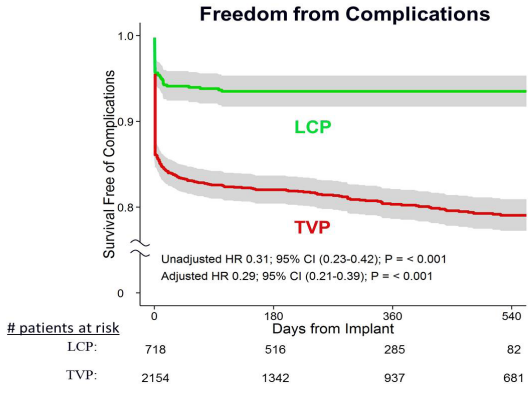

Figure 7: Freedom from complications from LCP device in comparison with matched controls who received transvenous pacing devices. Permissions pending.

Post explantation monitoring

Post explantation monitoring is similar to standard device explantation. Due to the vascular access patients will need 2-4 hours bed rest after hemostasis. Overnight monitoring for access site complications, vital signs, and telemetry for arrhythmia are appropriate. A post procedure x-ray to confirm all device components have been removed and evaluation for effusion is appropriate. Patients will need access site care and restriction on activity until adequate healing.

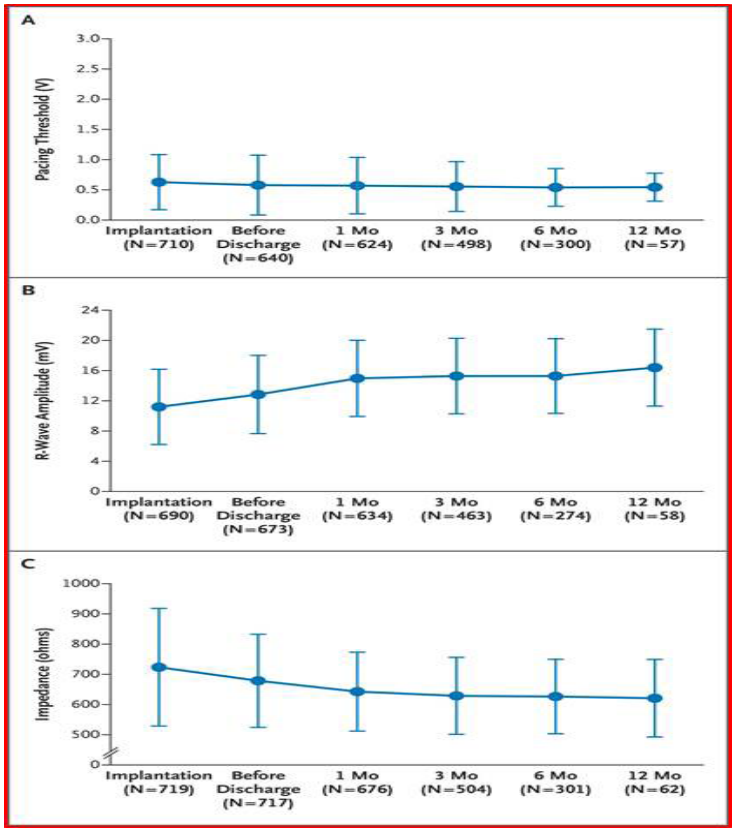

Figure 8: Electrical Performance Characteristics of the Transcatheter Pacemaker (TPS). Permissions pending.

Safety and Efficacy data

LCP system: The LEADLESS II trial [9], a prospective multicenter study, provided the initial safety and efficacy data for LCP device. The study used historical control group as a comparison. The primary efficacy end point was an acceptable pacing threshold (≤2.0 V at 0.4 msec) and acceptable sensing amplitude (R wave ≥5.0 mV, or a value equal to or greater than the value at implantation). The primary safety end point was freedom from device-related serious adverse events. Through a six month period primary safety endpoint was met in

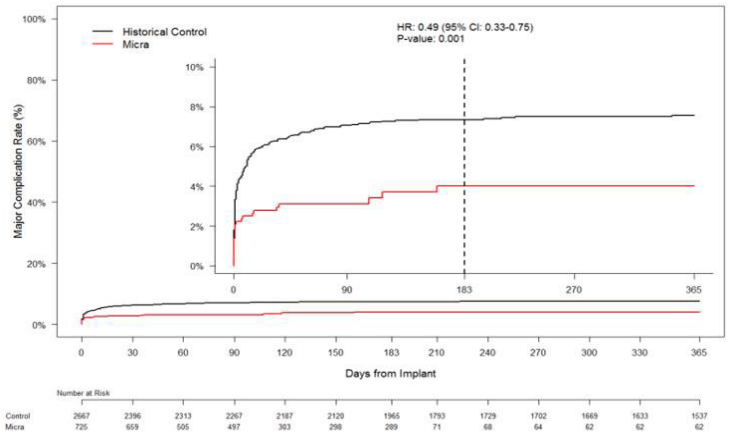

Figure 9: Major complications of Transcatheter Pacemaker (TPS) system in comparison with historical cohort who received transvenous pacing devices. Permissions pending.

270 of the 300 patients in the primary cohort (90.0%) and exceeded the pre-specified performance goal of 85% [Table 2]. The primary safety endpoint was met in 280 of the 300 patients at six months (93.3%) and exceeded the pre-specified goal of 86%. In the total cohort of 526 patients, device-related serious adverse events occurred in 6.5%, including cardiac perforation in 1.5% of the patients, device dislodgement in 1.1%, and device retrieval due to elevated pacing thresholds in 0.8%. All patients with device dislodgements had percutaneous retrieval. There were two deaths (0.4%) that were classified by the clinical events committee as procedure related [Table 3].

At one year follow-up of LEADLESS trial [10], there were no additional pacemaker-related adverse events reported. The mean pacing threshold at 6- and 12-month follow-up were, 0.40V and 0.43V at 0.4msec. R-wave amplitudes were 10.6mV and 10.3mV respectively. At the 12-month follow-up an adequate rate response was observed in all patients in whom it was activated. In comparison to matched controls, patients who received LCP device had a significantly improved freedom from complications (HR = 0.29 (0.21-0.39), p<0.001) [Figure 7]. Currently, the device implantation is on a voluntary hold from the company in a review of lost telemetry and pacing output in a very small proportion (<0.5%) of patients. No clinical consequences were reported due to this at present.

TPS system: Micra TPS study [11], a prospective multicenter study, provided the initial safety and efficacy data for TPS device. The primary efficacy end point was percentage of patients with low and stable pacing capture thresholds at 6 months (≤2.0 V at a pulse width of 0.24 msec and an increase of ≤1.5 V from the time of implantation). The primary safety end point was freedom from system-related or procedure related major complications. The primary efficacy end point was met in 292 of 297 patients in the primary cohort at six months (98.3%) and exceeded the prespecified performance goal of 80%. [Table 2] The primary safety endpoint was met in 96% patients and exceeded the prespecified goal of 83%.[8 In the total cohort of 725 patients, device-related serious adverse events occurred in 4%, including cardiac perforation in 1.6% of the patients, device dislodgement in none and device retrieval due to elevated pacing thresholds in 0.3% patients.

At one year follow up adequate device sensing and capture [Figure 8] was reported without any adverse events. In comparison to the historical controls who received transvenous devices, the study patients were older with more comorbidities. The Micra group had 51% fewer major complications, 54% fewer hospitalizations and 87% fewer system revisions (0.4% vs. 3.5%) due to complications compared to historic controls. [Figure 9] There are no reported cases of leadless system infections to date.[12]

Potential Limitations:

Currently available leadless device technology only allows single chamber operation and thus limits therapy only to a minority of patients. In patients with sinus rhythm requiring atrioventricular synchrony, dual chamber device therapy is more appropriate (P). Feasibility of multi-chamber operation with leadless pacemakers is yet to be seen. Utility of leadless pacemakers along with subcutaneous ICD and cardiac resynchronization therapy also needs to be studied.

The efficacy and safety seem acceptable in the midterm follow-up with leadless systems. The long-term effectiveness and overall battery longevity data in comparison to traditional pacemakers is currently not available and remains to be evaluated.

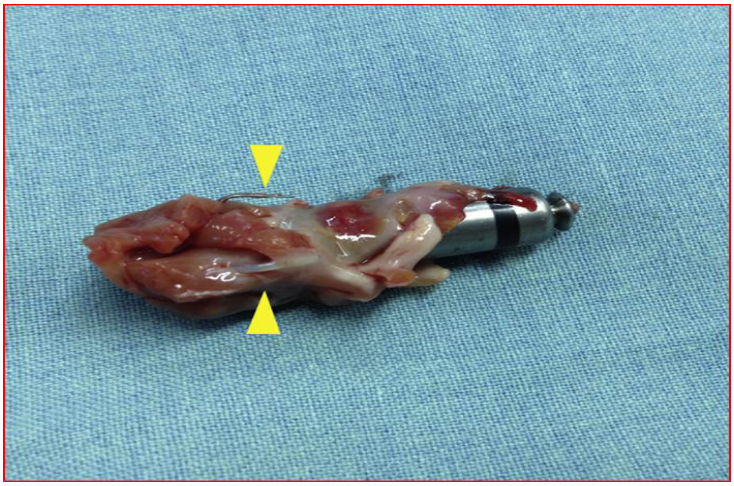

Figure 10: Autopsy specimen in a patient who received Micra device showing tissue growth and tines densely adhered to tissue. Permissions pending.

There is limited data regarding retrievability of the leadless devices at this time. The encapsulation and tissue growth over the device can result in challenges for extraction [Figure 10]. Feasibility and safety data on extraction of long-term chronic implants is not known. If devices are not retrievable, then the feasibility of co-implantation of additional pacemaker system/ systems and effect on cardiac function need to be studied.

Conclusions

As with any disruptive technology, a number of questions remain unanswered with the leadless pacing systems. Randomized clinical trials will be necessary to definitively determine whether the theoretical benefits of leadless systems will be superior to those of conventional pacemakers both from a safety perspective (fewer acute and chronic complications) and in terms of long-term performance and efficacy. However, comparison to historical controls and claims data supports the concept that eliminating leads and the surgical pocket significantly reduces complications. As the technology progresses, it is possible that pacing leads will become extinct. Pacing therapy has overcome some of the initial hurdles and skepticism faced by Hayman. Leadless pacing offers the potential of antibradycardia support with markedly reduced complications.

Future developments will include dual chamber leadless pacing, leadless cardiac resynchronization, and integration of leadless pacing with subcutaneous defibrillation.

Conflict Of Interest

None.

Disclosures

None.

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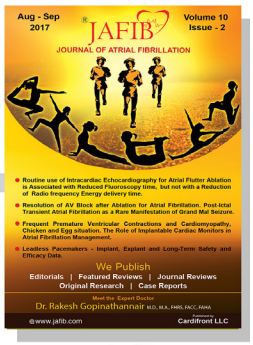

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Monitoring esophageal temperature during catheter ablation

Antonio Fasano

Abstract

I comment on a paper just appeared on JAFIB, aimed at providing an index quantifying the convenience of monitoring esophageal temperature during catheter ablation. The authors base their calculation on the data from four papers. I point out that the data from the two papers strongly against monitoring should be interpreted differently and I suggest how to retrieve more data for a more reliable determination of the said index. In addition, I briefly discuss the so-called antenna effect, sometimes put forward to discourage temperature monitoring.

Introduction

The just appeared paper by Koranne et al [1] has the merit of addressing a question of fundamental importance in the field of catheter ablation for pulmonary veins isolation (PVI): is it recommendable to monitor luminal esophageal temperature (LET)? Very appropriately, the authors try to provide an answer not just suggested by their own experience, but looking for some objective index based on data found in the literature reporting comparisons between monitored and non-monitored patients. The index they come out with is slightly in favor of a positive answer, concerning RF ablation (for cryoablation LET monitoring is rightly defined "vital"). Their determination is based on four papers only (unfortunately, there are not more of the same kind) and a considerable negative weight is brought in by two of them which suggest the existence of an interaction of the metallic body of the thermal sensors with the RF field, later become known as the "antenna effect", supposed to heat up the sensors, thus producing lesions on the surrounding tissue. About this phenomenon, Koranne et al quote a paper by Perez et al, where, based on a mathematical model, it is shown that conduction, and not the electromagnetic field, is the prevailing heat transfer mechanism towards sensors. Since around the antenna effect there has been a lot of misinformation with potentially dangerous implications, I wish to add a few comments. Fasano et al [2] have calculated the thermal and the electric field generated by an RF ablator during PVI, showing that the power deposited on the closest sensor is less than one millionth of a Watt. The reason for the electric field to be so weak in the esophageal region is that the field is strongly diverted towards the heart, owing to the larger electrical conductivity of blood. In addition to theoretical explanations, the following practical consideration explains very clearly that the antenna effect does not have any role: when the ablator is switched off it is commonly observed that LET keeps increasing for a while, thus proving that heat is flowing from the esophagus to the sensor (and with a timescale typical of conduction), not vice versa as the antenna effect would imply. That said, let us come back to Koranne's index. The data entering its determination are the number of lesions reported in the two group of patients. In the two papers against monitoring the ratios found were 5:0 and 12:1 (monitored vs. non-monitored). Nevertheless, erythemas (so just slight irritations, probably of mechanical rather than thermal origin) were included among lesions, along with real ulcers. Removing them, the ratios become 2:0 and 2:1, which would neatly push Koranne's index in favor of monitoring. I understand it would not be simple, but more data could be retrieved taking into account papers in which LET has been monitored and papers in which it has not. For instance in the paper by Sause et al [3] it was found that monitoring LET in a group of 184 patients with a cut off LET of 40°C reduced the incidence of lesions occurrence to a mere 1.6%, almost one tenth of the known average, which obviously includes non-monitored procedures. For lack of space here I cannot quote many other papers proving the importance of LET monitoring. It would be important for the benefit of patients that the authors of the paper here discussed could share at least part of my considerations.

Key Words

Atrial Fibrillation, Ablation, Esophageal lesions, Esophageal Temperature.

Disclosures

None.

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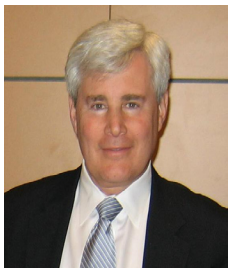

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