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- Relationship of Atrial Fibrillation to Outcomes in Patients Hospitalized for Chronic Obstructive Pulmonary Disease Exacerbation.
- Safety and Long-Term Success of Persistent Atrial Fibrillation Ablation Using THERMOCOOL SMARTTOUCH Catheter Real-World Experience.
- Left Atrial Volume Index Predicts Arrhythmia-Free Survival in Patients with Persistent Atrial Fibrillation Undergoing Cryoballoon Ablation.
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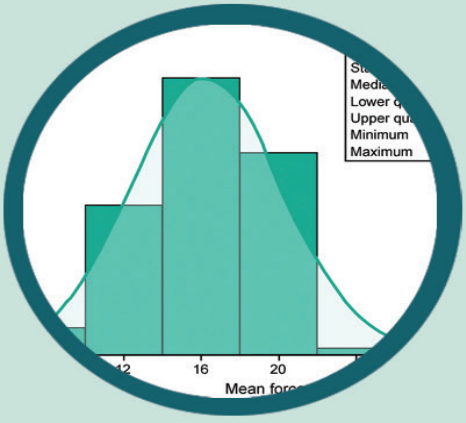

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Contents

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Editorial

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Learning More About Interatrial Block ...

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Issue 2

Volume 12

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

Dear Colleagues

Welcome to this issue of JAFIB. Congratulations to the APHRS team on a very successful Annual Meeting in Bangkok, Thailand! It was a well rounded meeting with excellent science being discussed. While cold blasts started hitting North America it was warm in this subtropical haven of amazing cuisine and culture.

Science related to Atrial Fibrillation (AF) continues to move forwards despite all the unrest around the world. In this issue of JAFIB, we have three manuscripts on inter atrial block. This apparently common electrocardiographic finding may have some very interesting diagnostic, therapeutic and prognostic implications. All in all, this may reflect the patient risk factor profile and atrial pathology that predicts a higher prevalence of AF and probably poor outcomes of therapy. A meta-analysis of the relationship between LAA morphology and systemic thromboembolism confirms the original findings of the Austin group that non-chicken wing morphology is predictive of higher event rates. Even though oversimplification of the anatomy into the four classic categories is often criticized it is possibly the most practical way of classifying left atrial appendages. The chicken wing and wind sail morphologies are probably less complex in their anatomic variation. Multiple lobes and more complex branching obviously increase the thrombogenicity of these LAAs. More recent work from Bartus etal (HEART Clot study) may provide more insights into the regional factors that play a role in explaining the individual variations in atrial thrombogenicity. Another systematic review of endocardial LAA closure device related complications highlights the potential for pulmonary, coronary and valve injury. Though rare it is important to understand these issues and be able to promptly recognize and treat and possibly prevent them. Case reports that highlight the impact of coronary ischemia on conduction system abnormalities and unusual causes of cardiac resynchronization therapy non-response.

The Indian Heart Rhythm Society (IHRS) has successfully organized their 11th Annual meeting in New Delhi. Physiologic pacing and Complex supraventricular tachycardia ablation took the main stage. On behalf of the JAFIB team we wish you all a happy Thanksgiving.

DJ Lakkireddy

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Systematic Review of Contiguous Vessel and Valve Injury Associated with Endocardial Left Atrial Appendage Occlusion Devices

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Abstract

Endocardial LAAO has been increasingly utilized in atrial fibrillation (AF) patients who are not suitable for long term oral anticoagulation. While overall procedural complications have decreased, rare complications like contiguous vessel and valve injury may be more frequently seen in the future with increase in the procedure volume. We performed a systematic search using predefined terms which reviewed all cases published in literature of contiguous vessel (pulmonary artery, pulmonary vein and left circumflex artery) and mitral valve injury caused by LAAO devices. Our results showed that Amplatzer Cardiac Plug (ACP) and Amplatzer Amulet devices were the most commonly used devices. Pulmonary artery perforation was the most commonly seen collateral vessel injury associated with LAAO. Close proximity of left atrial appendage to pulmonary artery was noted in all cases of pulmonary artery injury. Pulmonary artery injury commonly manifests as pericardial tamponade with hemodynamic collapse and is often fatal. Most common denominator of all the reviewed cases was the presence of an oversized LAAO device. In conclusion, collateral vessels and valve injury can be seen after LAAO mostly with double lobe devices such as ACP or Amulet. Increased awareness by the operators along with proper imaging and investigations could potentially mitigate such rare complications associated with LAAO.

Introduction

Left atrial appendage occlusion (LAAO) has emerged as an appealing alternative to stroke prophylaxis in patients with non-valvular atrial fibrillation (AF) who are poor candidates for anticoagulation [1]. While there are several available devices for LAAO, the Watchman (Boston Scientific Corp, Minneapolis, MN) and the Amulet (Abbott Medical, Chicago, IL) are the most commonly implanted devices for catheter-based endocardial LAAO, with a greater percentage of the Amulet device being used within Europe compared to non-European geographies [2]. With the prevalence of non-valvular AF estimated to increase across the globe [3], utilization of LAAO is likely to increase in the future. Since the sharp rise in post market release complications of Watchman, there has been a steady decline in reported rate of common procedure-related complications [4]. A few rare complications of LAAO are linked to the close anatomical proximity of the left atrial appendage (LAA) to adjacent vessels and valve in the heart. LAA lies close to the pulmonary artery anterosuperiorly and left superior pulmonary vein posteriorly, mitral valve inferiorly and the LAA covers an area over the left atrioventricular groove which contains the left circumflex artery [5]. Although rare, contiguous vessel or valve injury with LAAO devices is more likely to be seen in the future with an increase in the utilization of these procedures. In this paper, we aim to review all contiguous vessel and valve injuries associated with LAAO that have been published to date and also aim to understand the pathophysiology of these complications.

Key Words

Left atrial appendage occlusion, Amplatzer Cardiac Plug, Amplatzer Amulet, Collateral injury, Complications.

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Methods

We searched PubMed, EMBASE, CINAHL and Google Scholar from January 1, 2000 till March 15, 2019 using the following key words: "left atrial appendage closure," "Watchman," "Amplatzer Cardiac plug," "Amulet," "pulmonary vein," "pulmonary artery," "left circumflex artery" and "mitral valve". The goal of this systematic review was to collect all the cases of collateral vessel and valve injuries that occur as complications from LAAO devices. The flow chart of study selection is elucidated in [Figure 1].

Results

Comprehensive search revealed 12 publications from Asia, Europe, and Australia with description of 13 cases of contiguous vessels and mitral valve injury after LAAO [6-17]. The average age of the patients was 71.4 ± 8.2 years; 92% were Caucasians. Majority had persistent AF (62%). The most common type of injury after LAAO procedure was pulmonary artery injury. Most cases of pulmonary artery (PA) perforation occurred within 24 hours (62%) and were caused by Amplatzer Cardiac Plug and Amplatzer Amulet devices (92%). A case of delayed presentation after 6 months was also described where chronic pressure from the Amulet was found to kink the PA leading to occlusion of vasa vasorum and ischemic necrosis and perforation [13]. Stabilizing hooks of ACP/Amulet or metallic struts of Watchman were seen to cause the perforation of LAA and PA. In all cases, close proximity of LAA with PA was noted. PA perforation had a high mortality rate of 40%. The common presentation was sudden hemodynamic collapse with evidence of pericardial tamponade [Figure 2]. Less common contiguous vessel injuries included left inferior pulmonary vein compression due to atrial disc portion of ACP (10%) [6] as well as left circumflex coronary artery (LCX) compression by the lobe portion of the oversized ACP (10%) causing ST-segment elevation [9]. Pulmonary vein compression by ACP was diagnosed during a follow-up radiofrequency pulmonary vein isolation by low impedance in the ridge between left inferior pulmonary vein and LAA suggesting catheter contact with metal device. In the case of LCX compression, retrieval and repositioning of the device resulted in disappearance of ST elevation. There were three cases of mitral valve impingement and all were due to impingement of mitral leaflet by the outer disc of LAAO devices [15-17]. While two cases manifested as asymptomatic mitral regurgitation detected by imaging [15,17], one patient had recurrent syncope from possible dynamic obstruction of the valve by ACP [16]. The case of recurrent syncope required surgical removal of the device and LAA resection on the 4th post-operative day. Removal and reimplantation of a downsized device was required in the other case [17] while no information on the management was reported regarding the last case [15]. Detailed description of these cases is present in [Table 1].

Discussion

Our review of LAAO related contiguous vessel and valve injury provides comprehensive evaluation of a rare complications associated with the procedure. Contiguous vessel and valve injury from LAAO are rare but can add significant morbidity and mortality. With increasing utilization of LAAO for stroke prophylaxis, such complications are likely to be encountered more frequently in the future. Therefore, operators performing LAAO procedures should be cognizant of this complication.

The topographic relationship of LAA with neighboring structures is well known. However, the effect of LAAO devices on potentially causing injury to neighboring vessels and mitral valve is based on sporadic case reports. Furthermore, due to interindividual variation in LAA morphologies and diverse types and sizes of LAAO devices

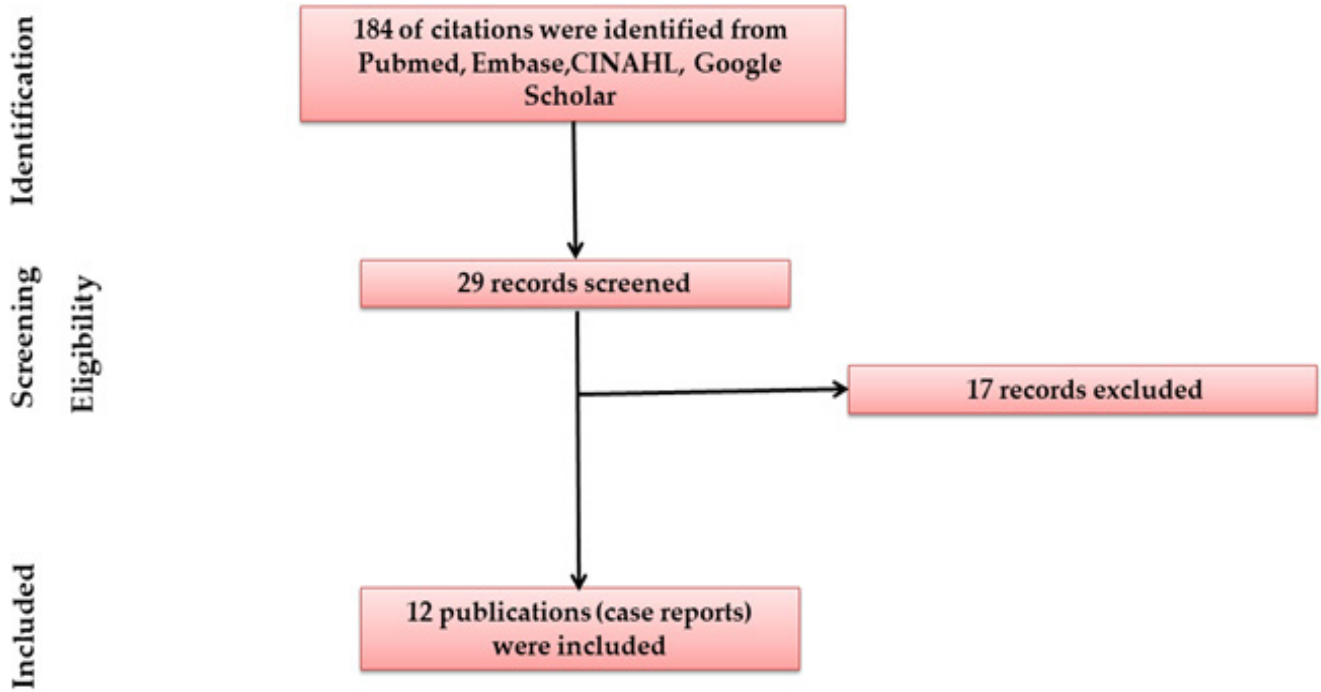

Figure 1: Flow chart of study selection

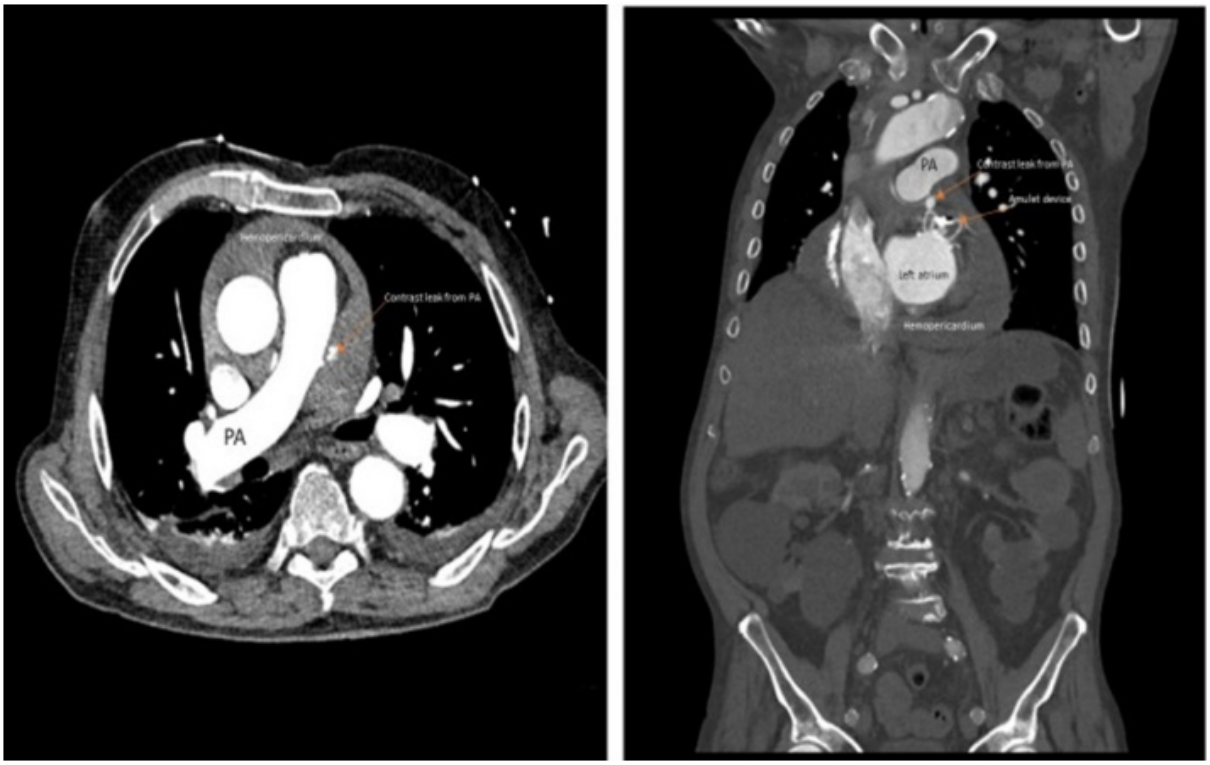

Figure 2: CT scan demonstrating contrast extravasation from main pulmonary artery with pericardial tamponade

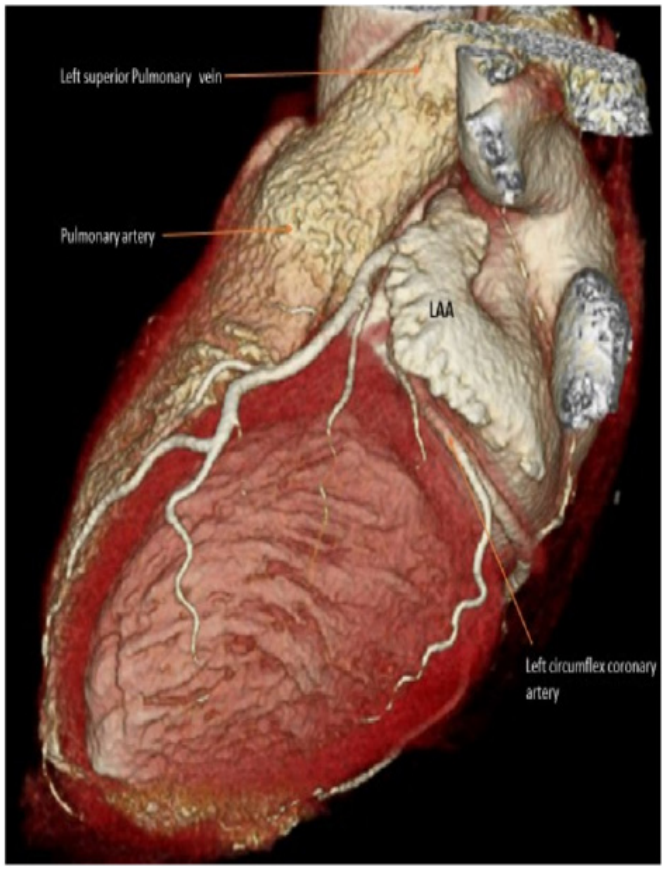

Figure 3: CT scan showing posteriorly directed LAA tucked underneath the pulmonary artery

used, 'one size fits all' recommendation cannot be made for preventing such adverse outcomes. Therefore, prevention and management of collateral injury related to LAAO should be individually addressed on a case by case basis. However, there may be certain anatomical and imaging characteristics that could enable providers to increase vigilance about the possibility of such complications. Anatomical proximity between LAA and vessels is a prerequisite for such complications. In fact, LAA may get in direct contact with main pulmonary artery in a significant number of patients undergoing LAAO [Figure 3]. In a review of 100 AF patients by cardiac-gated computed tomography angiogram of LAA, Halkin et al found 28% of patients had contact between LAA and PA in the proximal LAA (proximal 15mm extending into LAA from ostium or LAA before 1st major bend that is <15mm from ostium) and 65% had contact involving the distal LAA [18]. Proximal LAA contact poses increased vulnerability to injury where the anchoring hook of LAAO devices are usually situated after deployment. In a vast majority of cases, the landing zone of the lobe or disc-lobe devices is immediately distal to the LCX area and is away from the pulmonary artery or the main LCX trunk. This perhaps explains the rare incidence of these complications even though the ostial and distal portions of the LAA seem to be in closer proximity to the PA. This is again primarily determined by the shape of the LAA. Similarly, a recently published cardiac computed tomography (CT) evaluation in 48 patients with LAAO devices after 6 months of implantation revealed that the distance between occluder device and left upper pulmonary vein was affected by LAA morphology with cauliflower type having the closest proximity [19].

In the post-FDA approval experience of Watchman, pericardial tamponade occurred in about 1% of patients [4]. Similarly, in a

Table 1: Study and patient characteristics

Study	Country	Age (yr)*	Sex	AF type	LAAO type	LAAO size (mm)	CHA 2DS2 VASC	Reason for LAAO	Implantation	Diagnosed	Presenting Symptoms/ Signs	LAA characteristics	Injury	LAA and vessel relation	Management	Outcome
Pulmonary artery Injury																
Scislo et al 2018 (1st case)	Poland	67	F	Parox	Amulet	25	9	GI and intracranial bleeding	No issue	17 hrs post procedure	Chest pain, dyspnea, hemodynamic collapse	Winsock type, LZ-20mm	3mm postero lateral tear to MPA by anchoring hook	2mm groove between MPA and LAA	Thoracotomy and repair	Discharged alive
Scislo et al 2018 (2nd case)	Poland	62	M	Parox	Amulet	28	3	GI bleeding	No issue	3hrs post-procedure	Cardiac tamponade	Winsock type, LZ 23mm	3mm posterolateral tear of MPA by anchoring hook	No groove between MPA and LAA	Thoracotomy and repair	Discharged alive
Wang et al 2018	Australia	87	M	Persis	Amulet	31	6	Hemorrhagic stroke	No issue	6months post-procedure	Cardiac tamponade and collapse	LZ 25mm	2mm posterolateral tear from chronic pressure ofanchoring hook without erosion of LAA	-	Thoracotomy and repair	Discharged alive
Suwalski et al 2016	Poland	66	M	Persis	ACP	22	-	Intracranial hemorrhage	No issue	17 days post-procedure	Cardiac Tamponade	LAA origin 18mm, depth 24mm	2mm lateral surface tear by anchoring hook	-	Thoracotomy and repair	Discharged alive
Bianchi et al 2013	Italy	76	M	Persis	ACP	22	3	Intracranial hemorrhage	No Issue	3hrs post procedure	Cardiac tamponade and collapse	-	2mm tear by anchoring hook	-	Thoracotomy and repair	Discharged alive
Sepahpour et al 2013	Australia	72	F	Parox	Watchman	24	6	Complicated PCI and need for lifelong dual antiplatelet	Transient inf STEMI, no apparent reason and resolved by reimplantation with 2nddevice	16 days post procedure	Shock, PEA, could not be resuscitated	LAA orifice diameter 17mm, depth 35mm	10mm tear on superior and left aspect of MPA by a metallic strut of Watchman	-	Died	Died
Zwirner et al 2016	Germany	71	F	Persis	Amulet	-	-	Traumatic subdural hemorrhage	No issue	8hrs post-procedure	Patient was found pulseless, failed resuscitation	-	2mm tear on the pulmonary artery by a hook of amulet with punctiform tear of LAA	-	Died	Died
Hanazawa et al 2014	Germany	75	F	Parox	ACP	24	5	Subdural hematoma	No issue	24hrs post-procedure	Hypotensive, cardiac tamponade	LAA orifice diameter 18mm, depth 27mm	Perforation of LAA and leading to erosion of the bottom of the pulmonary artery	3D reconstruction of cardiac CT showed one lobe of LAA touched the inferior pulmonary artery	Died	Died
Pulmonary Vein Compression																
Ayati et al 2014	Germany	76	F	Persis	ACP	-	-	Risk of bleeding	No issue	3 months post-procedure	Worsening exertional dyspnea	-	LIPV compression diagnosed on CT and during PVI, mapping at the ridge between LIPV and LAA showed decreased impedance suggesting catheter contact with metal device	LIPV was compressed with atrial part of ACP	Successful PVI, ACP was left in place	Discharged alive

Left Circumflex artery Compression															
Katona et al 2015	Hungary	59	M	Persis	ACP	23	-	Recurrent head contusions	ST elevation in inferior leads	During procedure	ST elevation	LAA with huge ostium	After positioning of ACP inferior lead showing ST elevation	Coronary angiogram showing compression of proximal circumflex and device was seen sitting superficially.	After removal and repositioning of device STE disappeared.	Discharged
Mitral valve impingement															
Berrebi et al 2017	France	84	F	Pesis	Amulet	28	5	Hemorrhagic shock due to GI bleeding	No issue. Amulet was in contact with ant. Mitral leaflet but mitral valve kinetics was normal	6 weeks after procedure	Denovo mild mitral regurgitation on routine TEE at 6 weeks	LAA ostium 31 mm and neck 26mm	tear of A1 portion of anterior mitral leaflet	Progressive leaflet erosion by amulet outer disc	Not available	Not available
Cruz-Gonzalez et al 2014	Spain	72	F	Parox	ACP	24	5	GI bleeding	Pericardial tamponade needing tube drainage after transseptal puncture. Following ACP deployment, inferior part of the external disc appeared over posterior leaflet without any mitral valve dysfunction	Few days after LAAO	Recurrent syncope	LAA neck by angiography 22mm, -by TEE 19mm	Possible dynamic obstruction of valve by device causing syncope	Compression of posterior mitral leaflet by ACP	Surgical removal of device and left atrial appendage with resolution of syncope	Discharged alive
Walia et al 2016	Taiwan	61	M	Persis	ACP	26	5	Recurrent strokes and bleeding	Immediately post-implantation rhythmic movement of ACP disc edge and mild MR were noted	During the procedure	Rhythmic movement of disc edge and MR	Cauliflower morphology Base 21.8mm Depth 18.5mm	Disc impingement and MR	Outer disc of ACP causing mitral leaflet impingement	Removal of device and reimplantation of downsized ACP (24mm)	Discharged alive

*all were Caucasian, yr=year,parox=paroxysmal,persis=persistent,LAA=left atrial appendage LAAO=left atrial appendage occlusion, ACP=Amplatzer cardiac plug,mm=millimeter,GI=gastrointestinal, PCI=percutaneous coronary intervention, MI=myocardial infarction, PEA=pulseless electrical activity, STEMI=ST elevation myocardial infarction, LZ=landing zone,MPA=main pulmonary artery,LIPV=left inferior pulmonary vein, PVI=pulmonary vein isolation, MR=mitral regurgitation, STE=ST elevation

multicenter study of ACP involving 1047 patients, pericardial tamponade was noted in 1.2% (13/1047) with 1 case reported as being caused by pulmonary artery tear (0.09%) [20]. Majority of the bleeding complications after LAAO were able to be treated percutaneously without the need for cardiac surgery. Even though most of these bleeding complications were probably related to micro-perforation of the LAA from the hooks or struts, contiguous vessel injury remains a concern.

Our review has some important clinical implications. First, it underscores the importance of proper preoperative imaging study to define the relationship of LAA with surrounding structures. While transesophageal echocardiography is commonly used as standard modality, additional imaging such as CT scan needs to be considered in select cases. Second, it reinforces the importance of proper device sizing. Based on our cases, from mechanistic perspective, oversized LAA device can erode the vessel after perforating LAA or compress from outside without perforation. Similarly, the outer disc of larger devices can impinge on mitral valve leaflet and the left superior pulmonary vein ostium. Selecting a larger device is associated with risk of LAA perforation and cardiac tamponade in previous studies [21,22]. As a corollary of this, larger devices may be associated with contiguous vessel and valve injury. Sometimes the LAA may be behind the pulmonary artery especially the landing zone of the LAA where an oversized device could potentially exert significant radial forces leading to perforation through the anchors.

Study limitations

Our study has all the potential limitations of a systematic review. The data is retrospectively pooled and many anatomical and intraprocedural details are not readily available. The exact details of the degree of oversizing and degree of the compression of the lobe (ACP/Amulet) and or the main body (Watchman) are largely unknown. Oversizing and compression are almost always thought to be the underlying etiology in most of these cases. Whether it is truly the case or not cannot be accurately verified. But it is logical to hypothesize that significant oversizing can result in over compression with higher radial forces on the walls of the LAA and the contiguous vessels. Oftentimes, operators err on the side of oversizing to accomplish tighter seal of the LAA. This approach has to be reviewed with caution in light of the results of our study. Finally, the true incidence of the contiguous vessel or valve injury in the general population cannot be estimated from our study

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None

Conclusions

Thorough architectural knowledge of pulmonary artery, pulmonary vein, left circumflex artery and mitral valve leaflets in relation to LAA can help guide pre-operative and post-operative management, as well as anticipation of the rare complication of injury to the contiguous vessels and valve during LAAO procedures. Given increasing use of LAAO devices, we anticipate that these rare complications have a potential to increase in frequency in the future. Increased operator awareness along with proper preoperative imaging can potentially mitigate these rare complications.

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Contemporary Yield of 24-hour Holter Monitoring: Role of Inter-Atrial Block Recognition

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Abstract

Background

The diagnostic yield of 24-hour ECG Holter monitoring (24H) is currently overcome by alternative ECG monitoring techniques and it needs to be optimized. The recognition of inter-atrial block (IAB) has emerged as a reliable indicator of patients at risk of atrial fibrillation relapses, and its role enhancing the yield of 24H is yet to be determined. We hypothesized that a presumably low yield of 24H may be ameliorated by means of incorporating the assessment for IAB.

Methods

We retrospectively analyzed 1017 consecutive 24H registers performed in a Multidisciplinary Integrated Health Care Institution, in which a restrictive definition of diagnostic 24H findings was used. A univariate and multivariate regression analysis served to determine the variables associated with a higher 24H's yield, including the requesting medical specialty, type of indication and a number of clinical, echocardiographic and ECG variables, including IAB.

Results

The mean age of our population was 62 ± 17 years (55% males). The majority of 24H were indicated from the Cardiology department (48%). The overall yield was 12.8%, higher for the assessment of the integrity of the electrical conduction system (26.1%) and poorer for the assessment of syncope (3.2%) and cryptogenic stroke (4.6%). The variables associated with higher diagnostic performance were indication from Cardiology ($p < 0.001$), IAB ($p = 0.004$), structural heart disease ($p = 0.008$) and chronic renal failure ($p = 0.009$). Patients ≤ 50 years old only retrieved a 7% yield. In the multivariate analysis, indication from Cardiology and IAB remained significant predictors of higher 24H's yield. In a secondary analysis including echocardiographic data, only identification of IAB remained statistically significant.

Conclusions

The recognition of IAB and the type of indication are major determinants of a higher 24H's diagnostic yield and may help to optimize the selection of candidates.

Introduction

Twenty-four hour ECG Holter monitoring (24H) is useful for the documentation of brady- and tachy-arrhythmias. Regardless of its suboptimal yield and the implementation of alternative and more efficient monitoring techniques, the 24H remains as a first-line indication during the diagnostic work out of several cardiac disorders. This is probably due to a widespread access to the technique and its relatively low cost [1-5].

The reported diagnostic yield of 24 Hranges from 1-2% to 46% of cases [1-12]. Regardless of scarce direct comparative data, it can be assumed that both the type of indication and several underlying conditions (abnormal baseline 12-lead ECG, structural heart disease, advanced age and other) account to justify such highly variable diagnostic yield [6-8]. Furthermore, the definition of a diagnostic 24H is highly heterogeneous in the literature, with only a minority of series that find it compelling to establish a strict chronological relationship between symptoms and the 24H findings and/or to provide an unequivocal diagnosis with an impact on the patient's therapeutic management [10,13-16]. The influence of the medical specialty that requests the 24H in the diagnostic yield of the technique is also unknown.

The recognition of inter-atrial block (IAB) has been introduced in the clinical practice in the recent years, especially for the prediction of new-onset or recurrent atrial fibrillation (AF) and stroke [17,18]. Its impact on the diagnostic yield of 24H is unknown.

In this study we sought to analyze the variables associated with a highest diagnostic performance of 24H monitoring (including IAB) from a Multidisciplinary Integrated Health Care Institution, in which all medical specialties have equal access to this diagnostic tool, using a preliminarily defined and restrictive definition of diagnostic 24H's results.

Key Words

24-hour ECG Holter monitoring, Inter-atrial block, Atrial fibrillation.

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Material and Methods

Study Population

A retrospective cohort study was undertaken including all consecutive patients undergoing 24H in our Institution the years 2012 to 2018. All patients signed informed consent for the use of their clinical data. The following baseline variables were collected: type of indication, the requesting medical specialty, age, hypertension, underlying structural heart disease, chronic renal disease, sleep apnea, the longest PR interval on 12-lead ECG (if sinus rhythm was documented), sinus P-wave duration, QRS complex width, bifascicular and/or atrio-ventricular (AVB) block. Inter-atrial block (IAB) was defined as a sinus P-wave of > 120 ms, following standard criteria [17]. Left ventricular ejection fraction (EF) and left atrial diameter (LAD) were collected among the patients in whom the 24H was performed the years 2016 and 2017 and had previously undergone 2-D echocardiography at least one year before the Holter register. Left ventricular dysfunction was defined as an EF of < 50% (Simpson). Left atrial dilation was defined as a LAD of > 40 mm. Patients in whom the 24H could not be adequately interpreted due to a poor register's quality were excluded from the study.

24-hour Holter Monitoring: Technical Specifications

The 3-channel 24H register was obtained by positioning 7 electrodes at the thoracic surface: two at both infra-clavicular spaces, one at the superior sternal aspect, one at the right 4th inter-costal space at the mid-axillary axis, one at the right precordial region, one at the sub-xiphoid space and the last one (neutral electrode) at the right inferior costal area. The electrodes were connected to a Seer Light® recorder (General Electric, Milwaukee, Wi, US).

Type of Indication and Definition of Diagnostic Yield

The type of indication was preliminarily determined before data collection and classified into 8 categories: 1) Etiological study of syncope/pre-syncope; 2) Non-documented palpitations; 3) Integrity of the sinus and/or AV conduction upon clinical suspicion of sinus dysfunction and/or advanced/complete AVB; 4) Assessment of rate control in patients with permanent AF; 5) Cryptogenic stroke or systemic embolism; 6) Assessment of sudden death risk among patients with underlying arrhythmogenic cardiomyopathy; 7) Determination of the arrhythmia burden in patients with paroxysmal AF undergoing rhythm control strategy; 8) Other indications.

Atrial fibrillation was defined as an irregular atrial rhythm with a rate of > 300 bpm lasting more than 30 seconds, and non-sustained ventricular tachycardia as a ventricular rhythm of > 120 bpm lasting ≥ 3 beats and < 30 seconds. Supraventricular or ventricular tachycardia lasting < 30 seconds was not considered a diagnostic finding, unless a clear chronological relationship with the clinical symptoms was established.

In our Institution, a restrictive definition of a diagnostic 24H is used [Table 1]. In short, at least one of the following criteria needs to be met: 1) The finding encompasses a change in the patient's therapeutic management; 2) It provides a straight answer to a specific clinical question it is made; 3) The clinical symptomatology that promoted the indication for 24H appears during the ECG register (an exact chronological correlation between symptoms and ECG findings being compelling in the case of non-documented palpitations); 4) The following ECG findings are considered diagnostic regardless of an unclear symptom-ECG correlation: Mobitz-II 2nd degree AVB, advanced AVB (≥ 2 consecutive blocked P waves), complete AVB and sustained supra-ventricular or ventricular tachycardia (> 30 seconds).

When 24H is indicated for the assessment of the ventricular rate control in AF patients, the test may always be considered diagnostic (yield of 100%), as it provides a straight answer to the clinical question (criterion number "2"). For this reason, the type of indication was not incorporated into our regression analysis, since it could distort our logistic regression model. A descriptive analysis of the influence of the type on indication in the yield of 24H was performed instead.

Table 1: Definition of diagnostic 24H with respect to the type of indication.

Indication	Diagnostic Finding
Cryptogenic stroke	AF or atrial flutter paroxysm (> 30 seconds)
Sinus/AVN conduction disturbance	> 3-second sinus pauses during wakefulness or documentation of advanced/complete AVB
Syncope/pre-syncope	Any ECG register obtained during a clinical relapse or > 3 seconds of asystolic pause
Non-documented Palpitations /	Any ECG register obtained during a clinical relapse of the symptomatic palpitations
AF: Rhythm control	AF recurrence or atrial flutter documentation
Pacemaker dysfunction suspicion	Any sensing or pacing failure documented
Silent myocardial ischemia	ST-segment elevation or depression
Arrhythmogenic Cardiomyopathy	Documentation of sustained/non-sustained VT
Non-sustained arrhythmias	PAC/PVC count > 20% of the total beats or any sustained atrial/ventricular tachycardia

AF = Atrial fibrillation; AVB = Atrio-ventricular block; AVN = Atrio-ventricular node; PAC = Premature atrial contraction; PVC = Premature ventricular contraction; VT = Ventricular tachycardia.

Table 2: Patient baseline clinical characteristics with respect to the medical specialty that indicates the 24H register.

	Total (n = 212)	Cardiology (n = 88)	Other (n = 124)	P
Age	65,3 ± 17	66,2 ± 16	64,8 ± 18	0,57
Gender (female), %	49,1%	48,9%	49,2%	1
HT, %	60,4%	62,5%	58,9%	0,67
SHD	34,4%	50%	23,4%	< 0,001 *
EF (%, n = 143)	59,4 ± 8	59,7 ± 10	59,1 ± 7	0,68
LAD (n = 143)	41,9 ± 8	44,2 ± 9	40 ± 6	0,001 *
SA, %	8,9%	10,2%	8%	0,63
CRD, %	22,6%	27,3%	19,4%	0,19
P-wave duration	113,1 ± 20	117,2 ± 23	109,6 ± 18	0,02 *
PR interval	178,1 ± 45	187,5 ± 52	170 ± 36	0,02 *
QRS width	100,5 ± 20	102 ± 21	99 ± 19	0,34
AVB, %	20,3%	26,1%	16,1%	0,08
IVCD, %	11,8%	14,8%	9,7%	0,29

Values are expressed as mean ± standard deviation unless otherwise stated.
* p value of < 0.05 comparing Cardiology versus other medical specialties.
AVB = Atrio-ventricular block; CRD = Chronic renal disease; EF = Left ventricular ejection fraction; HT = Hypertension; IVCD = Intra-ventricular conduction delay (QRS width of > 120 ms); LAD = Left atrial diameter; SA = Sleep apnea; SHD = Structural heart disease.

Statistical Analysis

Continuous variables were defined as mean ± standard deviation. Discrete variables were expressed as absolute number and percentage. A chi square and a t-test were performed to evaluate differences between groups in discrete and quantitative variables, respectively. In those patients in whom the 24H was performed the years 2016-2017 (from whom clinical, ECG and echocardiographic variables were available), a descriptive comparative analysis was performed to assess for differences in baseline clinical characteristics and diagnostic yield of the 24H in Cardiology versus other specialties as the source of 24H indication. A univariate logistic regression analysis was performed in this population to determine the baseline variables associated with a diagnostic 24H. The variables obtaining a P value of < 0.10 in the univariate analysis (along with age and sex irrespective of their P value) were incorporated into a multivariate logistic regression model to identify independent predictors of diagnostic 24H. A secondary logistic regression analysis was performed in the 143 patients from whom echocardiographic data (including EF and LAD) was available. A bilateral P value of < 0.05 was considered statistically significant. The statistical analysis was performed with the 15.0 STATA software (StataCorp; Texas, US).

Results

Study Population

During the study period (2012-2018), a total number of 1017 24H were performed in 933 patients (mean age 62 ± 17 years, 515 -55%-male, range 1to 5 24H per patient). A total of 486 24H (48%) were indicated from the Cardiology department, 347 (34%) from General Medicine, 143 (14%) from Neurology and the remaining 41 (4%) from other departments.During the years 2016 and 2017, 212 24H registers corresponding to 210 patients (age 65 ± 17 years, 109 -51%- male) were included. The baseline clinical, ECG and echocardiographic characteristics of the latter study subpopulation are summarized in [Table 2]. Of note, the patients proceeding from the Cardiology department had a higher prevalence of structural heart disease (50% vs. 23.4%, p < 0.001), greater LAD (44.6 ± 9 mm vs. 40 ± 6 mm; 64% vs. 38% patients with LAD of > 40 mm, p = 0.001), longer sinus P-wave duration and higher prevalence of IAB (117.2 ± 23 ms vs. 109.6 ± 18 ms and 49% vs. 30%,respectively; p = 0.02), longer PR interval (187.5 ± 52 ms vs. 170 ± 36 ms,p = 0.02)and a statistical trend toward a higher likelihood of underlying baseline AVB of any degree (26.1% vs. 16.1%, p = 0.08).

The type of indication was also different depending on the petitionary medical specialty (p < 0.05), being the assessment of the cardiac conducting system the most frequent indication from Cardiology(24%), the evaluation of non-documented palpitations from General Medicine (63%), the etiological study of cryptogenic stroke from Neurology (55%) and the study of syncope from other departments (37%; Table 3).Other indications included asymptomatic frequent premature atrial (PAC) or ventricular (PVC) contractions (58%), unspecific dizziness episodes (15%) and pre-excitation syndrome (8%). No 24H was indicated for documentation of myocardial ischemia by means of ST segment analysis, with only one 24H indicated upon suspicion of pacemaker dysfunction.

Table 3: Type of 24H indication with respect to the petitionary medical specialty.

	Cardiology (n = 486)	General Medicine (n = 347)	Neurology (n = 143)	Other (n = 41)	Total (n = 1017)
Syncope/ presyncope	85 (17,5)	69 (20)	21 (15)	15 (37)	190 (19)
NDP	89 (18,3)	216 (63)	5 (3,5)	10 (24)	320 (32)
Sinus/AVN	114 (23,5)	23 (6,7)	37 (26)	2 (5)	176 (17)
AF (HRR)	75 (15,4)	6 (1,7)	0 (0)	7 (17)	88 (8,7)
Cryptogenic stroke	4 (0,8)	3 (0,8)	79 (55)	1 (2)	87 (8,6)
CM (SCD risk)	40 (8,2)	0 (0)	0 (0)	1 (2)	41 (4)
Parox AF	41 (8,4)	5 (1,4)	0 (0)	2 (4)	48 (4,7)
Other	38 (7,8)	25 (7,2)	1 (0,7)	3 (7)	67 (6,7)

Values are expressed as absolute number (percentage with respect to the corresponding specialty). AF (HRR) = Atrial fibrillation: Heart rate response; CM = Cardiomyopathy (assessment of sudden cardiac deatch risk); NDP = Non-documented palpitations; Parox AF = Paroxysmal atrial fibrillation (assessment of AF burden); Sinus/AVN = Assessment of the integrity of the sinus and atrio-ventricular node conducting system.

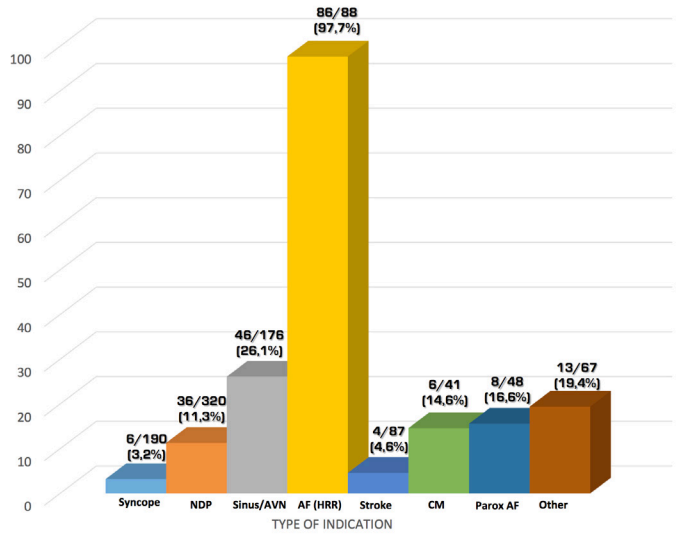

Figure 1: Diagnostic yield of 24H on the basis of the type of indication.

Values are expressed as proportion and percentage in each type of indication.
AF (HRR) = Atrial fibrillation: Heart rate response; CM = Cardiomyopathy (assessment of sudden cardiac deatch risk); NDP = Non-documented palpitations; Parox AF = Paroxysmal atrial fibrillation (assessment of AF burden); Sinus/AVN = Assessment of the integrity of the sinus and atrio-ventricular node conducting system.

Diagnostic Yield of 24-hour Holter Monitoring

The diagnostic yield of the 24H was 20.16% (205 out of the 1017 24H). After excluding the assessment of ventricular rate in permanent AF patients (n = 88), the yield decreased to 12.8% of cases (119 out of 929 registers).

Differences in the yield of 24H regarding the type of indication are depicted in Figure 1.

As expected, assessment of the ventricular rate in permanent AF patients achieved the highest diagnostic yield (86 out of 88 cases, 98%), not reaching a 100% percentage due to the performance of 2 consecutive 24H in 2 different patients, without additional diagnostic benefit of the second register. Assessment of the cardiac conducting system was accompanied by the second highest yield (46/176 cases, 26.1%). In 21 of these 46 patients, advanced and/or complete AVB was documented, a pacemaker being implanted in 15 of them. All 21 patients had some degree of baseline AVB (1st or 2nd degree AVB), and thus no diagnostic 24H was registered in patients with bifascicular block but without baseline AVB. Thirteen out of the 46 patients were diagnosed from sinus dysfunction, (pacemaker implantation in 7). Baseline sinus bradicardia/pauses had been documented in all these patients.

Importantly, the 2 indications achieving the highest diagnostic yield (ventricular rate control in permanent AF and assessment of cardiac conducting system) more frequently proceeded from the Cardiology department as compared to other sources: 85.2% vs. 14.8% and 64.8% vs. 35.2%, respectively.

Intermediate diagnostic yields were obtained for the study of paroxysmal AF in patients undergoing AF rhythm control, for the sudden cardiac death risk assessment in patients with underlying cardiomyopathy and for the evaluation of non-documented palpitations. In the evaluation of palpitations (yield of 36/320 cases, 11.3%), 10 cases were diagnosed from frequent PVCs/NSVT, 9 from sustained supraventricular tachycardia, 9 from non-sustained atrial tachycardia and 3 from frequent PACs. Normal sinus rhythm was never documented during symptomatic palpitations.

The indications yielding a poorer diagnostic performance were the etiological study of cryptogenic stroke and syncope (4.6% and 3.2%, respectively). No patient presented syncope recurrences during 24H registering.

Without considering permanent AF's rate control, the 24H derived from Cardiology had a diagnostic yield of 20.2% (83 out of 411 registers), higher than that obtained from General Medicine (9.1% -31 out of 341-), Neurology (3.5%) and other departments (2.9% -1 out of 34-).Importantly, patients proceeding from Cardiology also had a higher prevalence of structural heart disease (50% vs. 23%, p < 0,001), LA enlargement (64% vs. 38%, p = 0.001) and IAB (49% vs. 30%, p = 0.02) than those from other medical specialties.

Among the 212 patients undergoing a complete cardiologic assessment (including 2-D echocardiography), only 9 of them (4%) had documented AF relapses leading to anticoagulant and/or anti-arrhythmic drug therapy initiation. Seven out of the 9 episodes corresponded to newly diagnosed AF relapses. Interestingly, 7 out of these 9 patients (78%) had IAB.

Univariate and Multivariate Analyses

In our univariate analysis, the variables associated with a better diagnostic performance of the 24H register were indication from the Cardiology department (p < 0.001), underlying structural heart disease (p = 0.008), chronic renal failure (p = 0.009) and identification of IAB (p = 0.004; [Table 4]). Descriptively, the yield was manifestly low among patients ≤ 50 years old (7% as compared to a 24% percentage among patients > 50 years old), although not reaching statistical significance.Categorization of age by decades did not add relevant statistical significance.

In our multivariate analysis, the 24H indication from Cardiology (OR = 4.11; CI 95% [1.2 – 14.0]; p = 0.024) and the identification of IAB (OR = 4.14; CI 95% [1.3 – 13.4]; p = 0.018) remained as independent predictors of a higher diagnostic performance (Table4). The sensitivity/specificity/positive/negative predictive values for indication from Cardiology and IAB were 70%/59%/20%/93% and 61%/74%/26%/93%, respectively. More specifically, the recognition of IAB yielded sensitivity/specificity/positive/negative predictive values of 78%/73%/17%/98% in the identification of AF relapses prompting anticoagulant and/or anti-arrhythmic drug therapy initiation.In a secondary analysis to which the echocardiographic EF and LAD variables were incorporated (n=143),only IAB persisted as statistically significant(OR 3.71, CI 95% 1.03 – 13.3; p=0.044).

Discussion

Main Findings

To our knowledge, the present study is the largest unrestricted series of patients undergoing 24H monitoring in the literature. In contrast to prior series, 1) we newly incorporated all possible indications in a sole series of patients undergoing 24H monitoring; 2) we exhaustively analyzed the clinical, ECG and echocardiographic variables associated with a better diagnostic performance of the test, including IAB; 3) a rigorous and restrictive definition of diagnostic 24H was homogeneously and preliminary utilized; and 4) our Multidisciplinary Health Care Institution allowed for assessing for the differences in the yield of 24H related with the medical specialty indicating this diagnostic test.

Currently, alternative prolonged heart rhythm monitoring techniques have proven superior to the 24H in their diagnostic yield. It therefore becomes compelling to optimize the selection of the adequate candidates to 24H monitoring. Our univariate and multivariate analyses identifieda number of clinical, ECG and echocardiographic variables that were associated witha highest diagnostic performanceof this technique, with finally IAB becoming a major predictor of a high 24H's yield.

The yield of 24H was 12.8%, a percentage that was raised to 20.16% when permanent AF's rate control was included as an indication. Our study further identified the indications showing a manifestly low diagnostic yield: the etiological study of cryptogenic stroke and syncope. The indications for 24H derived from the Cardiology department and the presence of IAB were identified as predictors of a higher diagnostic performance in our multivariate analysis, although the former lost statistical significanceonce the echocardiographic variables were incorporated into our model. It is suggested by this that a thorough cardiologic evaluation (either performed or not by a cardiologist) should be undertaken prior to the indication of 24H. Such evaluation should incorporate a rigorous analysis of the clinical symptoms, the 12-lead ECG and suspicion and/or characterization of the underlying cardiac disease, if any.

Table 4: Univariate and multivariate logistic regression analysis of predictors of a higher diagnostic performance of 24H monitoring.

		Univariate	
Variable	**OR**	**CI 95%**	**P**
Age > 50 years	1,53	[0,56 – 4,23]	0,41
Gender (Female)	0,56	[0,26 – 1,18]	0,13
HT	0,98	[0,47 – 2,06]	0,96
SHD	2,70	[1,29 – 5,66]	0,008
EF	0,97	[0,92 – 1,01]	0,16
LAD > 40 mm	1,08	[1,03 – 1,14]	0,004
SA	0,57	[0,13 – 2,59]	0,48
CRD	2,80	[1,29 – 6,07]	0,009
IAB	5,07	[1,69 – 15,21]	0,004
PR interval	0,99	[0,99 – 1,01]	0,98
Baseline AVB	1,84	[0,74 – 4,61]	0,19
QRS width	1,01	[0,99 – 1,03]	0,291
QRS > 120 ms	1,57	[0,61 – 3,98]	0,37
BFB	0,96	[0,31 – 2,99]	0,94
Medical specialty (CA)	5,36	[2,36 – 12,15]	< 0,001
		Multiivariate	
Model #1	**OR**	**CI 95%**	**P**
IAB	4,14	[1,28 – 13,43]	0,018
CA	4,11	[1,20 – 14,04]	0,024
Model #2	**OR**	**IC 95%**	**P**
IAB	3,71	[1,03 – 13,3]	0,044

AVB = Atrio-ventricular block; BFB = Bifascicular block; CA = Cardiology department; CI = Confidence Interval; CRD = Chronic renal disease; EF = Left ventricular ejection fraction; HT = Hypertension; IAB = Inter-atrial block; IVCD = Intra-ventricular conduction delay (QRS width of > 120 ms); LAD = Left atrial diameter; OR = Odds Ratio; SA = Sleep apnea; SHD = Structural heart disease.
Model #1: Mutivariate analysis performed over the total study population (n=1017); Model #2: Secondary analysis performed after incorporating echocardiographic variables (n=143).

Prior Data

The notorious discrepancy among series with regard to the diagnostic yield of the 24H (ranging from a 1%to a 46%) appears justified by 3 reasons. First, the definition of a diagnostic 24H is not homogeneous. In the setting of non-documented palpitations, a very distinct criterion of diagnostic 24H findings is used, including a highly variable PAC/PVC/non-sustained tachycardia burden and a more or less exigent chronological correlation of such arrhythmias with the clinical symptoms [7,9,11,13,14]. In our study, such chronological correlation was considered compelling, without establishing a minimum arrhythmia burden above which a positive 24H result would be determined. Second, the source of patients derived for 24H monitoring is also variable among prior series, with a majority of them proceeding from non-multidisciplinary institutions. Finally, in the vast majority of prior studies only one or two types of indications of 24H are represented. Our study corroborates that the type of indication for 24H has a dramatic impact on its diagnostic performance.

Contemporary Role of 24H Monitoring in the Era of the Implantable Loop Recorder

Prolonged ECG monitoring, especially with implantable loop recorders, has proven to be superior and highly efficient as compared to 24H in different clinical scenarios, with a percentage of positive tests of up to 84% for the assessment of non-documented palpitations and up to 34% for the etiological study of syncope [11,19,20]. Parallel to this, the number of 24H indications seems not to decrease, probably due to the low cost and easy access to this test. Unnecessary indications may lead to an increment of the 24H patient's waiting list to unacceptable delays, with even a theoretical prognostic impact in patients with syncope, AV conduction disturbance or underlying cardiomyopathy. Such delay should be overcome by means of an accurate patient selection of candidates to 24H monitoring. Our study definitely helps to restrict the indications of 24H to selected indications and clinical scenarios that facilitate the 24H's diagnostic yield.

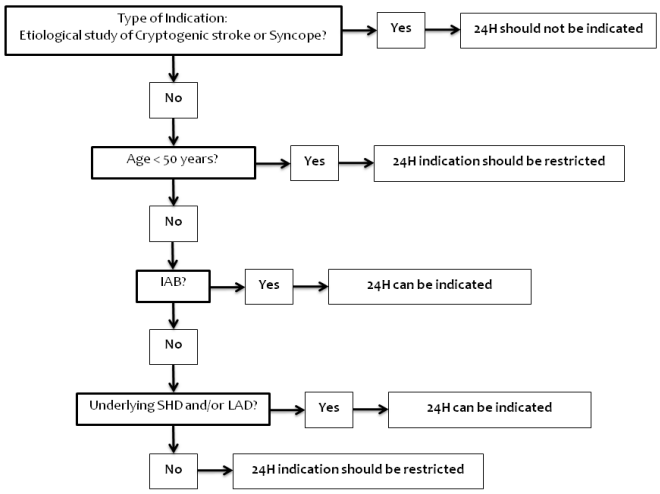

Figure 2: A suggested algorithm to guide indication for 24H monitoring.

On the basis of the results obtained in this study, a simplified stepwise algorithm is provided in order to optimize the diagnostic yield of 24H monitoring by means of a more accurate and restrictive selection of candidates.
IAB = Inter-atrial block; LAD = Left atrial dilatation; SHD = Structural heart disease.

The assessment of ventricular rate control in patients with permanent AF was considered almost always efficient in our study (98% of cases), since it provides a straight answer to the clinical question. Regardless of the apparently optimal diagnostic yield of this indication, alternative tests (especially a stress test) may provide a more 'physiological' characterization of the functional repercussion of permanent AF. Also considering that a more lenient AF's heart rate control is currently allowed, a restrictive use of 24H in this settingappears reasonable [21].

The acceptable yield of 24H for the assessment of the sinus/AV conduction (26.1%) appears grounded in a strong clinical/ECG suspicion of significant conducting system disturbance, as inferred from the observation of baseline sinus bradycardia, sinus pauses and/or 1st-2nd degree AVB among patients with positive 24H results in our series. In contrast, the presence of bifascicular block as an isolated finding (without additional AVB of any degree) did not enhance a

higher diagnostic performance. We therefore believe that, among asymptomatic patients, the sole finding of baseline bifascicular block should not become an indication for 24H in the search of advanced AVB.

The assessment of sudden death risk in patients with arrhythmogenic cardiomyopathyand of the arrhythmia burden in AF patients undergoing a rhythm-control strategy (yield of 14.6% and 16.6% in our series, respectively)is generally accepted, and we thus do not recommend revisiting such indication. Periodical 24H monitoring may indeed increase the ability of the technique to pick up AF relapses to up to 40% of cases [22].

In patients with non-documented palpitations (yield of 11.3%), alternative techniques to 24H should be considered, restricting initial 24H monitoring to patients with frequent (daily) symptoms. Otherwise, the primary use of external loop recorders or direct electrophysiological study (in selected patients with underlying cardiomiopathy, > 5-min episodes and sudden termination)is encouraged [23,24].

The 24H's diagnostic performance in the etiological study of syncope (3.2%) and cryptogenic stroke (4.6%) is unacceptably poor, and alternative diagnostic tools appear mandatory, from a sole carotid sinus massage (which has a higher performance than 24H in unselected patients with syncope) up to the indication of an electrophysiological study and/or implantable loop recorder implantation [3-5,7,14-17,20,25].

Predictors of a Higher Diagnostic 24H Yield: Role of Inter-Atrial Block

Three aspectsjustify the identification of IAB as a predictor of a higher 24H's diagnostic performance. First, the prevalence of IAB is associated with aging andwith underlying structural heart disease, two conditions that favor a higher incidence of both bradi- and tachy-arrhythmias. Second, IAB is indicative of an underlying impaired inter- and intra-atrial conduction as a consequence of an electrical/structural atrial remodeling process. Such pathological process specifically predisposes to the development of AF as the cause of palpitations, as it was demonstrated in our series by 7 out of the 9 documented AF relapses showing IAB with fair sensitivity (78%), specificity (73%) and negative predictive values (98%). The positive predictive value was, however, very low (17%), probably due to the somewhat low prevalence of IAB and, specially, the very low incidence of "de novo"AF documentation by means of 24H in our patient population. [17]. Finally, IAB is commonly linked to sinus dysfunction and/or AVB, and therefore the identification of IAB indirectly increments the likelihood of registering significant sinus dysfunction or advanced AVB. Our findings suggest that IAB identifies a subpopulation of patients in whom the likelihood of a positive 24H is higher. However, considering the prior evidence, the indication for 24H should also be settled on a strong clinical suspicion of significant bradi- or tachy-arrhythmias. The overall principle of a low diagnostic yield of 24H in the diagnosis of AF should, in our opinion, be maintained, since IAB not only "predicted" AF documentation, but it especially was accompanied by an overall higher diagnostic yield irrespective of the 24H's findings. We thus believe our findings should not prompt indication of 24H in the search of AF relapses on a routine basis, with the possible exception of patients undergoing AF ablation, in whom routine post-procedural 24H is the rule.

In our multi-variate analysis, the source of 24H indication (Cardiology department) determined a higher diagnostic yield of the technique. In our secondary analysis in which echocardiographic variables were included, however, it was confirmed that such apparent 'superiority' of the diagnostic performance of 24H proceeding from Cardiology is inherent to a selection bias of patients with a higher prevalence of underlying cardiomyopathy ($p < 0.001$), LAD ($p = 0.001$) and IAB ($p = 0.02$). It should be further noted that the type of indications that yielded a higher diagnostic performance (AF's rate control and assessment of sinus/AV conduction) were more frequently processed from Cardiology. Finally, although not becoming statistically significant in our series, a manifestly low yield of 24H in patients ≤ 50 years old (7% in our study) is in agreement with prior series. It therefore appears reasonable to encourage the use of this technique only in highly selected patients when age is under 50 years.

Altogether, an approximated suggested algorithm to guide the use of 24H taking into account all variables associated with an optimized diagnostic yield of this technique in our series (thus incorporating the identification of IAB) is provided in [Figure 2].

Limitations

This single-center study may have the limitations inherent to generalization of results from a single source of patients. Regardless of the inclusion of consecutive patients, the retrospective nature of this study may also be considered a significant limitation. Non-systematic echocardiographic data collection may have influenced the analysis of the predicting role of the variables EF and LAD. Although the vast majority of patients with AF documentation prompting a therapeutic change had underlying IAB (7 out of 9, 78%), a correlation analysis between IAB and AF documentation was not performed due to the very low incidence of AF during 24H registering. Finally, the assessment of silent myocardial ischemia and pacemaker dysfunction was not adequately analyzed in our study due to underrepresentation of both indications.

Conclusion

The type of indication and the identification of IAB dramatically influence the diagnostic performance of 24H, with other additional clinical, ECG and echocardiographic variables worthwhile to be considered in order to enhance an optimal patient selection of candidates to this diagnostic tool. The diagnostic yield of 24H for the etiological study of syncope and cryptogenic stroke is prohibitively low. The apparent higher efficiency of the test when it is indicated from a Cardiology department appears to be essentially influenced by an indirect selection of patients in whom the 24H's diagnostic yield is particularly high.

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Left Atrial Volume Index Predicts Arrhythmia-Free Survival in Patients with Persistent Atrial Fibrillation Undergoing Cryoballoon Ablation

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Abstract

Background

Pulmonary vein isolation (PVI) using cryoballoon ablation (PVI-C) is increasingly performed as a first-line strategy for the treatment of patients with persistent atrial fibrillation (PersAF); however, follow-up data and predictors of procedural success are lacking.

Objective

To study the efficacy of PVI-C in patients with PersAF, focusing on predictors of procedural success.

Methods

By retrospective review, 148 consecutive patients with PersAF who underwent PVI-C were analyzed. The impact of several variables on outcome was evaluated in univariate and multivariate analyses and Cox proportional hazards regression models.

Results

After a mean follow-up of 19.2±10.9 months, 75 (50.7%) patients remained arrhythmia-free without the need for antiarrhythmic drug therapy. Patients with a normal left atrial volume index (LAVI) achieved a 71.0% arrhythmia-free survival. LAVI was the most powerful predictor of procedural success.

Conclusions

Arrhythmia-free survival after PVI-C in select patients with PersAF are promising. Moreover, LAVI is a valuable measurement to help guide ablation strategy and predict outcome when using cryoballoon ablation.

Introduction

Pulmonary vein isolation (PVI) by catheter ablation is a well-established technique for the treatment of patients with persistent atrial fibrillation (PersAF).[1] Although the ideal treatment strategy for patients with PersAF remains incompletely defined, a PVI-only approach by cryoballoon ablation has been demonstrated to be an effective and reasonable therapy as a stand-alone treatment for patients with PersAF during the index procedure.[2-7] Also, cryoballoon ablation is non-inferior to radiofrequency current catheter ablation, and a PVI-only strategy has been found to be non-inferior to PVI plus the addition of linear and complex fractionated atrial electrogram ablation in patients with atrial fibrillation (AF).[8-10]

Most available data on PVI using cryoballoon ablation (PVI-C) in patients with PersAF involve small studies, short follow-up duration, and limited post-procedure monitoring. The focus of this retrospective analysis is to study the efficacy of PVI-C in a larger patient population with PersAF over a longer follow-up period. Specifically, we sought to identify predictors of procedural success that might guide treatment approach and ablation strategy.

Key Words

Catheter ablation, Cryoablation, Cryoballoon, Left atrial volume index, Persistent atrial fibrillation, Pulmonary vein isolation.

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Methods

Patients

Consecutive patients with symptomatic PersAF (refractory to medical therapy) who underwent PVI-C (Arctic Front Advance; Medtronic, Inc.) between March 2013 and January 2015 at the Meijer Heart Center (Spectrum Health Heart and Vascular, Grand Rapids, MI) were retrospectively analyzed by two independent reviewers. All data was obtained by review of the electronic medical record, and any incongruent data was appropriately adjudicated by the two independent reviewers. Approval for the study was granted by Spectrum Health's institutional review board. Patients who had undergone prior catheter ablation and/or had less than 3 months of follow-up post-procedure were excluded from the analysis.

PersAF was defined as AF lasting continuously for greater than 7 days but less than one year.[1] Patients with longstanding persistent AF lasting continuously for greater than one year were excluded. All

patients were refractory and/or intolerant to at least one antiarrhythmic drug (AAD) or in normal sinus rhythm on amiodarone prior to catheter ablation. Amiodarone failure was defined as recurrence of AF requiring cardioversion or catheter ablation following a standard loading period (typically 400mg twice daily for two weeks), or adverse side effects necessitating discontinuation. Demographic data and baseline characteristics were collected on all 148 patients [Table 1].

Cryoballoon Ablation Procedure

All patients underwent catheter ablation at Spectrum Health Heart and Vascular (Grand Rapids, MI) where more than 400 cryoballoon ablation procedures are performed annually. PVI was performed by a total of five board-certified cardiac electrophysiologists using standard protocols.[11] In brief description, all patients underwent a pre-operative transesophageal echocardiogram to exclude left atrial (LA) appendage thrombus, and all subjects were treated under general anesthesia. Groin access was obtained using ultrasound guidance in all patients. Immediately following groin access, a heparin bolus was delivered in advance of the transseptal puncture, and activated clotting time was monitored every twenty minutes with a goal of 350-400 sec. Initial transseptal puncture was performed using either a BRK or Baylis RF needle (Baylis Medical) depending on the operator. An electrophysiology study was completed in all patients prior to ablation.

Table 1: Baseline patient characteristics (N=148).

Characteristic	Value
Age (y)	62.2±9.1
Sex: male	106 (71.6%)
Body mass index (kg/m2)	32.8±6.2
CHA2DS2-VASc score	2.0±1.3
AF duration (months)	37.4±44.9
Persistent AF duration (months)	8.2±14.9
Number of cardioversions prior to ablation	2.1±1.1
Amiodarone failure	64 (43.0%)
Co-morbid conditions	
Hypertension	110 (74.3%)
Left ventricular hypertrophy	15 (10.2%)
Type II diabetes	31 (21.1%)
Coronary artery disease	42 (28.4%)
Prior myocardial infarction	11 (7.4%)
Prior percutaneous coronary intervention	11 (7.4%)
Prior coronary artery bypass surgery	8 (5.4%)
Congestive heart failure	31 (21.0%)
Chronic kidney disease	21 (14.3%)
Chronic obstructive pulmonary disease	16 (10.8%)
Obstructive sleep apnea	72 (48.7%)
CPAP* compliance (N=72)	52 (72.2%)
Echocardiographic parameters	
Left ventricular ejection fraction	55.2±6.7
Left atrial diameter (cm; N=141)	4.4±0.5
Left atrial volume index (ml/m^2; N=135)	36.5±8.1

* CPAP= continuous positive airway pressure

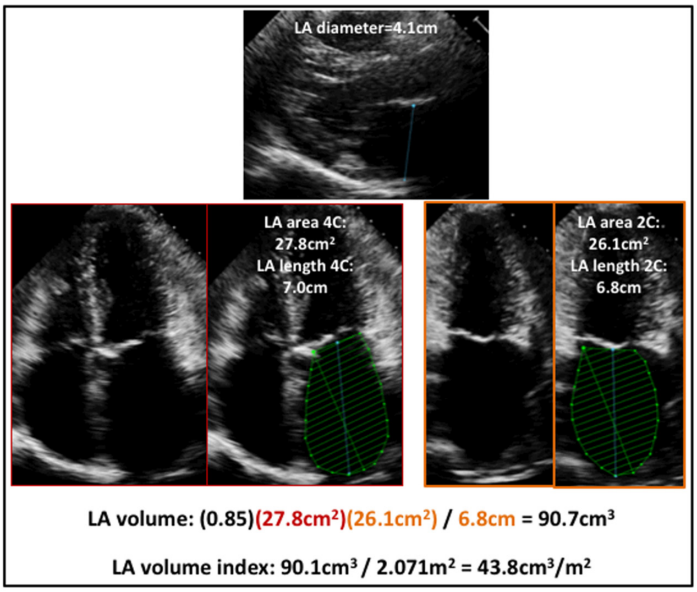

Figure 1: Sample left atrial volume measurement in a patient with a moderately dilated left atrium. Note that atrial size is underappreciated by left atrial diameter.

An over-the-wire method was used to deliver the cryoballoon and sheath (FlexCath; Medtronic, Inc.) into the left atrium. All patients were treated with the 28-mm cryoballoon and 20-mm Achieve mapping catheter. The number of freeze applications per PV was operator-dependent, but most patients received two (180-second) freeze applications. It was at the operator's discretion to perform a single-freeze application based on time-to-isolation, temperature achieved at 60 sec, and/or cryoballoon thaw times. Esophageal temperature monitoring was performed in all cases. Phrenic pacing and monitoring were performed during ablation over the right-sided PVs. Cardiac mapping with EnSite (St Jude Medical) was used in most cases to guide diagnostic catheters, and evaluate post-procedural LA electrophysiology by voltage mapping. PV entrance and exit block were proven in all patients.

Echocardiography

All patients underwent transthoracic echocardiography prior to PVI-C to measure LA dimensions, to assess for the presence of significant valvular heart disease, and to record left ventricular ejection fraction. If these studies were performed by a referring hospital, then the images from the study were obtained for review. All echocardiography studies were reviewed and interpreted by a single board-certified echocardiographer. The LA diameter was measured in the long-axis parasternal view in the anterior-posterior dimension at end-ventricular systole.

The area-length method was used to calculate LA volume index (LAVI).[12] All measurements were performed in the standard apical 4-chamber (A4C) and 2-chamber (A2C) views at end-ventricular systole. LA volume was calculated using the equation (0.85 × A1 × A2)/L, where A1 was the planimetered area measured in the A4C view, A2 was the planimetered area measured in the A2C view, and

L was the shortest length measured in A4C and A2C from the back wall of the atrium to a line across the mitral valve hinge points. The LAVI was then derived by dividing LA volume by body surface area. This calculation is demonstrated in [Figure 1]. LA size was categorized using standard criteria.[12] Specifically, LA sizes were grouped into four separate cohorts, including: normal (<34 ml/m2), mildly enlarged (34-41 ml/m2), moderately enlarged (42-48 ml/m2), and severely enlarged (>48 ml/m2). Repeat echocardiography was performed in the event of symptoms such as hypotension, tachycardia, chest pain, or shortness of breath.

Complications

Catheter ablation procedure-related adverse events were categorized into major, moderate, and minor complications. Major complications included stroke or transient ischemic attack, myocardial infarction, pericardial tamponade, PV stenosis, emergency cardiac surgery, resuscitation, or atrioesophageal fistula. Moderate complications included hematoma requiring transfusion (major bleeding), femoral arteriovenous fistula, pseudoaneurysm, or persistent phrenic nerve paresis (PNP). Specifically, persistent PNP was defined as any PNP that remained present at the end of the ablation procedure. Minor complications including small hematoma (not requiring transfusion) and transient PNP were not quantified in this study. Transient PNP was defined as any PNP that resolved prior to the end of the ablation procedure.

Data Collection and Follow-up

Routine follow-up assessments were conducted in accordance with a standard protocol at our center. All follow-up clinic visits were scheduled at 3 months and 12 months post-procedure, then annually if the patient remained free of arrhythmias and symptoms. Each follow-up clinic visit focused on AF-related symptoms to determine arrhythmia recurrence. A 14-day patch monitor was routinely ordered at 6- and 12-months post-procedure in all patients for detection of any occult AF, and as needed thereafter to assess symptoms.

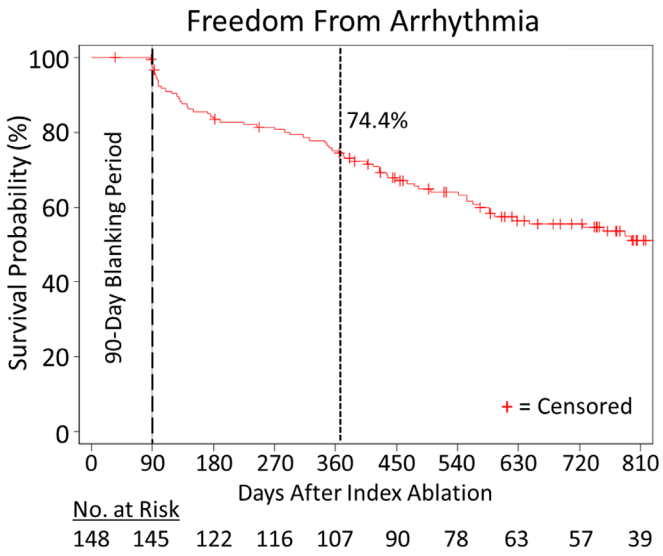

Figure 2: Arrhythmia-free survival without antiarrhythmic drug therapy following pulmonary vein isolation by cryoballoon ablation.

Long-term Efficacy

The primary efficacy endpoint for this study was defined as the freedom from atrial arrhythmia (AF, atrial flutter, and/or atrial tachycardia) outside of a landmark 90-day blanking period following the index cryoballoon ablation procedure with no usage of AADs during the 12-month follow-up period. Within the blanking period, no early recurrence of atrial arrhythmia events were counted against the long-term clinical outcome. Patients who achieved complete success had no detected atrial arrhythmia recurrence (> 30 sec) or symptoms of AF post-ablation and did not require AAD therapy beyond the blanking period. Patients who had confirmed detection of a recurrence of atrial arrhythmia (>30 sec) after the blanking period, required AADs, underwent repeat catheter ablation, and/or degenerated to permanent AF with adoption of a rate control strategy (because of symptom resolution in AF post-ablation) were deemed procedural failures.

Statistical Analysis

Descriptive statistics were used to summarize patient characteristics, procedural characteristics, safety, and follow-up. Numeric variables are shown as mean ± standard deviation. Categorical variables are

Table 2: Cryoballoon ablation procedural characteristics (N=148).

Characteristic	Value
Procedural time (min)	112.2±42
Fluoroscopy time (min)	15.8±11.1
Cryoablation time (min)	27.4±7.0
Acute PVI* success rate (treated veins/target veins)	585/585 (100%)
Adjunctive radiofrequency ablation for PVI (patients)	10 (6.8%)
Nadir cryoballoon temperatures (°C)	
Left superior pulmonary vein (N=140)	-48.3±5.9
Left inferior pulmonary vein (N=140)	-44.6±4.7
Right superior pulmonary vein (N=148)	-46.9±13.8
Right inferior pulmonary vein (N=148)	-45.2±6.1
Left common pulmonary vein (N=8)	-41.1±8.4

* PVI= pulmonary vein isolation

Table 3: Procedural complications (N=148).

Characteristic	N (%)
Moderate complications (Total)	5 (3.4)
Persistent diaphragmatic paralysis	3 (2.0)
Hematoma	1 (0.7)
Femoral pseudoaneurysm	1 (0.7)
Arteriovenous fistula	0 (0.0)
Major complications (Total)	0 (0)
Stroke/transient ischemic attack	0 (0.0)
Pericardial tamponade/effusion	0 (0.0)
Pneumothorax/hemothorax	0 (0.0)
Pulmonary vein stenosis	0 (0.0)

shown as count with frequency (%). All arrhythmia recurrence graphs were completed using a Kaplan-Meier estimate method. Univariate Cox regression models were used to determine what variables were significant by themselves in predicting arrhythmia recurrence. A significance level of P<0.10 was used for the first round of cuts. After those cuts were made the variables that had a p-value less than 0.10 were included in a multivariate Cox regression model to determine the final predictors of arrhythmia recurrence. To determine the final predictors, backward selection was used with a significance level of P<0.05. Fishers Exact test or one-way ANOVA were used to further examine demographic characteristics after multivariable analysis. All statistical analyses were generated using SAS (SAS Enterprise Guide software, Version 7.1, SAS Institute Inc, Cary, NC).

Results

From August 2013 to November 2015, a total of 200 consecutive subjects with PersAF underwent a PVI-C. Forty-nine patients had previously undergone radiofrequency catheter ablation and were excluded from this analysis. One patient required an emergent coronary artery bypass graft within three months of PVI-C, underwent a concomitant Maze procedure, and was also excluded. Two patients did not have adequate follow-up of at least 6 months post-procedure. Finally, 148 patients were included in this analysis. Clinical outcomes were determined by retrospective chart analysis performed by two independent reviewers with initial agreement in 138/148 (93.2%) of cases. The ten cases with conflicting outcome data were appropriately adjudicated by the study authors.

Table 4: Post-procedure follow-up and monitoring (N=148).

Characteristic	N (%)
Follow-up clinic visit with accompanying ECG	146 (98.7)
Long-term rhythm monitoring	126 (85.1)
14-day patch monitor	104 (70.3)
30-day event monitor	9 (6.1)
Loop recorder	6 (4.1)
Pacemaker implant	11 (7.4)

Baseline Characteristics

Baseline patient characteristics are summarized in [Table 1]. The mean age was 62.2±9.1 years, and 28.4% of the subjects were women. Mean BMI was 32.8±6.2 kg/m2, and 43.0% of patients failed amiodarone therapy prior to ablation either because of ineffectiveness or side effects. The time from the diagnosis of paroxysmal and PersAF to catheter ablation was 37.4 months and 8.2 months, respectively. On average, patients had two prior direct-current cardioversions before the index PVI-C.

Procedural Data and Complications

Mean procedure time was 112.2±42 minutes, and the mean fluoroscopy time was 15.8±11.1 minutes. Acute PVI was achieved in 100% of the cases. Ten patients (6.8%) required adjunctive radiofrequency catheter ablation performed on a total of eleven PVs to achieve complete electrical PVI. In those aforementioned cases, the adjunctive radiofrequency ablations were required over the inferior aspect of the right inferior PV (4 patients), inferior aspect of the left inferior PV (3 patients), anterior aspect of the right superior PV (3 patients), and anterior aspect of the left inferior PV (1 patient). The procedural data are shown in [Table 2], including cryoballoon nadir temperatures during cryoballoon ablation. There were no major complications, and moderate complications occurred in five patients [Table 3]. Three patients experienced PNP (lasting beyond the end of the procedure), all of which completely resolved within 6 months. One patient developed a hematoma, and one patient had a femoral pseudoaneurysm.

Echocardiographic Characteristics

Mean LA diameter measured 4.4±0.5cm, and the mean LAVI measured 36.5±8.1 ml/m2 [Table 1]. Raw echocardiography data for review and analysis was available on 135 (91.2%) patients, and LA dimensions could not be measured and confirmed in 13 (8.8%) patients. Using LAVI, 62 (45.9%) patients had a normal LA size (29.8±3.1 ml/m2), 42 (31.1%) patients had a mildly enlarged LA (37.5±2.3 ml/m2), 18 (13.3%) patients had a moderately enlarged LA (44.7±1.4 ml/m2), and 13 (9.6%) patients had a severely enlarged LA (53.5±3.4 ml/m2).

Table 5: Arrhythmia-free survival model.

	Univariate Analysis				Multivariate Analysis			
Covariate	Coefficient (bi)	HR [exp(bi)]	95% CI	P-value	Coefficient (bi)	HR [exp(bi)]	95% CI	P-value
Number of pre-procedure electrical cardioversions	0.17	1.18	(0.98-1.44)	0.086				0.114
Nadir LSPV*balloon temperature	0.04	1.04	(1.00-1.08)	0.056	0.04	1.05	(1.00-1.09)	0.034
Left atrial AP diameter	0.05	1.05	(1.01-1.10)	0.026	-0.07	0.93	(0.88-0.99)	0.021
Hypertension	0.56	1.75	(0.94-3.26)	0.076				0.860
Left atrial volume index				<0.001				0.003
1-Normal	(0.00)	(1.00)			(0.00)	(1.00)		
2-Mild	1.10	3.00	(1.65-5.45)		1.13	3.11	(1.62-5.95)	
3-Moderate	0.76	2.14	(1.00-4.57)		0.88	2.41	(0.89-6.51)	
4-Severe	1.96	7.07	(3.36-14.89)		1.58	4.86	(1.69-13.98)	

*LSPV= left superior pulmonary vein

Table 6: Demographic analysis by left atrial volume index subcategories.

	Left atrial volume index				
Variables	Normal (N=62)	Mild (N=42)	Moderate (N=18)	Severe (N=13)	P-value
Age	60.6±9.6	62.2±8.8	61.9±7.1	68.3±10.4	0.054
Hypertension	38 (61.3%)	35 (83.3%)	16 (88.9%)	10 (76.9%)	0.030
Left atrial A/P diameter	40.7±3.9	44.2±4.5	48.6±3.8	49.8±5.3	<0.001
Prior CABG	0 (0%)	4 (9.5%)	2 (11.1%)	2 (15.4%)	0.010
Valvular heart disease	3 (4.8%)	5 (11.9%)	6 (33.3%)	1 (7.7%)	0.013

* CABG= coronary artery bypass

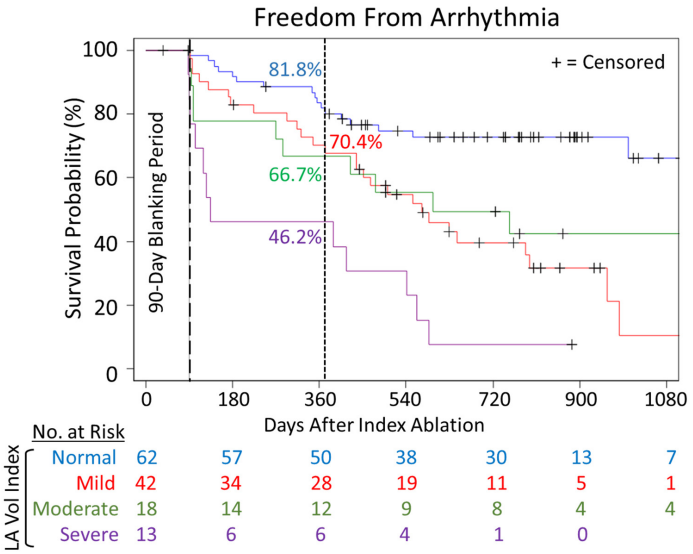

Figure 3: Examination of sub-groups (by left atrial volume index) from normal to severe left atrial enlargement.Arrhythmia-free survival without antiarrhythmic drug therapy following pulmonary vein isolation by cryoballoon ablation.

Clinical Success Rate

One-year complete arrhythmia-free success rate was 74.4% (95% CI, 66.4-80.7%). After a mean follow-up of 19.2±10.9 months, 75 patients (50.7%) patients remained in sinus rhythm without any evidence of AF recurrence off AAD therapy [Figure 2].

Post-Procedure Electrocardiographic Monitoring

Follow-up clinic visit with accompanying ECG was completed by 98.7% of patients (146/148). During follow-up, 126 (85.1%) patients were evaluated with some form of long-term monitoring, and 104 (70.3%) patients received a 14-day patch monitor. Typically, 14-day monitors were placed at 6- and 12-months post-procedure. Nine patients (6.1%) were fitted with a 30-day event monitor, six patients (4.1%) were monitored with an implantable loop recorder, and eleven patients (7.4%) had pacemakers. These data are summarized in [Table 4].

Predictors of Arrhythmia Recurrence

LAVI was identified as a primary predictor of arrhythmia recurrence (P=0.003) [Table 5]. LA diameter and cryoballoon nadir temperature were also predictors of arrhythmia recurrence (P=0.021 and P=0.034; respectively). Multiple covariates (including age, BMI, OSA, valvular heart disease, and prior coronary artery bypass graft) did not predict procedural success [Table 1].

Predictive Value of LAVI

Patients with a normal LAVI achieved 71.0% arrhythmia-free survival during the long-term follow-up period. Patients with mildly and moderately enlarged atria achieved 33.3% and 38.9% arrhythmia-free survival, respectively. Patients with a severely dilated LA (by LAVI) only achieved 7.6% arrhythmia-free survival. These results (including one-year success rates) are displayed in [Figure 3]. Further evaluation of all patient baseline characteristics by LAVI sub-groups uncovered five unique interactions [Table 6]. Patients with severe LA dilation (by LAVI) were generally older in age compared to the normal, mild, and moderate sub-groups of patients (P=0.054). Also, patients with normal LAVI had a lower baseline incidence rate of hypertension, prior coronary artery bypass graft, and/or valvular heart disease (P=0.030, 0.010, and 0.013; respectively). Finally, LA diameters (A/P) were progressively larger from normal to severe LAVI, as expected (P<0.001); however, LAVI remained the most predictive baseline characteristic regarding long-term arrhythmia-free survival.

Discussion

Our study has two important clinical findings. First, PVI-C used in the treatment of patients with PersAF is safe and effective, which is in agreement with other large multicenter real-world observations.[4-8] Second, the data demonstrated that LAVI is a strong predictor of PVI-C procedural success in patients with PersAF. Previous associations have only been described in paroxysmal AF populations.[13-14]

LAVI as a Predictor of Procedural Outcome

It is established that LA volume predicts AF-free survival during radiofrequency catheter ablation,[15-16] and similarly, predicts response in patients with paroxysmal AF treated by PVI-C.[13-14] Yet, LAVI remains unstudied in a large cohort of PersAF patients treated by PVI-C. In fact, many studies of cryoballoon ablation in the treatment of AF fail to measure LAVI, but instead only report linear LA dimension.[2,4-8] Similar to our findings, LA diameter (A/P) has not been shown to be a reliable or strong predictor of procedural success in most studies.[2,4-8] However, the pitfalls of using LA diameter as a surrogate for LA size have been appreciated for several years.[17] It is known that atrial enlargement can occur predominately in the superior-inferior dimension, with relative preservation of the anterior-posterior dimension. This is illustrated in [Figure 1], where a LA diameter measurement underestimates the true LA size. LA volume has consistently outperformed both LA diameter and area in the prediction of cardiovascular outcomes including AF, stroke, TIA, myocardial infarction, heart failure, and death.[17]

LA enlargement is often a consequence of increased atrial pressure

and hemodynamic overload, triggering stretch receptors with release of angiotensin and TGF-ß, and activation of fibroblasts leading to collagen deposition.[18] Atrial fibrotic burden has been correlated with arrhythmia recurrence following ablation.[19] Although the dominant paradigm has been that all patients with PersAF have more advanced atrial remodeling and should undergo substrate modification in addition to PVI, our data suggests that LA size as determined by LAVI may be more important than AF type.

In our analysis, patients with PersAF and normal LAVI were observed to have success rates similar to patients with paroxysmal AF undergoing PVI with the second-generation cryoballoon. Chierchia [20] and Furnkranz [21] reported one-year arrhythmia free survival in 83% and 84% of patients, respectively, undergoing cryoballoon ablation for paroxysmal AF. This compares to our one-year success rate of 82% in patients with a normal LAVI. Similarly, the PLAAF score predicts that PersAF is only one of five risk factors for AF recurrence and that a long-term freedom from AF can be predicted in male patients with non-enlarged LA, normal 4-PV anatomy, and who have a shorter history of AF.[13] Based on these findings, it is reasonable to approach initial ablation using a PVI-only strategy in patients with PersAF and a normal LAVI.

For patients with significant atrial enlargement, especially severely dilated LA by volume index, a PVI-only strategy is likely to fail. Although there is not consensus on how to approach non-PV trigger elimination and substrate modification after effective PVI, there are several strategies that have been proposed including posterior wall ablation, superior vena cava and appendage isolation, ligament of Marshall ablation, trigger mapping, and hybrid ablation techniques. [22,23] Our data show that patients with mild-to-moderately dilated LA can still have a favorable outcome with a PVI-only strategy, and in patients with multiple co-morbidities, this strategy may be preferable to a higher-risk ablation procedure with extensive substrate modification.

Moderate-to-severe LAVI was the primary predictor of failure to achieve long-term arrhythmia-free survival. Importantly, in this study, patients with moderate and severe LAVI were older, hypertensive, had prior coronary artery bypass graft, and/or had a history of at least moderate valvular heart disease. Consequently, other baseline characteristics may be of importance when considering an ablation strategy, and usage of scoring systems (e.g., PLAAF) may be an imperative part of the final decision.[13]

Complications

Moderate complications occurred in 3.4% of patients and were limited to either persistent phrenic injury or groin complications. We observed PNP in 2% of our patient population (although rates of PNP after PVI with the second-generation cryoballoon can range up to 5.5%).[21] Access-site complications occurred in 1.4% of our patients, which is comparable to previously reported rates.[1] There were no major complications, and minor complications were not assessed.

Limitations

Our study was a single-center, retrospective, observational analysis without a control group. In addition, a large percentage (45.9%) of our patients were found to have a normal LAVI, which may (in part) explain our favorable outcome data. All consecutive patients with PersAF undergoing an index PVI-C were included (reducing but not eliminating selection bias since not all patients with PersAF were offered ablation). We also did not assess the outcome on AAD therapy without ablation.

Our follow-up period is moderate in duration and not necessarily predictive of longer-term outcomes. We also recognize that intermittent rhythm monitoring as used in this study is inferior to continuous monitoring with an implantable loop recorder. However, 85% of our patient population underwent some form of long-term monitoring, mostly using a 14-day patch monitor. This is an improvement over most historical trials which use clinic follow-up and 24-hour Holter monitors for post-ablation arrhythmia surveillance.[1] Also, we did have a 98.7% clinic follow-up rate, and chart analysis performed by two independent reviewers with initial agreement in 138/148 (93.2%) of cases.

LAVI was meticulously calculated by a board-certified echocardiographer. However, LAVI by echocardiography is imperfect, and other techniques such as three-dimensional echocardiography or cardiac CT/MRI may provide a more accurate assessment.

Although one physician operator did perform intermittent single-shot ablation, because of the date range of the collection (2013-2015), only 8 pulmonary veins were treated using this technique. This precluded us from making any meaningful analysis of single vs two-shot ablation. It is now acknowledged that single-shot protocols are widely adopted, and that cryoballoon usage parameters are important towards outcomes. Unfortunately, use parameters were not evaluated in the current study.

Conclusion

Arrhythmia-free survival after PVI-C in selected patients with Pers AF are promising. LAVI is a valuable measurement to help guide ablation strategy and predict outcome when utilizing cryoballoon ablation.

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Left Atrial Appendage Morphology as a Determinant for Stroke Risk Assessment in Atrial Fibrillation Patients: Systematic Review and Meta-analysis

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Abstract

Background

Atrial fibrillation (AF) is a leading source of emboli that precipitate cerebrovascular accident (CVA) which is correlated with left atrial appendage (LAA) morphology. We aimed to elaborate the relationship between CVA and LAA morphology in AF patients.

Methods

Medline and EMBASE databases were thoroughly searched between 2010-2018 for studies that included atrial fibrillation patients and classified them into two groups based on CVA occurrence. Four different LAA morphologies (chicken wing CW, cauliflower, cactus and windsock) were determined in each group by 3D TEE, MDCT or CMRI. New Castle Ottawa Scale was used to appraise the quality of included studies. The risk of CVA before cardiac ablation and/or LAA intervention in CW patients was compared to each type of non-CW morphologies. The extracted data was statistically analyzed in the form of forest plot by measuring the risk ratio (RR) using REVMAN software. P value and I square were used to assess the heterogeneity between studies.

Results

PRISMA diagram was illustrated showing 789 imported studies for screening. Three duplicates were removed, and the rest were arbitrated by 2 reviewers yielding 12 included studies with 3486 patients including 1551 with CW, 442 with cauliflower, 732 with cactus, and 765 with windsock. The risk of CVA in CW patients was reduced by 41% relative to non-CW patients (Total RR=0.59 (0.52-0.68)). Likewise, the risk of CVA in CW patients was less by 46%, 35% and 31% compared to cauliflower (Total RR =0.54(0.46-0.64)), cactus (Total RR =0.65(0.55-0.77)) and windsock (Total RR =0.69(0.58-0.83)) patients respectively. Low levels of heterogeneity were achieved in all comparisons (I^2 <35% and p value > 0.1).

Conclusions

Patients with non-CW morphologies (cauliflower, cactus and windsock) show a higher incidence of CVA than CW patients. For that reason, LAA appendage morphology could be useful for risk stratification of CVA in AF patients.

Introduction

Atrial fibrillation AF is the most common sustained arrhythmia with an estimated prevalence of 1-1.5% in the general population and up to 10% in the elderly.[1-3] AF has been associated with significant morbidity, mortality, and healthcare resource utilization and costs.[4][5]AF is associated with a five-fold increase in the risk of cardioembolic stroke,[5]and is implicated in approximately 25% of strokes in patients over 80 years of age.[5]

Key Words

Atrial fibrillation, Left atrial appendage, Stroke.

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Stroke prevention is a top clinical priority and a focus of ongoing investigation.The left atrial appendage (LAA) has been implicated in more than 90% of cardioembolic strokes in AF.[6-8] The anatomic characteristics of the LAA could underlie some of this risk and could be particularly important in identifying patients with lower CHA2DS2-VASc score that would benefit from thromboprophylaxis.[6-8] One of these features is the LAA morphology or shape. Four different types of LAA morphology: 1) chicken wing 2) wind sock 3) cauliflower and 4) cactus. These morphologies can be defined by echocardiography, cardiac computed tomography (CT) or cardiac magnetic resonance imaging (CMRI).[9]

For that purpose, we aimed to perform a systematic review/meta-analysis study to summarize and statistically analyze the prevalence

of stroke/TIA associated with each type of LAA morphology. We aimed to determine whether there is an association between the risk of TE and the shape of LAA in patients with AF, especially those with low CHA2DS2-VASc score.

Methods

Search strategy

Ovid MEDLINE database from 1946 to November 29, 2018 and Embase database from 1988 to November 29, 2018 were searched by a professional librarian (PE) for all articles that addressed LAA morphology in patients with AF and were published between January 2010 and November 2018. The following keywords were used to perform the literature search: (atrial fibrillation OR AF) AND (left atrial appendage OR LAA OR left atrial appendage morphology OR left atrial appendage anatomy, OR left atrial appendage geometry OR left atrial appendage shape, OR left atrial appendage hemodynamic) AND (stroke, transient ischemic attack, cardioembolic event, thromboembolism, or cerebrovascular attack) AND (cardiac magnetic resonance imaging OR 3D transesophageal echocardiography OR multi gated cardiac computed tomography). Furthermore, we reviewed references listed in bibliographies of two comprehensive review articles to ensure that all relevant studies were included in our search.[10,11]

Study design and Selection criteria

We performed a systematic review/meta-analysis in accordance with PRISMA guidelines. A PRISMA-style flow diagram was prepared to clarify the total number of references retrieved by search and how many articles were excluded during the screening process and the final number of included studies utilized for data extraction.

All the references were imported to Covidence systematic review software (Veritas Health Innovation, Melbourne, Australia)and then underwent an accurate screening process by two independent reviewers (AA and JF) based on title and abstract followed by full text review to determine the final included studies for data extraction. Any discrepancies were resolved by discussing with a third independent reviewer (DA).

All included studies met the following criteria: 1) included patients with AF in whom multi-gated cardiac CT, CMRI or (3D TEE) were carried out before a cardiac ablation, 2) LAA morphology characteristics were obtained, 3) all patients were classified according to the shape of LAA, and 4) the rate of cardioembolic stroke/TIA was documented in each LAA appendage shape.

Studies that were published before January 2010, not published in English, limted to imaging results after cardiac ablation, basic science/animal studies, review articles, case reports, pediatric studies, included pregnant patients, commentaries, editorials, conference papers or posters were excluded from our review.

Table 1: Demographics and general characteristics of all included patients.

Author/year	Type of study	Sample Size	Male	Age	DM	HTN	Hyperlipidemia	Patients with CHADS2 ≥2	Patients with CHA2DS2-VASc≥2	Stroke/TIA	Imaging
Di Biase 2012(25)	Prospective	932	734 (78.8%)	59 ±10	40(4.3%)	450 (48.3%)	218 (23.4%)	127 (13.6%)	N/A	78 (8.4%)	MDCT (433) or MRI (499)
Khurram 2013(20)	Retrospective	678	507 (74.8%)	59±9.7	44 (6.5%)	327 (48.4%)	N/A	113 (16.6%)	274 (40.4 %)	65 (9.6%)	MDCT
Kimura 2013(26)	Retrospective	80	66 (82.5%)	58.6 ± 6	N/A	N/A	N/A	11 (13.8 %)	N/A	30 (37.5%)	MDCT
Kong 2014(27)	Retrospective	219	143 (65.3%)	59 ±7.5	19 (8.7%)	80 (36.5%)	N/A	15 (7%)	77 (35.2%)	26 (11.9%)	MDCT
Kosiuk 2014(28)	Retrospective	85	50 (58.8%)	64 ±11	19 (22%)	63 (74.1%)	N/A	N/A	Median: 3 (2-4)	23 (27.05%)	MDCT
Lee 2014(29)	Retrospective	218	166 (76.4%)	61±9.5	33 (15%)	113 (51.8%)	49 (22.5%)	N/A	Mean: 1.5 +/-1.2	67 (30.7%)	MDCT
Fukushima 2015(24)	Retrospective	96	72 (75 %)	59 ±10.2	12 (13%)	46 (47.9%)	34 (35.4%)	19 (19.8%)	19 (19.8%)	10 (10.4%)	3D-TTE MDCT
Kelly 2017(30)	Retrospective	332	278 (83.7%)	55 ±13	48 (15%)	200 (60.2%)	N/A	N/A	162 (48.8%)	16 (4.8%)	MDCT
Nedios2015(31)	Retrospective	100	88 (88%)	55 ±9	N/A	46 (46%)	23 (23%)	0 (0%)	0 (0%)	25 (25%)	MDCT
Petersen 2015 (32)	Retrospective	131	86 (65.6%)	68±11.6	23 (18%)	62 (47.3%)	N/A	N/A	82 (62.7%)	16 (12.2%)	3D-TEE
LEE 2015(23)	Retrospective	360	302 (63.7%)	64 ± 7	77	224 62.2%	75 (20.8%)	N/A	Mean: 1.75 +/-1.15	160 (44.44%)	3D-TEE MDCT
Lee 2017(33)	Retrospective	255	150 (58.8%)	65 ±7	33 (13%)	55 (21.6%)	N/A	95 (37.25%)	95 (37.25%)	170 (66.7%)	MDCT

Table 2: The distribution of different LAA shape with number and percentage of stoke events in each shape.

Author/year	Sample Size	Chicken Wing		Cauliflower		Cactus		Windsock	
		Total number	Stroke patients	Total number	Stroke patients	Total number	Stroke patients	Total number	Stroke patients
Di Biase 2012 (25)	932	451	20 (4.4%)	24	4 (16.7%)	278	35 (12.6%)	179	19 (10.6%)
Khurram 2013 (20)	678	306	24 (7.8%)	68	11 (16.17%)	125	15 (12%)	179	15 (8.38%)
Kimura 2013 (26)	80	14	3 (21.4%)	32	18 (56.3%)	4	2 (50%)	30	7 (23.3%)
Kong 2014 (27)	219	114	6 (5.26%)	29	7 (24.13%)	24	3 (12.5%)	52	10(19.2%)
Kosiuk 2014 (28)	85	25	5(20%)	30	13 (43.3%)	19	4 (21.05%)	11	1 (7.7%)
Lee 2014 (29)	218	110	33 (30%)	22	7 (31.8%)	24	7 (29.2%)	62	20 (32.3%)
Fukushima 2015 (24)	96	12	1 (8.3)	16	3 (18.8)	37	4 (10.8)	31	2 (6.5%)
Kelly 2017 (30)	332	190	9 (4.7%)	44	4 (9%)	15	0	83	3 (3.6%)
Nedios 2015 (31)	100	32	6 (19)	40	11 (28)	18	5 (28)	10	3 (30%)
Petersen 2015 (32)	131	56	6 (10.7%)	11	0	20	4 (20%)	44	16 (13.6%)
LEE 2015 (23)	360	155	55 (35.4%)	50	29 (58%)	108	52 (49.48 %)	47	24 (51.06%)
Lee 2017 (33)	255	86	41 (47.6%)	72	66 (91.67%)	60	41 (68.33%)	37	22 (59.4%)
Total	3486	1551	209 (13.5%)	438	173 (39.4%)	732	172 (23.5%)	765	142 (18.6%)

Data extraction

Three independent authors (AA, JF, and JS) participated in data extraction using standardized protocol and reporting forms. Any discordances were resolved by consensus with the fourth reviewer (DA).Demographics (sample size, age, gender and smoking status), clinical characteristics (hypertension, diabetes mellitus, hyperlipidemia, CHA2DS2 or CHA2DS2-VASc score), employed imaging modality (multi gated cardiac CT, CMRI or (3D TEE)), type of LAA shape (chicken wing (CW), non-chicken wing which includes cactus, cauliflower and windsock) and number of strokes in each shape were extracted.

Quality appraisal

Newcastle-Ottawa quality assessment scale (NOS)[12] was utilized to appraise the quality of all included studies. The checklist form for cohort studies of NOS was considered for our assessment. It consists of three categories: Selection which contains four subcategories (representativeness of the exposed cohort, selection of the non-exposed cohort, ascertainment of exposure and demonstration that outcome of interest was not present at start of study), comparability (are cohort groups compared to study controls) and outcome which comprises of three subcategories (assessment of outcome, was follow-up long enough for outcomes to occur?, adequacy of follow-up of cohorts). Studies werethen classified into one of three categories: a) goodquality 6-7 points b) fair quality 3-5 points and c)poor quality 0-2 points.

Statistical analysis

Continuous variables were expressed as means and standard deviations (SD), whereas dichotomous and categorical variables were presented as number of cases (n) and percentages (%). Review Manager (RevMan 5.3; Copenhagen, Denmark)[13] was employed to execute the statistical meta-analysis in the form of forest plots. In our analysis, data were analyzed using Cochran-Mantel-Haenszel Estimate for a Risk Ratio(RR) in the fixed-effects model.[14] A confidence interval of 95% (95% CI) was selected for the effect size. Heterogeneity was assessed by Chi-square, and I^2 tests, and publication bias was determined using funnel plots. Homogeneity was indicated when p-value > 0.1 and I^2 <50% [15] and absence of publication bias was defined when all studies (dots) exist within the funnel in a symmetrical manner.

We prepared four forest plots to evaluate the risk of stroke/TIA between chicken wing versus non-chicken groups and chicken wing versus each of the subtypes of non-chicken wing morphology.

Results

Study selection

Our literature search yielded 789 references which were imported to Covidence systematic review software (Veritas Health Innovation, Melbourne, Australia). Three duplicates were removed, and 786 articles entered the title and abstract screening process. Subsequently, 714 articles were irrelevant, and 72 studies were assessed for final eligibility by reviewing thefull-text version. As a result, twelve studies fulfilled the inclusion criteria and were included in data extraction and meta-analysis, whereas 50 studies were excluded due to the following reasons: wrong outcomes in 42 studies, wrong patient population in 2 studies, wrong study design in one study, two non-English articles, three conference papers.

Demographics and clinical characteristics

We analyzed 3,486 patients whom their data were included and analyzed in our meta-analysis. [Table 1] shows the demographics and characteristics of all included patients. Male gender wasnoted in 72.3% of the final sample. The mean age was 60.6 years old. About 49.5 % (in eleven studies only) and 15 % (in nine studies) were having hypertension and diabetes mellitus respectively. LAA morphology was determined by multi gated cardiac CT in eleven studies, CMRI in one study and (3D TEE) in three studies. The overall prevalence of cardioembolic stroke in the studied population was 20 (n = 696).

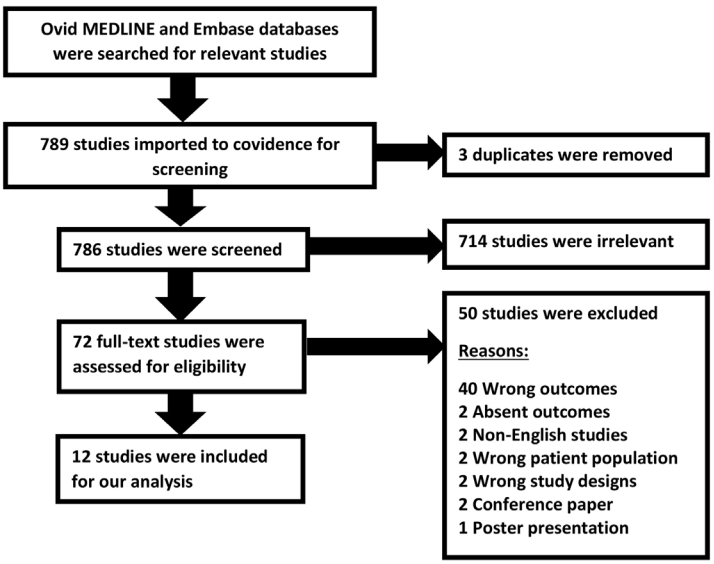

Figure 1: **The PRISMA flow diagram and summarizes the process search strategy.**

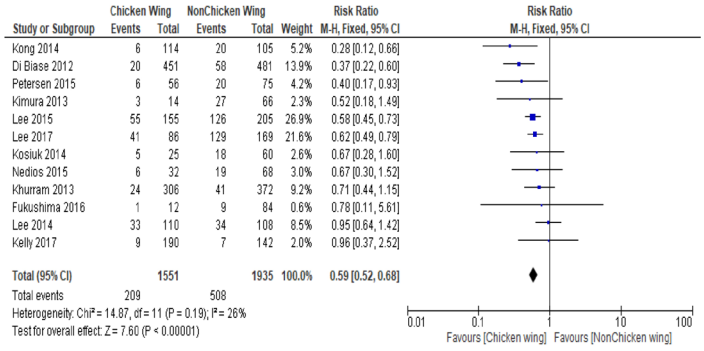

Figure 2: **Forest plot compares the risk of cardioembolic events (stroke, TIA) between CW patients and non-CW patients.**

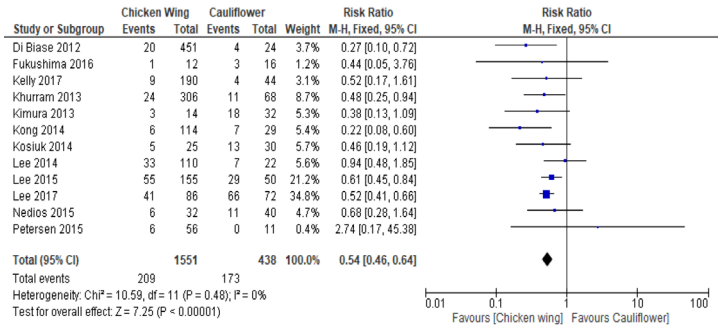

Figure 3: **Forest plot compares the risk of cardioembolic events (stroke, TIA) between CW patients and cauliflower patients.**

[Table 2] describes thedemographics and general characteristics of all included patients.

LAA morphology and cardioembolic stroke/TIA rate

All patients were classified into four groups based on the shape of the LAA. Chicken wing (CW), cauliflower, cactus and windsock morphologies were indentified in 1551, 442, 732, and 765 patients respectively.

In terms of the distribution of cardioembolic stroke/TIA events among different groups, 209 of 1,551 CW patients (13.5%) developed stroke whereas 487 of 1,935 non-CW patients (25.2%) developed stroke events. Among non-CW patients, stroke events were reported in 173 of 438 cauliflower patients (39.4%), 172 of 732 cactus patients (23.5%) and 142 of 765 windsock patients (18.6%). Table 3 demonstrates the distribution of different LAA shapes with number and percentage of stoke events in each shape

As shownin [Figure 2] the risk of cardioembolic stroke/TIA in CW patients was associated with 41% fewer events relative to non-CW patients (Total RR=0.59; 95% CI [0.52-0.68]).On comparison with each type of non-CW shape, we found that the risk of cardioembolic stroke/TIA in CW patients was less by 46%, 35%, 31% compared to cauliflower ([Figure 3]; total RR =0.54; 95% CI [0.46-0.64]), cactus ([Figure 4]; total RR =0.65; 95% CI [0.55-0.77]), and windsock ([Figure 5]; total RR =0.69; 95% CI [0.58-0.83]) respectively.

Homogeneity was achieved in all analyses (p value = 0.19 and I square = 26 % in [Figure 2], p value = 0.48 and I square = 0% in [Figure 3], p value = 0.57 and I square = 0% in [Figure 4] and p value = 0.14 and I square = 32% in [Figure 5]).

Quality assessment

In accordance with the scoring system of NOS, all studies scored three stars on selection category, two stars on comparability and one star on the outcome. Thereby, all studies were regarded as good quality studies, and none of them were of fair or poor-quality.

Publication bias

The meta-analysis of CW vs non-CW, CW vs cauliflower, CW vs cactus, and CW vs windsock demonstrated a symmetrical distribution of all included studies on either side of ther overall effect line (RR line) in funnel plots, suggesting no significant publication bias in the study literature. [Figure 6] demonstrates the funnel plots for all comparisons.

Discussion

The main goal of our study was to assess the risk of cardioembolic stroke in patients with AF based on different morphologies of the LAA. Theincluded studies enrolled a totalof 3,486 patients who underwent cardiac CT, MRI or TTE to evaluate the LAA characteristics prior to cardiac ablation and all studies reported rates of cardioembolic stroke/TIA according to LAA morphology. Our main findings suggested that 'chicken wing' morphology was

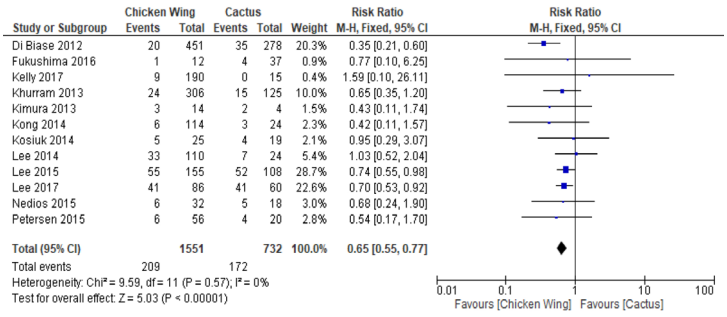

Figure 4: **Forest plot compares the risk of cardioembolic events (stroke, TIA) between CW patients and cactus patients.**

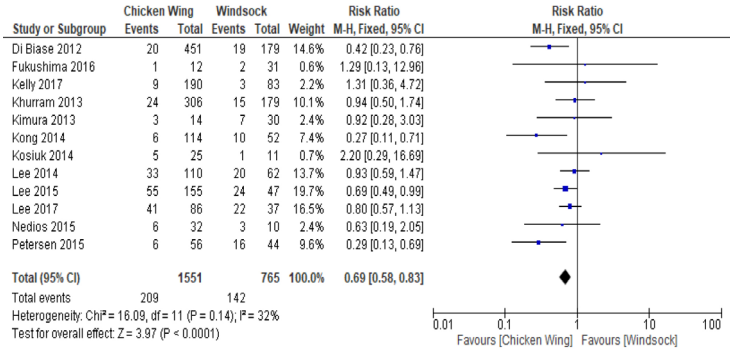

Figure 5: **Forest plot compares the risk of cardioembolic events (stroke, TIA) between CW patients and windsockpatients.**

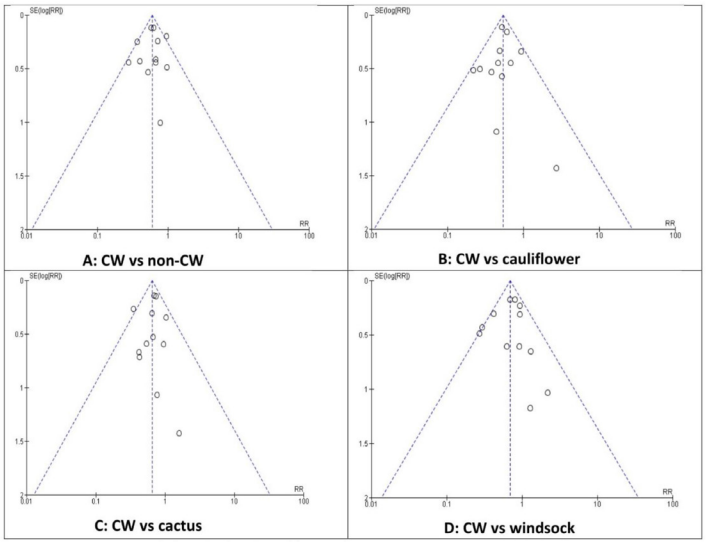

Figure 6: **Funnels plots for detecting the publication bias for all comparisons.**

associated with fewer thromboembolic events compared with other morphologies. Among non-CW morphologies, the cauliflower shape poses the highest risk rate of thromboembolic events followed by cactus and windsock, in descending order.

It is well known that AF is a strong precipitating factor for the development of embolic stroke, and thus necessitating a thromboembolic prophylaxis. CHA DS²-VASc scoring system has been widely employed as the most precise tool to stratify the risk of stroke in AF patients. CHA²DS² stands for (Congestive heart failure (1 point), Hypertension (1 point), Age (> 65 = 1 point, > 75 = 2 points), Diabetes (1 point), previous Stroke/transient ischemic attack (2 points).[16] According to this score, all guidelines have advised against prophylactic anticoagulant for low risk patients who are defined as patients with score of 0 whereas thromboprophylaxis is recommended for high risk patients who achieved 2 points or more. Aside from that, there is still a sort of inconsistency between guidelines in deciding whether intermediate risk patients with score 1 need thromboprophylaxis or not. For those patients, oral anticoagulant is recommended according to the American College of Cardiology/American Heart Association/Heart Rhythm Society guidelines 2014 [17] whereas female gender as the sole risk factor is the only exception based on the European Society of Cardiology Class II a Recommendation 2016 [18]. Therefore, these conflicts foster the necessity for adding other factors that could help in the decision-making for thromboprophylaxis in intermediate-risk patients.

Anatomical, morphological and hemodynamic abnormalities in LAA occur in setting of AF. Increased stasis, endothelial dysfunction, and tissue injury due to comorbidities associated with AF as attributed by Virchow's triad result in thrombus formation and subsequent stroke.

Based on the findings of our analysis, we strongly believe that different shapes of LAA are associated with different stroke risk rates in patients with AF. Non-CW shape, especially cauliflower is considered a risk factor for stroke development in those patients. Thereby, the addition of such a factor in stratifying the risk of stroke would be highly beneficial and facilitate the decision-making regarding thromboprophylaxis especially in low CHA2DS2-VASc score.

On the other hand, several morphological and functional abnormalities including LAA orifice area, LAA depth, LAA volume and LAA flow velocity have been studied in several observational studies.[19-24] It has been shown that the increase in LAA orifice area, depth and volume and decrease in LAA velocity are strongly associated with increased stroke risk in AF.[19-24] These changes are attributable to blood pooling and stasis triggered by AF itself. Therefore, a systematic review and meta-analysis of all studies that address these parameters should be done in order to demonstrate the final association between these variables and the risk of embolic stroke and try to find a cut-off values that could help in assessing the risk of thromboembolism in AF patients. Importantly, CW morphology has been associated with a smaller LAA orifice area (p=0.013) and higher LAA emptying velocity (p<0.001) compared to non-CW shape [23]. These results further confirm the importance

of non-CW shape as a predictor for the emergence of cardioembolic stroke in AF patients.

In summary, patients with non-CW morphologies (cauliflower, cactus and windsock) were associated with a higher incidence of embolic stroke/TIA than CW patients. LAA appendage morphology maybe useful inrisk stratification of thromboembolic events and decision-making regarding thromboprophylaxis in AF patients.

Conclusion

Patients with non-CW morphologies (cauliflower, cactus and windsock) show a higher incidence of CVA than CW patients. For that reason, LAA appendage morphology could be useful for risk stratification of CVA in AF patients.

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Safety and Long-Term Success of Persistent Atrial Fibrillation Ablation Using THERMOCOOL SMARTTOUCH® Catheter: Real-World Experience

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Abstract

Background

To investigate the real-world clinical experience of persistent atrial fibrillation (persAF) ablation using the THERMOCOOL SMARTTOUCH® catheter with contact force (CF)-sensing ability in a prospective, multicenter registry.

Methods

Patients with persAF (excluding long-standing persAF) undergoing ablation were enrolled. Primary adverse events (AEs), 12-month success, quality of life (QoL), and correlation of success with CF were assessed.

Results

Overall, 150 patients with persAF (age 61.6 ± 9.4 years; 76.0% male; 90.7% Caucasian; left ventricular ejection fraction 56.9% ± 10.3%; left atrial diameter 41.5 ± 7.9 mm) underwent catheter insertion (safety cohort); 142 met eligibility criteria and were ablated (evaluable cohort). Confirmation of entrance block for all targeted pulmonary veins was achieved in 99.3% of patients. The primary AE rate was 4.0% (6/150), and 12-month success was 63.1% (95% confidence interval: 54.2%-71.4%). A non-significant trend towards higher success was observed in patients with isoproterenol/adenosine challenge vs. those without (73.1% vs. 60.2%, respectively; P=0.065). Investigators stayed within their pre-selected CF working range (catheter-tissue contact stability) 79.7% ± 12.7% of the time. When investigators stayed within the CF range ≥80% vs. <80% of the time, ablation success was 69.2% vs. 58.5%, respectively (P=0.285). QoL improved significantly at 6 months and was sustained through the 12-month follow-up (P<0.0001).

Conclusions

Symptom control in a real-world setting of persAF ablation using the THERMOCOOL SMARTTOUCH® catheter was 63.1%, with significant improvements in QoL, and trended non-significantly towards increased success in patients receiving isoproterenol/adenosine challenge and when investigators stayed within their pre-selected CF range ≥80% of the time.

Introduction

Atrial fibrillation (AF) frequently progresses from paroxysmal to persistent AF (persAF). Unlike paroxysmal AF ablation, an optimal ablation strategy for persAF beyond pulmonary vein isolation (PVI) is unclear; long-term success rates remain low, and success varies depending upon the technique employed [1,2].

In patients with paroxysmal AF, use of a contact force (CF)-sensing catheter improves the success of catheter ablation compared to a traditional non–CF-sensing catheter (74%-96% vs. 64.1%-82%, respectively) [3-8]. However, limited data exist on long-term success rates in patients with persAF treated with CF-sensing catheters [1]. Based on the Heart Rhythm Society (HRS)/European Heart Rhythm Association (EHRA)/European Cardiac Arrhythmia Society (ECAS) recommendations, the minimum chronic acceptable success rate (objective effectiveness endpoint for a clinical trial) for persAF at the 12-month follow-up is 40% [9].

Although consensus is lacking regarding the preferred treatment strategy for persAF, improving the safety and quality of lesions

Key Words
Ablation, Electrophysiology, Atrial Fibrillation.

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by using a CF-sensing catheter may improve outcomes. This observational registry evaluated the real-world safety and 12-month success rate of catheter ablation in drug-refractory persAF ablation using an open-irrigated, CF-sensing catheter.

Methods

Study Design

THERMOCOOL SMARTTOUCH® registry, a prospective, open-label, multicenter, observational registry, was designed to evaluate the real-world safety and long-term success of persAF ablation using an open-irrigated, CF-sensing catheter (THERMOCOOL SMARTTOUCH® Catheter; Biosense Webster, Inc., Diamond Bar, California). Data were collected between August 30, 2012, and June 28, 2014, at 24 centers in Europe, Australia, and Canada. An institutional review board and/or ethics committee approved the study at each participating center. The study was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonisation Harmonised Tripartite Guidelines for Good Clinical Practice. All patients provided written informed consent to the study protocol.

Study Population

Data were included for all persAF patients enrolled in the registry who were ≥18 years of age and had failed at least 1 anti-arrhythmic drug (class I or class III/atrioventricular nodal blocker). Prior AF ablations were permitted. PersAF was defined in accordance with the HRS/EHRA/ECAS expert consensus statement as continuous AF that is sustained beyond 7 days [9]. Episodes of AF requiring electrical or pharmacological cardioversion after ≥48 hours of AF, but prior to 7 days, were also considered as persAF episodes. Continuous AF was further defined as AF that is documented to be present on all electrocardiogram (ECG) monitoring performed during a defined period of time [9]. Data from patients with long-standing persAF (continuous AF for >12 months duration) [9] were excluded. Patient exclusion criteria included AF secondary to electrolyte imbalance, thyroid disease, or reversible or non-cardiac causes; atrial myxoma, intramural thrombus, tumor, or other abnormalities preventing catheter use; unstable angina; congenital or medical abnormalities or any other disease preventing ablation; New York Heart Association functional class III or IV or uncontrolled heart failure; an implanted cardioverter-defibrillator; prior coronary artery bypass graft or other cardiac or valvular surgery or awaiting such procedures within 12 months; severe pulmonary disease; contraindication to anti-coagulation medications; a documented thromboembolic event in the previous 12 months; or life expectancy of <12 months.

Catheter Ablation

The ablation catheter has been described in detail elsewhere [10,11]. Briefly, the 7.5-Fr THERMOCOOL SMARTTOUCH® CF-sensing catheter has a 3.5-mm electrode tip and 6 open-irrigation holes. Before ablation, transthoracic echocardiogram, cardiac imaging, or both were performed as warranted for detection of thrombus per each institution's standard practice. PVI with confirmation of entrance block was verified for all targets [9], and pulmonary veins (PVs) were isolated as needed. Before ablation, 3-dimensional electro-anatomical mapping was performed using the CARTO® 3 system (Biosense Webster, Inc., Diamond Bar, California). The irrigation flow rate varied with radiofrequency (RF) power setting (recommended settings: 17 mL/minute for ≤30 W; 30 mL/minute for 31-50 W).

The investigator could perform additional ablation of non-PV targets such as left atrial (LA) linear lesions (e.g., left inferior PV-mitral annulus [LIPV-MA] and cavotricuspid isthmus), sites with complex fractionated atrial electrograms (CFAEs), superior vena cava isolation, and other AF focal lesions, as deemed necessary. Post-ablation isoproterenol infusion (≤20 µg/minute) or intravenous adenosine administration (6- to 12-mg bolus) was recommended to detect PV reconnection or confirm elimination of all AF foci. Operators were encouraged to check for bidirectional block after linear lesion delivery as per the institution's current best practices. Investigators were allowed to perform repeat ablations, as well as continue a previously ineffective drug at the same or lower dose during the effectiveness evaluation period.

Anti-coagulation was recommended 30 days before ablation, and an activated clotting time of 300-400 seconds was recommended during ablation. Anti-coagulation was recommended for the first 3 months after ablation and subsequently during the effectiveness evaluation period according to current guidelines [12].

CF Working Ranges

A CF working range was pre-selected by each investigator based on experience. CF data points were sampled and stored every 50 milliseconds during RF application, translating into ≥90,000 data points per case. Each data point was analyzed to determine whether or not it was within the pre-specified working range for each case. The distribution of average CF per ablation was calculated across the collected data points. Thereafter, the percentage of time that the investigator was within the pre-selected CF working range was calculated by the number of data points within the working range/total data points × 100.

Effectiveness and Procedural Outcomes

Patients were followed-up by telephone at 3, 6, and 12 months after index ablation. Acute success was defined as confirmation of entrance block for all targeted PVs. Long-term (12 months) success was defined as patient-reported freedom from symptomatic AF assessed at each follow-up time point. Other assessments included total fluoroscopy time, fluoroscopy dose, total procedure time, RF application time, CF during ablation, and correlation of long-term success with CF. Quality of life (QoL) improvements were assessed at 6 and 12 months using the validated 20-item Atrial Fibrillation Effect on Quality-of-life (AFEQT) questionnaire, which contains 4 conceptual domains (symptoms, daily activities, treatment concern, and treatment satisfaction) from which global and individual domain scores are calculated [13].

Safety Outcomes

Primary adverse events (AEs) were defined as the incidence of early-onset (≤7 days of the index procedure) procedure- or device-related serious AEs such as directly related death; atrioesophageal fistula;

atrial perforation/pericardial effusion; cardiac tamponade; myocardial infarction; stroke/cerebrovascular accident; thromboembolism; transient ischemic attack; diaphragmatic paralysis; pneumothorax; heart block; PV stenosis or pulmonary edema; respiratory insufficiency; pericarditis; vascular access complication, including symptomatic PV stenosis (≥70% reduction in PV diameter from baseline computed tomography/magnetic resonance angiography scan or PV gradient >10 mm Hg on post-procedure echocardiography); and atrioesophageal fistulas (including those that occurred >7 days after the procedure). All AEs were adjudicated by an independent Clinical Events Adjudication Committee and were monitored until they were resolved.

Statistical Analyses

The safety cohort comprised all patients who underwent insertion of the registry catheter, and the evaluable cohort comprised all patients who met eligibility criteria and underwent ablation with the THERMOCOOL SMARTTOUCH® catheter in compliance with the study protocol. Analysis of procedural data, effectiveness endpoints, and QoL was based on the evaluable cohort. The number and percentage of patients with confirmed entrance block for all targeted PVs, freedom from symptomatic AF recurrence (patient-reported), and procedural or peri-procedural AEs were summarized with corresponding 2-sided 95% exact binomial confidence intervals (CIs). Probability of freedom from patient-reported symptomatic AF recurrence through the 12-month follow-up in the evaluable cohort, as well as in patients with and without prior ablation and those with and without post-ablation isoproterenol/adenosine challenge, was determined using Kaplan-Meier estimates. Distributions of average CF and percentage of time with CF measurements within pre-selected ranges were plotted. Descriptive statistics and logistic regression models were used to assess the correlation of long-term success with average CF, percentage of time CF measurements were within the working range pre-selected by the investigator, and percentage of time CF measurements were within the pre-selected range dichotomized at a value of 80%. Change in QoL from baseline to each follow up visit, based on overall AFEQT and sub-scale measures, was assessed using the 1 sample Student's t test. Logistic regression models were used to identify predictors of 12 month success. Covariates that were significant at P values <0.10 in the univariate regression analysis were entered into the multivariate regression analysis. Only those covariates that remained significant at P values <0.10 were included in the final multivariate regression model. The statistical significance level was set at 0.05 for 2-sided tests. All statistical analyses were performed using SAS software version 9.3 (SAS Institute Inc., Cary, North Carolina).

Results

A total of 150 patients with persAF were enrolled in the registry: 150 patients who had the study catheter inserted comprised the safety cohort, and 142 patients who met the inclusion/exclusion criteria and underwent ablation using the study catheter in compliance with the study protocol comprised the evaluable cohort [Figure 1]. Baseline demographics and patient characteristics were similar between the safety and evaluable cohorts: mean ± standard deviation (SD) age was 61.6 ± 9.4 and 61.6 ± 9.6 years, respectively, and most patients were male (76.0% and 75.4%, respectively) and Caucasian (90.7% and 90.8%, respectively; [Table 1]).

Primary AEs

Primary AEs occurred in 4% of patients (6/150; 95% CI: 1.5-8.5): atrioesophageal fistula (1), cardiac perforation (1), stroke (1), arteriovenous fistula (1), vessel puncture site hematoma (1), and vascular pseudoaneurysm (1; [Table 2]). The atrioesophageal fistula case resulted in death 1 month after the index ablation procedure and was considered procedure related and possibly device related. After discharge, this patient presented to a different institution with pulmonary symptoms and was diagnosed with an atrioesophageal fistula. The patient's ablation procedure, which involved PVI with additional ablation of non-PV targets, was performed under general anesthesia without the use of esophageal probe or esophageal pre-imaging by an investigator who had previous experience with the study catheter. The patient had no significant comorbidities, and ablation parameters were within normal limits (average [min max] CF: 12 g [4-27 g]; the majority of ablation points were below 20 g of CF; average power: 19 W; highest infusion rate: 17 mL/minute; and average electrode temperature: 39˚C). The case of cardiac perforation occurred at the time of mapping, and no RF energy was delivered. Other than the atrioesophageal fistula case, all other AEs were considered non–device-related and resolved without sequelae at follow-up.

Acute Success and Procedural Outcomes

PVs were targeted in 141/142 (99.3%) ablation procedures. Acute success with confirmation of entrance block for all targeted PVs was achieved in 99.3% of patients (141/142; 95% CI: 96.1% 100.0%). Non-PV targets comprised LA linear lesions in 72 (50.7%) patients, including LIPV-MA in 23 (16.2%) patients and cavotricuspid isthmus in 31 (21.8%) patients. Other targets included sites with

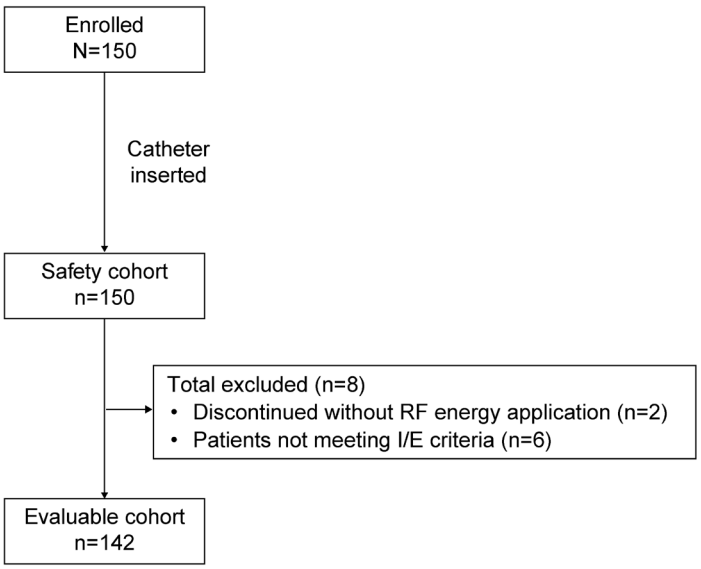

Figure 1: **Patient enrollment**
I/E, inclusion/exclusion; RF, radiofrequency

Table 1: Patient demographics and baseline characteristics

Variable	Safety cohort (n=150)	Evaluable cohort (n=142)
Age a years		
Mean ± SD, n	61.6 ± 9.4	61.6 ± 9.6
Median	62.0	62.0
Min/max	36.0/80.0	36.0/80.0
Sex, n (%)		
Male	114 (76.0)	107 (75.4)
Female	36 (24.0)	35 (24.6)
Child-bearing potential	1/36 (2.8)	1/35 (2.9)
Not of child-bearing potential	35/36 (97.2)	34/35 (97.1)
Race, n (%)		
Black or African American	1 (0.7)	1 (0.7)
White or Caucasian	136 (90.7)	129 (90.8)
NA	13 (8.7)	12 (8.5)
Patient history, n (%)		
AF duration, mean ± SD, years	4.6 ± 4.76	4.6 ± 4.78
Atrial flutter	42 (28.0)	41 (28.9)
Hypertension	82 (54.7)	76 (53.5)
Diabetes	18 (12.0)	18 (12.7)
Structural heart disease	34 (22.7)	33 (23.2)
Prior thromboembolic events	12 (8.0)	11 (7.7)
NYHA class, n (%)		
None	70 (46.7)	65 (45.8)
I	34 (22.7)	34 (23.9)
II	45 (30.0)	43 (30.3)
Unknown	1 (0.7)	0 (0.0)
Patients who had at least 1 previous AF ablation, n (%)	36 (24%)	33 (23.2)
Failed anti-arrhythmic drug class, n (%)		
I/III at baseline	117 (78.0)	114 (80.3)
II/IV only	26 (17.3)	25 (17.6)
Baseline anti-arrhythmic medications, n (%)		
I/III, using at baseline	129 (86.0)	124 (87.3)
II/IV, using at baseline	74 (49.3)	72 (50.7)
LVEF, %, mean ± SD, min/max	56.9 ± 10.3[b], 30.0/72.0	56.5 ± 10.7[c], 30.0/72.0
LA dimension, mm, mean ± SD, min/max	41.5 ± 7.9[d], 26.0/60.0	42.0 ± 8.2[e], 26.0/60.0

Values are n (%) unless specified otherwise
AF, atrial fibrillation; LA, left atrial; LVEF, left ventricular ejection fraction; NA, not available (from France and Monaco); NYHA, New York Heart Association; SD, standard deviation
[a]Age at time of informed consent; [b]n=29; [c]n=26; [d]n=27; [e]n=24

CFAEs in 26 (18.3%) patients and other AF foci in 13 (9.2%) patients. The mean (SD; n) fluoroscopy time and dose were 24.5 (20.7; 138) minutes and 1.8 (3.1; 73) Grays, respectively. The mean (SD; n) total procedure and RF application times were 171.3 (64.0; 138) and 42.8 (22.8; 132) minutes, respectively.

Table 2: Primary adverse events

System organ class/ preferred term	Patients, n/N (%)	Events, n	Device relatedness	Procedure relatedness
Cardiac perforation	1/150 (0.7)	1	No	Yes
Atrioesophageal fistula	1/150 (0.7)	1	Possibly	Yes
Stroke	1/150 (0.7)	1	No	Possibly
Vascular access complication				
Arteriovenous fistula	1/150 (0.7)	1	No	Yes
Vessel puncture site hematoma	1/150 (0.7)	1	No	Yes
Vascular pseudoaneurysm	1/150 (0.7)	1	No	Yes

Long-Term Success

By Kaplan-Meier analysis, freedom from symptomatic AF at 12 months after the index ablation procedure was 63.1% (82/130; 95% CI: 54.2%-71.4%) with a mean of 1.03 ablations [Figure 2A]. Success rates did not differ between patients with or without prior AF ablation (P=0.557; [Figure 2B]). A non-significant trend towards a higher success rate was observed in patients who received an isoproterenol/adenosine challenge at the end of the ablation procedure (73.1% [95% CI: 0.55%-0.85%] vs. 60.2% [95% CI: 0.50%-0.69%], respectively; P=0.065; [Figure 2C]).

CF and its Correlation With 12-Month Success

The mean (SD) CF recorded during the index ablation procedures was 16.2 (4.0) g in the safety cohort and 16.1 (4.0) g in the evaluable cohort [Figure 3]. When dichotomized at a mean CF of 16 g, a non-significant trend of correlation was observed between higher average CF and 12 month effectiveness (odds ratio [OR]: 1.12; 95% CI: 0.99-1.27; P=0.08).

For the index ablation procedures in which CF data were available in the evaluable cohort, the majority of the CF working ranges pre-selected by the investigators were set between a low of 5 g and a high of 40 g (71.8% [61/85] between 5 and 40 g; 18.8% [16/85] between 10 and 40 g). Investigators remained within their pre-selected CF working ranges for a mean (SD) of 79.7% (12.7%) of the time in the evaluable cohort. Sub-group analysis (dichotomized at the mean) showed that long-term success tended to increase when investigators remained within their pre-selected CF working range ≥80% vs. <80% of the time; however, this difference did not reach statistical significance (69.2% vs. 58.5%, respectively; P=0.285; [Figure 4]).

Predictors of 12-Month Success

Multivariate logistic regression analysis of factors for 12-month effectiveness outcomes showed that male gender and isoproterenol/adenosine challenge after ablation were associated positively with the odds of 12-month success, with the association being statistically significant for the latter (OR: 2.84; 95% CI: 1.05-7.67). The presence of prior thromboembolic events and pre-existing congestive heart failure trended towards a negative association with 12-month success [Table 3].

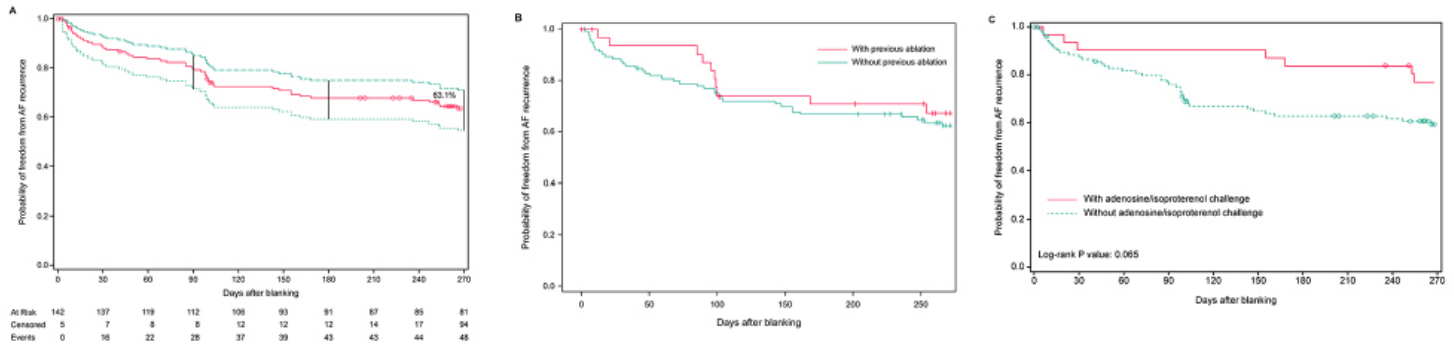

Figure 2: Kaplan-Meier analysis of 12-month success; freedom from symptomatic AF in (A) evaluable cohort (n=142), (B) evaluable cohort stratified as patients with or without prior AF ablation, and (C) evaluable cohort stratified as patients with or without a post-ablation isoproterenol/adenosine challenge AF, atrial fibrillation

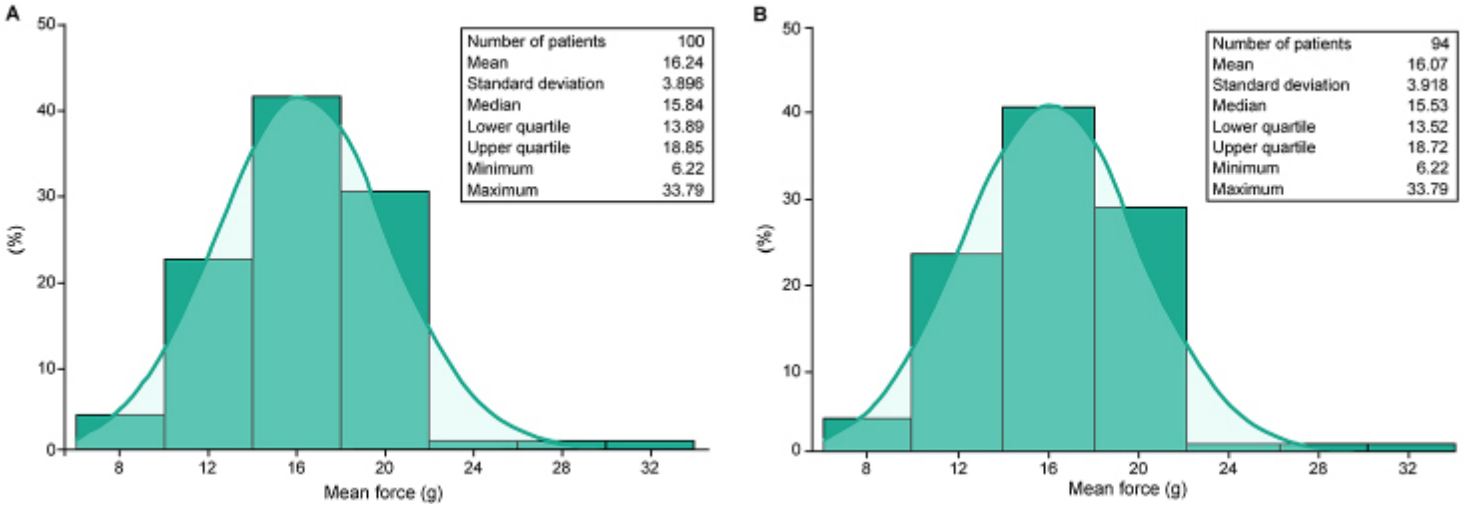

Figure 3: Distribution of average CF per ablation procedure by continuous variable analysis in (A) safety cohort (n=150) and (B) evaluable cohort (n=142)
CF, contact force

QoL

Patients' QoL improved significantly overall and on all subscales of the AFEQT questionnaire (P<0.0001) at 6 months; these improvements were sustained through the 12-month follow-up [Figure 5].

Discussion

Results from this prospective, multicenter registry demonstrate the real-world experience of persAF ablation with the THERMOCOOL SMARTTOUCH® catheter with a 12-month success rate of 63.1% and significant improvements in patients' QoL. Success rates did not differ between patients with and without prior AF ablation, but increased substantially to 73.1% in patients who received an isoproterenol/adenosine challenge after ablation (73.1% vs. 60.2%; P=0.065). Of note, the reported success rates were with a mean of 1.03 ablations per patient suggesting that these observations mimicked/were similar to a single procedure setting. Overall, 6 of the 150 patients who underwent catheter insertion experienced a primary AE, resulting in an AE rate of 4%. Three of these 6 AEs were vascular access complications, which could have been avoided by performing ultrasound-guided puncture.

We identified weak associations between CF and clinical outcomes. An increase in the percentage of time (≥80%) within the CF working range pre-selected by the investigator, which is indicative of catheter-tissue stability, was associated with significant improvement in long term success in the paroxysmal AF population [6], whereas a non-significant trend was observed in the present study involving patients with persAF. Additionally, a non-significant trend of correlation was observed between higher average CF dichotomized at 16 g and 12 month effectiveness. We did not perform any correlation analysis of CF with safety, as the event rate was too low and would preclude any clinically meaningful conclusions. The lack of any strong findings of correlation between CF parameters examined and clinical outcomes suggests that factors in addition to CF, such as optimal ablation strategy and patient selection, may be important to consider in persAF ablation.

Unlike paroxysmal AF ablation where PVI has long been considered the cornerstone of ablation strategy, variations in ablation strategies exist, and much is unknown or debatable with regard to

Table 3: Potential risk factors for 12-month success (evaluable cohort, n=142)

		Univariate analysis			Multivariate analysis	
Factors	n	OR (95% CI)	P value	n	OR (95% CI)	P value
Age	130	0.98 (0.94 1.01)	0.202			
Male vs. female	130	2.03 (0.89 4.65)	0.094	130	2.26 (0.936 5.446)	0.070
Isoproterenol/adenosine challenge	130	2.42 (0.95 6.16)	0.063	130	2.84 (1.049 7.671)	0.040
Total fluoroscopy dose, Grays	66	1.01 (0.84 1.21)	0.952			
Total fluoroscopy time, minutes	126	0.99 (0.97 1.01)	0.166			
Highest infusion rate, mL/minute	97	1.01 (0.97 1.05)	0.734			
Total procedure time, minutes	126	1.00 (0.99 1.01)	0.997			
Longest power duration, seconds	89	1.00 (1.00 1.00)	0.268			
Number of RF applications	115	1.00 (0.99 1.01)	0.912			
Total RF application time, minutes	121	1.00 (0.99 1.02)	0.811			
Any thromboembolic event	130	0.27 (0.06 1.12)	0.071	130	0.22 (0.048 1.047)	0.057
Percentage of CF in range >80%	85	1.45 (0.60 3.48)	0.407			
Mean distal temperature, °C	86	0.89 (0.74 1.08)	0.226			
Mean CF, g	86	1.08 (0.96 1.23)	0.199			
Mean impedance, Ω	86	1.02 (1.00 1.04)	0.114			
Time of lateral inaccuracy, %	86	1.00 (0.93 1.07)	0.920			
Time of force metal severity: 2 or above, %	86	1.00 (0.97 1.03)	0.910			
AF episode in past 12 months	129	0.98 (0.36 2.69)	0.971			
Duration of AF, years	129	0.97 (0.90 1.04)	0.399			
History of congestive heart failure	130	0.34 (0.11 1.03)	0.057	130	0.37 (0.116 1.152)	0.086
History of hypertension	129	0.88 (0.43 1.80)	0.727			
History of ischemic cardiomyopathy	130	1.18 (0.21 6.69)	0.852			
History of non-ischemic dilated cardiomyopathy	129	0.27 (0.05 1.53)	0.138			
History of significant valve disease	130	0.58 (0.04 9.49)	0.703			
History of diabetes	130	0.81 (0.29 2.30)	0.697			
History of transient ischemic attacks	130	0.19 (0.02 1.83)	0.149			
History of pulmonary embolus	129	1.19 (0.11 13.48)	0.888			
History of atrial flutter	130	1.74 (0.77 3.93)	0.180			
History of atrial tachycardia (LAT and RAT)	130	1.18 (0.21 6.69)	0.852			
History of AV node re-entry tachycardia	130	1.17 (0.10 13.31)	0.896			
History of ventricular tachycardia	130	0.28 (0.05 1.56)	0.145			
History of ventricular fibrillation	130	0.19 (0.02 1.83)	0.149			
History of left ventricular hypertrophy	130	1.03 (0.28 3.71)	0.968			
Mean power, W	86	0.96 (0.86 1.07)	0.481			
LA diameter parasternal long axis view	21	0.93 (0.82 1.05)	0.262			
LVEF (%)	23	1.04 (0.96 1.12)	0.367			

AF, atrial fibrillation; AV, atrioventricular; CF, contact force; CI, confidence interval; LA, left atrial; LAT, left atrial tachycardia; LVEF, left ventricular ejection fraction; OR, odds ratio; RAT, right atrial tachycardia; RF, radiofrequency; W, watts

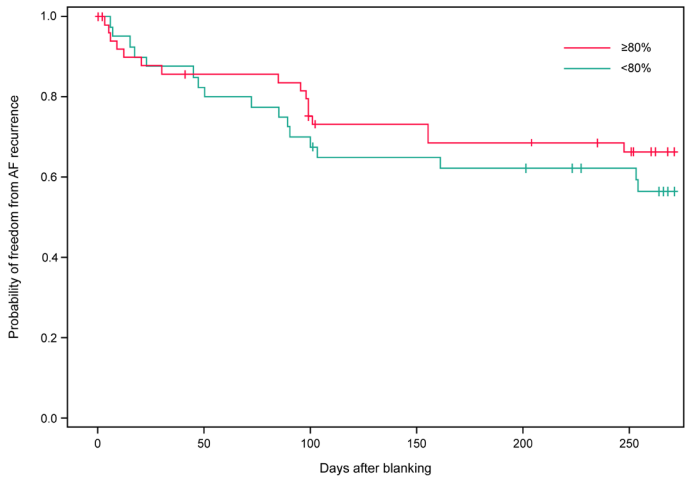

Figure 4: Kaplan-Meier estimates for time to first AF recurrence through 12 months stratified at 80% (investigators working in their pre-selected CF ranges ≥80% vs. <80% of the time) (evaluable cohort, n=142)
AF, atrial fibrillation; CF, contact force

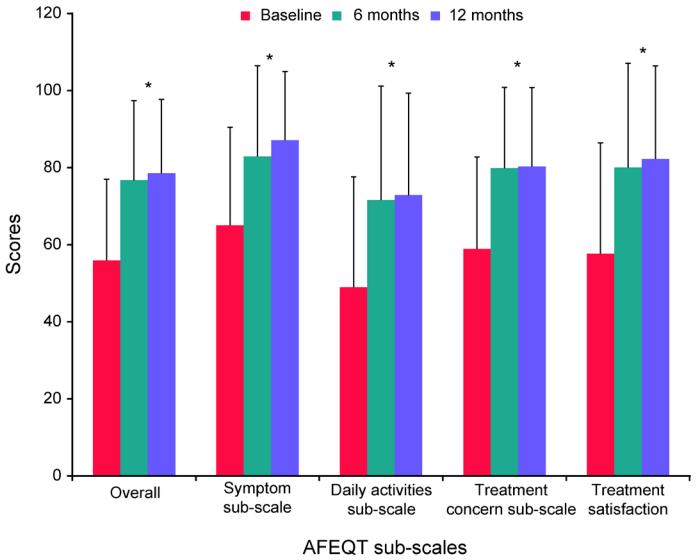

Figure 5: Quality of life based on the AFEQT questionnaire (evaluable cohort, n=142)
***P<0.0001 compared with baseline**
AFEQT, Atrial Fibrillation Effect on QualiTy-of-life

what is considered the optimal treatment strategy in persAF ablation [1,2]. In the STAR AF II trial, no differences in clinical outcomes were observed between persAF ablation groups who received PVI only and those who received additional linear ablation or CFAE ablation [1]. A meta-analysis of persAF ablation, however, suggested that additional linear ablation, but not CFAE ablation, within the left atrium may result in reduction of AF recurrence [14]. In addition, atrial fibrosis was associated with a likelihood of recurrent arrhythmia [15], and box isolation of fibrotic areas in a sub-group of non-paroxysmal AF patients with identified low-voltage areas resulted in a long-term (12-month) success rate of 72% [16]. Taken together, a tailored ablation strategy based on appropriate patient selection and the extent of cardiac disease presentation appears to be a logical approach. In our registry, approximately half of the ablation procedures included additional LA linear ablations, and a small number of procedures included other ablation targets such as CFAE and other AF foci. The contribution of these additional ablation targets to the overall success rate needs to be examined further, especially in an era in which operators can now be more certain of creating lesions with the advent of CF-sensing catheters and CF stability algorithms.

Comparison of our observed 12-month success rates with those of other studies is difficult due to differences in ablation strategies employed and definitions of endpoints. Nonetheless, the overall success rate reported from this registry is, for the most part, similar to or slightly better than previously reported outcomes in other persAF studies using non–CF-sensing catheters [1,17,18]. Together with the observed non-significant trend of CF stability towards improved effectiveness outcome, the data suggest a role of the real-time CF-sensing catheter in persAF ablation.

This registry was conducted when the CF-sensing catheter was newly available and, therefore, the investigators' use of CF technology represents that of early experience. At the time of enrollment, workflow was less defined, and CF stability was less understood and may not have been achieved in some cases. The importance of CF stability in ablation outcomes is supported by a recent sub-analysis of the SMART-AF trial showing that adequate and stable CF correlates with optimal long-term success in paroxysmal AF ablation [19]. It is conceivable that with more experience and proper use of CF, the weak CF trend observed in the current registry may be amplified. Also, the use of CF in linear ablation strategies makes intuitive sense if the underlying hypothesis of benefit from additional linear lesions holds true. While conflicting data exist in the percutaneous ablation space [1,2], the outcomes of surgical intervention for persAF are more encouraging, and it is at least theoretically possible that improved tools will improve outcomes for percutaneous linear ablation strategies [20]. The combination of CF technology and a tailored ablation strategy based on patient selection or cardiac disease presentation might therefore result in better treatment success for persAF ablation. This hypothesis needs to be evaluated in future studies.

An interesting observation from this registry is the improved odds of success at 12 months in patients who received an isoproterenol/adenosine challenge immediately after ablation to uncover dormant conduction (OR: 2.84; 95% CI: 1.05-7.67), suggesting that complete PVI and/or AF non-inducibility is important to achieve optimal success. This is consistent with a previous meta-analysis of persAF ablation showing that PVI is important in improving success rates [14].

Atrioesophageal fistula is a known, but rare and potentially devastating, complication of AF ablation. In the present study, an unfortunate fatal atrioesophageal fistula case was reported. Although the CF and ablation parameters used in this patient were within normal ranges, the event further emphasizes the need to exercise strong caution when creating lesions involving ablation on the posterior LA wall, especially in close proximity to the esophagus. Esophageal visualization or luminal temperature monitoring may be helpful to minimize the occurrence of esophageal injury, which was not used in this case. In addition, the biophysical benefits of using a catheter with stable CF and its impact on lesion creation and energy delivery while performing a PVI cannot be overlooked [21]. Also, PVI alone is insufficient for treatment of persistent AF. This is again borne out of the fact that there is a trend to better outcomes when vein isolation via isoprenaline/adenosine is checked suggesting that additional ablation may be needed in this patient population [22,23].

Some limitations need to be considered when interpreting the results of this study. Firstly, the study lacked a control group. Also, the long-term success of ablation was patient-reported, and documentation by ECG and trans-telephonic monitoring were not mandated. Data regarding persistent AF ablation using CF-sensing catheters with a modest sample size are limited; therefore, correlations observed in this study do not imply causative mechanisms as the dataset was not designed for formal hypothesis testing. Information on achievement of bidirectional block was not recorded in the database. No restrictions were placed on the ablation technique, potentially affecting outcomes; however, this scenario reflects real-world clinical practice. Furthermore, patients with long-standing persAF and those with advanced heart failure were excluded from enrollment in the registry; therefore, the results may not be generalizable to these patient populations.

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Disclosures

Tom De Potter, Hugo Van Herendael, Richard Balasubramaniam, Decebal-Gabriel Laţcu, Sharad C. Agarwal, and Antonio Pani have no conflicts of interest to declare.

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Author contributions

Tom De Potter and Matthew Wright have contributed towards conception/design, acquisition/analysis/interpretation of data, drafting the article, and critical revision of the article. Hugo Van Herendael has contributed towards acquisition/interpretation of data and critical revision of the article. Richard Balasubramaniam has contributed towards conception/design, acquisition of data, and critical revision of the article. Decebal-Gabriel Lațcu, Sharad C. Agarwal, and Antonio Pani have contributed towards acquisition of data and critical revision of the article. Lee Ming Boo has contributed towards data analysis/interpretation, drafting the article, and critical revision of the article. Baohui Zhang has contributed towards conception/design, data analysis/interpretation, statistical analysis, and critical revision of the article. All authors have approved the manuscript and are accountable for all aspects of the work.

Conclusion

In this report of persAF ablation using the THERMOCOOL SMARTTOUCH® catheter in a real-world registry, the 12-month symptom control rate was 63.1%, with a non-significant trend towards improved success in patients with a post-ablation isoproterenol/adenosine challenge and when investigators stayed within a pre-selected CF working range ≥80% of the time. Results suggest that creating optimal/durable lesions at PVs is as important as the ablation strategy/sites, for which catheter-tissue contact stability may provide further improved success, although this correlation will need to be examined further.

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Relationship of Atrial Fibrillation to Outcomes in Patients Hospitalized for Chronic Obstructive Pulmonary Disease Exacerbation

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Abstract

Introduction

Chronic Obstructive Pulmonary Disease (COPD) is a major cause of hospitalization and is associated with an increased incidence of atrial fibrillation (AF). The impact of AF on in-hospital outcomes, including mortality, in patients hospitalized for COPD exacerbation is not well elucidated.

Methods

We used the National Inpatient Sample database to examine discharges with the primary diagnosis of COPD exacerbation and compared mortality, length of stay and costs in patients with AF compared to those without AF. The study adjusted the outcomes for known cardiovascular risk factors and confounders using logistic regression and propensity score matching analysis.

Results

Among 1,377,795 discharges with COPD exacerbation, 16.6% had AF. Patients with AF were older and had more comorbidities. Mortality was higher (2.4%) in the AF group than in the no AF group (1%), p <0.001. After adjustment to age, sex and confounders, AF remained an independent predictor for mortality, OR:1.44 (95% CI 133 – 1.56, p <0.001), prolonged length of stay, OR:1.63 (95% CI 1.57 – 1.69, p <0.001) and increased cost, OR: 1.45 (95% CI: 1.40 – 1.49, p <0.001).

Conclusions

Among patients with COPD exacerbation, AF was associated with increased mortality and higher resource utilization.

Introduction

Chronic obstructive pulmonary disease (COPD) is a major cause of resource utilization and hospitalization worldwide. Patients with COPD also have increased risk of cardiovascular mortality and development of arrhythmias, including atrial fibrillation (AF) [1-6]. Studies showed worse outcomes and symptom burden in patients with AF when associated with COPD, compared to those without COPD, beyond what was explained by the classical cardiovascular risk factors [7]. Although the relationship is bidirectional, little is known about the impact of atrial fibrillation on patients hospitalized for COPD exacerbation. The aim of this study was to examine the mortality and costs associated with AF in a cohort of patients hospitalized for COPD exacerbation.

Key Words

Atrial fibrillation, Chronic Obstructive Lung Disease, COPD, Arrhythmia, In-hospital mortality, National Inpatient Sample, ICD code.

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Methods

The study used discharge records from the National Inpatient Sample (NIS) database. The NIS is the largest all-payer hospitalization database in the United States and is available to the public. It is part of the Healthcare Cost and Utilization Project (HCUP) and sponsored by the Agency for Healthcare Research and Quality (AHRQ). Data was analyzed for the years 2012 to 2014 due to similarities in the sampling design. For these years the NIS provided a 20% stratified sample from all hospital discharges nationwide excluding rehabilitation and long-term care units. It contains approximately 7 million discharge records per year and contains a weight variable

(DISCWT) that allows calculation of national estimates amounting to 35 million records or 97% of all discharges nationwide. The NIS is a discharge level database and does not provide longitudinal information about readmissions and multiple hospitalizations for the same patient. Information provided includes demographic data, principal diagnosis and up to 29 associated secondary diagnoses addressed during the hospitalization, procedures performed, payer data and total charges [8].

We included records of those patients ≥ 18 years of age hospitalized for COPD exacerbation as the primary diagnosis identified by the International Classification of Diseases, 9th Revision- Clinical Modification (ICD-9-CM) code 491.21 [9]. The study divided the records into two groups - the AF group and no AF group - based on the presence of AF (identified by the ICD-9 code 427.31) as a secondary diagnosis. We excluded patients with missing data on sex, age, mortality and length of stay (LOS). Patient with an indicator for transfer to another acute hospital were excluded to reduce the risk of record duplication.

The primary outcome was in-hospital mortality. Secondary outcomes included prolonged LOS defined arbitrarily as LOS > 90th percentile (8 days) and high total charges defined as charges >90th percentile (54,785 $) for patients with COPD exacerbation.

The analysis compared the baseline characteristics and outcomes between between the two groups. To adjust for known confounders, we incorporated covariables with significant differences in univariate analysis into a logistic regression model to calculate the adjusted Odds Ratio (AOR). The final model included age, sex and cardiovascular risk factors such as hypertension, obesity, hyperlipidemia, history of coronary artery disease obstructive sleep apnea (OSA), and the presence of myocardial infarction. We also adjusted for the need for mechanical ventilation, acute kidney injury, and the presence of pneumonia or sepsis. Furthermore, the analysis added the numerical Charlson Index to the model. The Charlson Index is often used to predict mortality in studies based on administrative databases [10]. The score is based on 17 indicators for comorbidities that affect the in-hospital mortality such as myocardial infarction, heart failure, diabetes mellitus with or without complications, chronic kidney disease, rheumatic disease, cerebrovascular disease, hemiplegia, cancer, COPD and AIDS. Higher score indicates more comorbidities and correlates with an increased risk of death [11]. All covariables were identified using the relevant ICD-9 codes illustrated in supplementary file 1. We created a secondary logistic model adjusting for all above variables included in the Charlson index excluding COPD. Continuous variables were compared using student t-test. Categorical variables were compared using Chi-square test. Data analysis used Stata software version 14 (StataCorp LP, College Station, TX).

The study used propensity score matching analysis to generate matched control group for the AF group. Using weighted results, we matched patients with AF in a "nearest neighbor" algorithm with 1:1 ratio to matched controls. Matching was based on a single propensity score which was derived from multiple variables and comorbid conditions that can affect the development of AF and influence the outcomes [12]. Covariables used in the propensity score analysis include age, sex, Charlson score, AKI, HTN, history of chronic coronary artery disease, obesity, use of mechanical ventilation, OSA, the presence of sepsis or pneumonia. To ensure adequate matching, a balance of >10% of the standardized difference between the AF and the control groups was deemed as significant [13]. The analysis subsequently compared the outcomes using Mc Nemar test for correlated binary proportions [12] .

The Rochester Regional Health Institution Review Board exempted the study as no identifying personal information was included in the database.

Results

The study included a total of 1,377,795 "weighted" discharges with a primary diagnosis of COPD exacerbation. AF was present in 45,769 16.6%. Mean age was 68.56, women 55.5 %. The overall in-hospital mortality rate was 1.25 %.

Those with atrial fibrillation were older and had more comorbidities [Table 1]. Mortality rate was higher in the AF group compared to the no-AF group; 2.4% versus 1%, p <0.001. On multivariable regression analysis, AF was associated with AOR: 1.46 (95% CI 134 – 1.59, p <0.001) for in-hospital mortality. Other independent predictors of mortality are demonstrated in [Table 2]. After propensity score matching, AF was associated with relative risk 1.48 (1.35 - 1.62) for in-hospital mortality. Table 3 illustrates the baseline characteristics post propensity score matching. AF was also associated with prolonged LOS, AOR: 1.631.63 (95% CI 1.57 – 1.69, p <0.001), and high costs, AOR: 1.45 (95% CI: 1.40 – 1.49, p <0.001) (supplementary file1).

Discussion

Most of the studies that examined the relationship between AF, COPD and outcomes focused on AF population. In this study, we found a high prevalence of AF (16.6%) in patients hospitalized for COPD exacerbation regardless of onset. This is similar to prior studies with an estimated prevalence of 15%. [14] In a retrospective study of COPD patients referred for Holter monitoring, AF was found in 23% of patients. The prevalence increases with COPD severity [2,5]. Several mechanisms have been postulated to explain the high prevalence such as the presence of common cardiovascular risk factors including smoking, underlying atherosclerosis, heart failure, inflammation, and OSA. Furthermore, the effect of beta-agonists, hypoxia, inducing higher sympathetic drive and altering automaticity, and hypercapnia, by increasing atrial refractoriness, have been postulated [15]. Reports from the Malmo project have adjusted for several of these mechanisms highlighting the possibility of reduced lung volumes as an independent predictor for the development of AF [5].

In our study, AF was associated with 1.46 times the odds of in-hospital mortality. Several prospective studies have elucidated the higher mortality associated with AF in the general population and in a selected subgroup of patients [16,17]. Limited data is available on the impact of AF on outcomes of COPD specifically [18]. As in our study, the effect on mortality remained significant after the

Table 1: Baseline characteristics

Variable	Atrial fibrillation (N=228,845)	No Atrial fibrillation (N= 1,148,940)	Overall (N= 1,377,785)	p-value
Age (mean, 95% CI)	74.9 (74.77 - 74.95)	67.3 (67.27 - 67.36)	68.57 (68.52 - 68.61)	<0.001
Female sex	110,915 (48.5%)	654,015 (56.9%)	764,925 ()	<0.001
Essential hypertension	117,945 (51.5%)	614,600 (53.5%)	732,545 53.2% ()	<0.001
Coronary artery disease	103,935 (45.4%)	331,380 (28.8%)	435,315 (31.6%)	<0.001
Acute kidney injury	28,425 (12.4%)	82,815 (7.2%)	111,240 (8.1%)	<0.001
Mechanical ventilation	7,240 (3.2%)	23,780 (2.1%)	31,020 (2.3%)	<0.001
Sepsis	3,415 (1.5%)	10,895 (0.9%)	14,310 (1.0%)	<0.001
Myocardial infarction	25,835 (11.3%)	91,875 (8.0%)	117,710 (8.5%)	<0.001
Congestive heart failure	122,650 (53.6%)	270,360 (23.5%)	393,010 (28.5%)	<0.001
Diabetes mellitus	72,500 (31.7%)	301,375 (26.2%)	373,875 (27.1%)	<0.001
Diabetes with Complications	8,380 (3.7%)	33,880 (2.9%)	42,260 (3.1%)	<0.001
Obstructive sleep apnea	31,895 (13.9%)	118,935 (10.4%)	150,830 (10.9%)	<0.001
Morbid obesity	18,485 (8.1%)	82,540 (7.2%)	101,025 (7.3%)	<0.001
Chronic renal disease	52,890 (23.1%)	139,345 (12.1%)	192,235 (14.0%)	<0.001
Pneumonia	52,710 (23.0%)	239,315 (20.8%)	292,025 (21.2%)	<0.001
Cerebrovascular accident	9,370 (4.1%)	32,230 (2.8%)	41,600 (3.0%)	<0.001
Ventricular tachycardia	5,540 (2.4%)	9,465 (0.8%)	15,005 (1.1%)	<0.001
Ventricular fibrillation	155 (0.07%)	370 (0.03%)	525 (0.04%)	<0.001
Charlson Index (mean)	2.96 (2.94 - 2.97)	2.27 (2.27 - 2.28)	2.39 (2.38 - 2.39)	<0.001
In-hospital mortality	5,440 (2.4%)	11,805 (1.0%)	17,245 (1.3%)	<0.001

Table 2: In-hospital mortality and independent predictors of mortality

Variable	OR	p-value	95% CI	
Atrial fibrillation	1.45	<0.001	1.33	1.58
Age (per year)	1.05	<0.001	1.05	1.05
Female sex	0.96	0.268	0.89	1.03
Acute kidney injury	2.04	<0.001	1.86	2.23
Charlson Index	1.12	<0.001	1.10	1.15
Pneumonia	1.23	<0.001	1.14	1.34
Hypertension	0.93	0.082	0.86	1.01
Sepsis	4.06	<0.001	3.50	4.70
Coronary artery disease	0.87	0.001	0.80	0.94
Hyperlipidemia	0.78	<0.001	0.72	0.84
Obstructive sleep apnea	0.66	<0.001	0.57	0.76
Morbid obesity	0.77	0.004	0.65	0.92
Mechanical ventilation	24.37	<0.001	22.24	26.72

Table 3: Post-propensity score characteristics and outcomes.

Variable	AF (N= 45,769)	No AF (N= 45,769)	SD
Age (mean)	74.86	75.01	-1.4
Female sex	48.5%	48.4%	0.1
Charlson Index (mean)	2.96	2.99	-1.8
Acute kidney injury	12.4%	12.3%	0.5
Pneumonia	23.0%	22.2%	2.1
Hypertension	51.5%	51.6%	-0.1
Sepsis	1.5%	0.9%	5.5
Obstructive sleep apnea	13.9%	12.9%	3.3
Morbid obesity	8.1%	7.1%	3.5
Mechanical ventilation	3.2%	2.0%	7
Coronary artery disease	45.4%	45.6%	-0.4
Hyperlipidemia	43.3%	43.7%	-0.9
In-hospital mortality	2.4%	1.6%	6
Ventricular tachycardia	2.4%	1.1%	10.8
Ventricular fibrillation	0.07%	0.04%	1.5
Prolonged length of stay (> 8 days)	12.2%	8.1%	14.2
High charges (> 54785 dollars)	16.3%	11.1%	15.4

adjustment for known cardiovascular risks and comorbidities. In this report, patients with AF were less likely to be females and had more comorbidities; notably heart failure, coronary artery disease and OSA. Work is ongoing to reflect the progress in our understanding of the multidirectional influence these risk factors [10,19,20]. AF may constitute a surrogate for worse cardiovascular risks, via coronary artery disease or heart failure. For example, in a multinational prospective study, heart failure was the main causes of death in patients with AF [21]. Our analysis adjusted for these variables, but the impact remained significant. A study of post myocardial infarction patients found increased risk of ventricular fibrillation in patients presenting with chronic AF [22]. In our study, there was increased ventricular fibrillation in the AF group, but the rates were low to explain the increased mortality. Furthermore, the presence of history of prior history of coronary artery disease was not associated with increased mortality during the short in-hospital stay. Patients with known coronary artery disease are often on medical therapy including statin, beta-blockers and aspirin which provide protective effect. Interestingly, ventricular tachycardia was increased in the AF group up to 2.4% versus 1.1 after propensity matching. It was not possible to differentiate between sustained and non-sustained ventricular tachycardia in this database, and therefore would not explain the

excess mortality. It leaves the possibility of AF as an independent predictor of mortality in COPD as seen in the general population.

In addition to worse mortality, our analysis showed increased resource utilization. The presence of AF was associated with higher rates of prolonged LOS even after adjustment for confounders. COPD exacerbation constitutes one of the major causes for hospitalization in the US. Further study is needed to examine the impact of AF control, rhythm or rate, and use of beta-blockers on resource utilization.

Limitations of this study include the lack of characterization of AF subtypes in our cohort as new onset, paroxysmal or permanent. The analysis also did not account for continuous variables such as heart rate, blood pressure, ejection fraction, lipid profile, and the use of medications including beta-blockers and anticoagulants. Despite the use of logistic regression and propensity score matching, retrospective studies carry the risk of missing unaccounted confounding variables. Administrative databases rely on ICD-9-CM codes to identify covariables and study subjects. Coding practices may be inconsistent among participating hospitals and may be influenced by reimbursement value and the condition of interest [23,24]. Data entries included in the NIS are discharge level rather than patient level and do not account for readmission and so allows for duplication [25]. We aimed to reduce the duplication risk by the exclusion of patients with an indicator for transfer to another acute care facility. The database doesn't provide longitudidal follow-up for patient. Nevertheless, the NIS databases representation has been validated against the center for Medicare and Medicaid Services. We included patients with a principal diagnosis of COPD exacerbation to generate the most representative cohort of patients hospitalized primarily for COPD exacerbation.

The study used the strength of the NIS database with it's large sample size. It used 2 approaches to adjust for multiple confounding variables, logistic regression and propensity matching analysis, with consistent results. This is one of the few reports that examined the impact of AF specifically on in-hospital mortality in COPD exacerbation. Our findings may suggest that there is an opportunity to look at AF as a detrimental event in COPD exacerbation. Whether a tailored management approach is of prognostic value remains to be studied.

Conclusion

The presence of AF in patients hospitalized for COPD exacerbation was associated with increased risk of inpatient mortality, prolonged LOS and higher costs.

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Guest Editorial

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Role of Interatrial Block Recognition: A closer look to the Bayés Syndrome

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Interatrial block(IAB) refers to conduction disorders located between the right and the left atrium, and it was found to be a substrate for the development of atrial fibrillation (AF). The pathophysiology of IAB is directly related to a block in the Bachmann's bundle area. IAB has a prevalence of 1% in the global population of middle age people, and 2% among patients with valvular heart disease and cardiomyopathies. IAB was found to be an independent predictor of AF in different clinical entities [1-6]. It was demonstrated that advanced IAB was strongly associated with a higher risk of AF recurrence one year following pharmacological cardioversion, independent of the antiarrhythmic drug utilized [3]. In addition, the presence of pre-existent advanced IAB was associated with a higher risk of AF recurrence post catheter ablation for paroxysmal AF [7], and the presence of advanced IAB predicts new-onset AF after successful cavo-tricuspid isthmus ablation in patients with typical atrial flutter and no history of AF [8].

In this issue of the Journal of Atrial fibrillation, Bazan V, et al. [9] reported an interesting study investigating the role of IAB in enhancing the yield of 24 hour Holter ECG monitoring for the prediction of atrial arrhythmias. The authors should be congratulated for presenting the largest unrestricted series of patients undergoing 24 hour Holter monitoring in the literature. The authors retrospectively analyzed 1017 consecutive 24 hour Holter monitoring recordings performed in a Multidisciplinary Integrated Health Care Institution. A univariate and multivariate regression analysis served to determine the variables associated with a higher 24 hour Holter's yield.The mean age of their population was 62±17 years (55% males). The overall yield was 12.8%, higher for the assessment of the integrity of the electrical conduction system (26.1%) and lower for the assessment of syncope (3.2%) and cryptogenic stroke (4.6%). The variables associated with higher diagnostic performance were indication from Cardiology (p< 0.001), IAB (p= 0.004), structural heart disease (p= 0.008) and chronic renal failure (p= 0.009). Patients less than 50 years of age only retrieved a 7% yield. In the multivariate analysis, indication from Cardiology and IAB remained significant predictors of higher 24 hour Holter's yield. However, in a secondary analysis including echocardiographic data, only identification of IAB remained statistically significant. Therefore, the authors concluded that the recognition of IAB and the type of indication are major determinants of a higher 24 hour Holter's diagnostic yield and may help to optimize the selection of candidates [9].

Of interest, among 212 patients undergoing a complete cardiologic assessment, only 9 of them (4%) had documented AF relapses leading to anticoagulant and/or anti-arrhythmic drug therapy initiation [9]. Seven out of the 9 episodes corresponded to newly diagnosed AF relapses. Interestingly, 7 out of these 9 patients (78%) had IAB. The recognition of IAB yielded a sensitivity of 78%, a specificity of 73%, a positive predictive value of 17%, and a negative predictive value of 98% in the identification of AF relapse prompting anticoagulant and/or anti-arrhythmic drug therapy initiation [9]. As the authors mentioned, the positive predictive value was very low probably because of the low prevalence of IAB and, specially, the very low incidence of "de novo" AF documentation by means of 24 hour Holter monitoring in their population. Although 78% of their patients with AF documentation had underlying IAB, the authors could not perform an adequate correlation analysis between IAB and AF documentation because of the very low incidence of AF during the 24 hour Holter monitor recording.

Also, in large series of in-hospital population, Asad N, and Spodick DH [10] identified a prevalence of IAB in 47% in their screened population, with a higher prevalence in the subgroup above 60 years of age [10]. Bayés de Luna A, et al. [4] reported a series of patients with similar echocardiographic parameters and with long-term follow-up

Key Words

Interatrial Block Recognition, Atrial Fibrillation (AF), Pathophysiology, Interatrial Block (IAB).

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to analyze the incidence of atrial tachyarrhythmias in 16 patients with advanced IAB, and compared them with 22 patients with partial IAB. At one year of follow-up, the incidence of arrhythmias was 80% in the advanced IAB group and, 20% in the partial IAB group. At 30 months of follow-up, the advanced IAB group presented a higher incidence of atrial flutter/fibrillation (15/16, 93.7%), compared with the control group with partial IAB (6/22, 27.7%) (p< 0.0001). Moreover, the 24 hour Holter monitoring showed that the prevalence of frequent premature atrial contractions was much more frequent in advanced than inpartial IAB patients (75% versus 25%, respectively). These patients should be closely followed using long-term monitoring in order to capture a first episode of AF to proceed with further therapeutic management.

Cosio FG et al performed an interesting study in patients with IAB using intracardiac mapping, demonstrating the retrograde activation of the left atrium in these patients with block in the Bachmann´s bundle area [11]. Holmqvist F et al. [12] studied the characteristics of the P-wave morphology according to the way of atrial activation and the relation of this pattern with AF. Indeed, the P wave of the electrocardiogram may show alterations that can be associated with atrial arrhythmias. Hordof AJ et al. [13] found a statistical association between the low resting membrane potential and a prolonged P wave duration. Josephson ME et al. [14] reported that a prolonged interatrial conduction time was significantly related to abnormal P wave morphology. Interesting to note that neither left atrial size nor atrial pressure overload was found to correlate well with abnormal P wavemorphology [14]. We have previously demonstrated that patients with a predisposition to develop AF have significantly longer P wave duration, PA intervals, inter and intra-atrial intervals, and atrial conduction delays [15]. We observed that the P wave duration was significantly longer in patients who had abnormal atrial endocardial electrograms (137±17 ms) than in those who did not(125±15 ms, P< 0.02). Both the intraatrial (54±12 ms) and interatrial (101±14 ms, P< 0.001) conduction times were also significantly longer in patients who had abnormal atrial endocardial electrograms [15]. An abnormally prolonged and fractionated atrial electrogram may reflect inhomogeneous local electrical activity related to a delayed and non-uniform anisotropic conduction through fibrotic atrial myocardium, and was closely related to the vulnerability of the atrial muscle to develop AF [15-18].

Therefore, in the evaluation of patients with altered P wave morphology in the electrocardiogram, it is very important to keep in mind that patients who have a greater susceptibility to develop AF possess abnormally prolonged and fractionated atrial endocardial electrograms, a significantly longer P wave duration, a significantly longer intra-atrial and inter-atrial conduction time of sinus impulses; and a significantly higher incidence of induction of sustained AF [16-18]. Awareness of this strong association in IAB patients may lead to better therapeutic management in individual patients.Due to this strong association of IAB, atrial conduction defects, and abnormal atrial endocardial electrograms with AF, there is a necessity of further studies to shed more light in characterizing the Bayés syndrome in different clinical scenarios, and to better understand the substrate of atrial fibrosis, along with the probability of earlier institution of anticoagulation and antiarrhythmic drugs.

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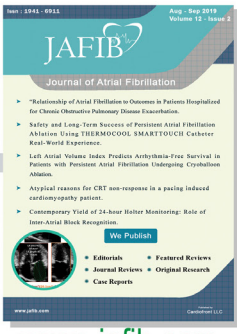

Left Septal Fascicular Block Following Alcohol Septal Ablation for Hypertrophic Obstructive Cardiomyopathy

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Abstract

Left septal fascicular block, or blockage of the middle fibers of the left bundle branch, is known to be suggestive of a critical proximal obstruction of the left anterior descending coronary artery before its first septal perforator branch. We describe the case of a 68-year-old male who exhibited this transient intraventricular dromotropic disturbance following alcohol septal ablation for hypertrophic obstructive cardiomyopathy.

Introduction

Percutaneous alcohol septal ablation (ASA) has emerged as an alternative treatment to surgical myectomy for the reduction of left ventricular outflow tract (LVOT) gradient in hypertrophic obstructive cardiomyopathy (HOCM) [1]. Several studies have reported high functional and hemodynamic success of ASA in symptomatic patients with HOCM [2-4]. Acute electro cardiographic changes seen in previous studies after ASA are right bundle branch block, ST-segment deviation, and Q wave formation [5,6]. We present a case of left septal fascicular block (LSFB) which appeared secondary to ASA for HOCM.

Case presentation

A 68-year-old male with previously known HOCM was admitted for ASA. At admission, the patient's heart rate was 70 bpm and blood pressure was 106/68 mm Hg; there were no detectable murmurs or other cardiac signs. His laboratory test results were with in normal limits. Transthoracic echocardiography showed a preserved left ventricular (LV) systolic function (LVEF 50%) and severe concentric LV hypertrophy with LVOT obstruction. There was severe systolic anterior motion of the mitral valve and a peak pressure gradient across the LVOT of 120 mmHg at rest. There were no significant valvular abnormalities noted. A 12-lead electro cardiogram (ECG) obtained prior to the procedure showed sinus rhythm with left atrial enlargement, LV hypertrophy with a strain pattern, and a QRS duration of 85 ms [Figure 1]. The patient underwent a successful AS aprocedure and echocardiographic measurement demonstrated a significantly reduced peak LVOT gradient of 30 mmHg. An ECG obtained immediately after the procedure showed sinus rhythm with right bundle branch block (RBBB), left axis deviation, and prominent anterior QRS forces in the right precordial leads V1-V2 [Figure 2] and [Figure 3]. One day following the procedure, the patient's clinical condition deteriorated and he was subsequently admitted to the coronary care unit (CCU). An ECG showed Mobitz type Iatrioventricular block with left posterior fascicular block and right axis deviation [Figure 4]. Echocardiography showed a slightly impaired LV systolic function (LVEF 40%) with no changes in the peak LVOT gradient (30 mm Hg). While in the CCU, the patient developed complete heart block. He was scheduled for a temporary pacemaker insertion but his clinical condition further deteriorated and he expired due to cardiogenic and septic shocks, in spite of efforts at resuscitation.

Discussion

We describe the case of a patient who developed transient LSFB following ASA for HOCM. Pérez Riera et al [7] previously analyzed the dromotropic disturbances (vector-electro cardiographic) and possible anatomic causes provoked by selective alcohol injection in the septal branch in 10 patients undergoing percutaneous treatment of HOCM. Prior to the procedure, 7 out of 10 patients had LV hypertrophy with a strain pattern, as reported in the present case.

The ECG criteria for LSFB have been previously defined [8-11]. In the present case, all the criteria proposed in 2011 [8] were fulfilled [Table 1]. The presence of an intermittent pattern on ECG/VCG, as part of the requisites to recognize a new ECG dromotropic disturbance,

Key Words

Alcohol septal ablation, Hypertrophic cardiomyopathy, Left septal fascicular block.

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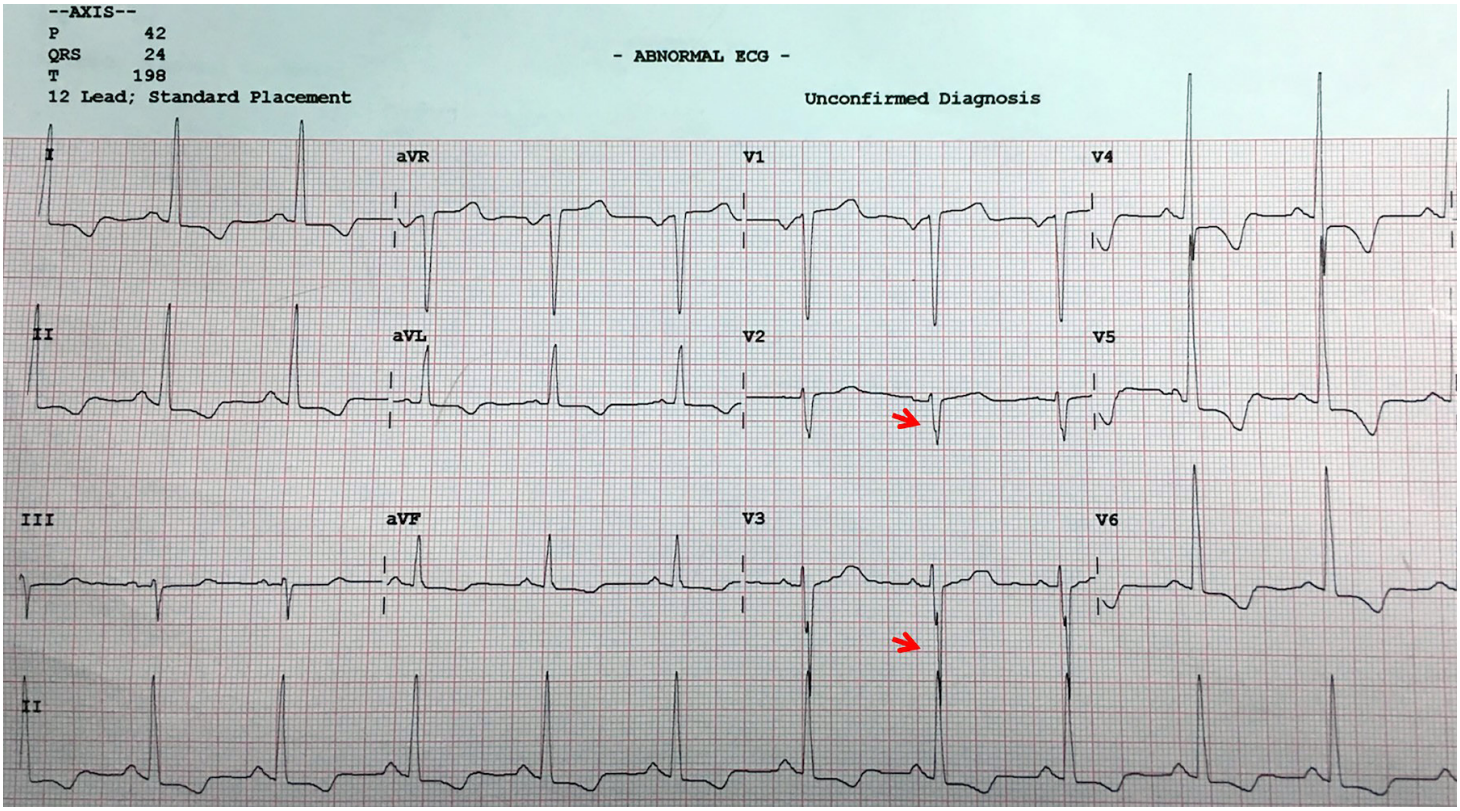

Figure 1: **ECG obtained before the procedure.**

ECG diagnosis: P duration 120 ms, terminal mode negative of P in V1 > 40 ms, Morris index >0.04 mm/s, QRS axis +24°, QRS duration 85 ms, positive Sokolow-Lyon index >35 mm, strain pattern of repolarization, insinuation of fragmented QRS (red arrows). Conclusion: left atrial enlargement + left ventricular hypertrophy + fragmented QRS (fQRS on the surface ECG can be used as an indirect marker to predict the presence of fibrosis in HCM).
Note: The association of LAE + LVH + fQRS. This pattern is very frequent in hypertrophic obstructive cardiomyopathy.

Table 1: **Diagnostic criteria of left septal fascicular block.**

Criteria for LSFB	Presence in the case
Presence of PAF of QRS	Yes
Normal QRS duration or discrete increase when not associated with other blocks	Yes
Unaltered frontal plane leads when isolated	Yes
Prolonged R-wave peak time in V1 and V2 ≥ 40 ms	Yes
R-wave voltage in V1 ≥ 5 mm	Yes
R/S ratio in V1 and V2 > 2	Yes
S-wave depth in V2 < 5 mm	Yes
Embryonic and/or transient q wave in V2 or V1 and V2	Yes
R-wave voltage in V2 ≥ 15 mm	Yes
RS or Rs patterns in V2 and V3 with R-wave “in crescendo” from V1-V3 and decreasing from V5-V6	Yes
Absence of q wave in V5, V6 and lead I	Yes

is considered mandatory [12]. LSFB is one of the many causes that is responsible for the appearance of prominent anterior QRS forces in the horizontal plane (precordial leads). The transitory nature of the electro cardiographic findings, as seen in the present case, rules out the possibility of other causes for prominent anterior forces, such as normal variant, athlete’s heart, RBBB, obstructive and nonobstructive hypertrophic cardiomyopathy, erroneous placement of the precordial leads, vector cardiographic right ventricular hypertrophy, andothers as described else where [11].

The mechanism of LSFB following ASA can be explained with septal fibrosis following the alcohol injection. Septal fibrosis causes a predominance of RBBB, which differs from myectomy, that causes left bundle branch block [7]. In the present case, LSFB was accompanied with a typical left anterior fascicular block and complete RBBB with left axis deviation. However, the patient developed Mobitz type Iatrioventricular blockand the LSFB disappeared. We speculate that the transient appearance of LSFB with prominent anterior forces could be a sign of new onset acute coronary syndromeand should raise the suspicion of a critical obstruction of the left anterior descending (LAD) coronary artery before the first septal perforator branch [13], as a complication of ASA. However, this could not be diagnosed on time as the patient’s clinical condition dramatically deteriorated and the patient expired.

Conclusion

We present a case of transient LSFB following ASA for HOCM. This clinical scenario should raise the suspicion of a critical proximal LAD occlusion before the first septal perforator branch. Physicians should be attentive to this pattern for the need of immediate coronary angiography.

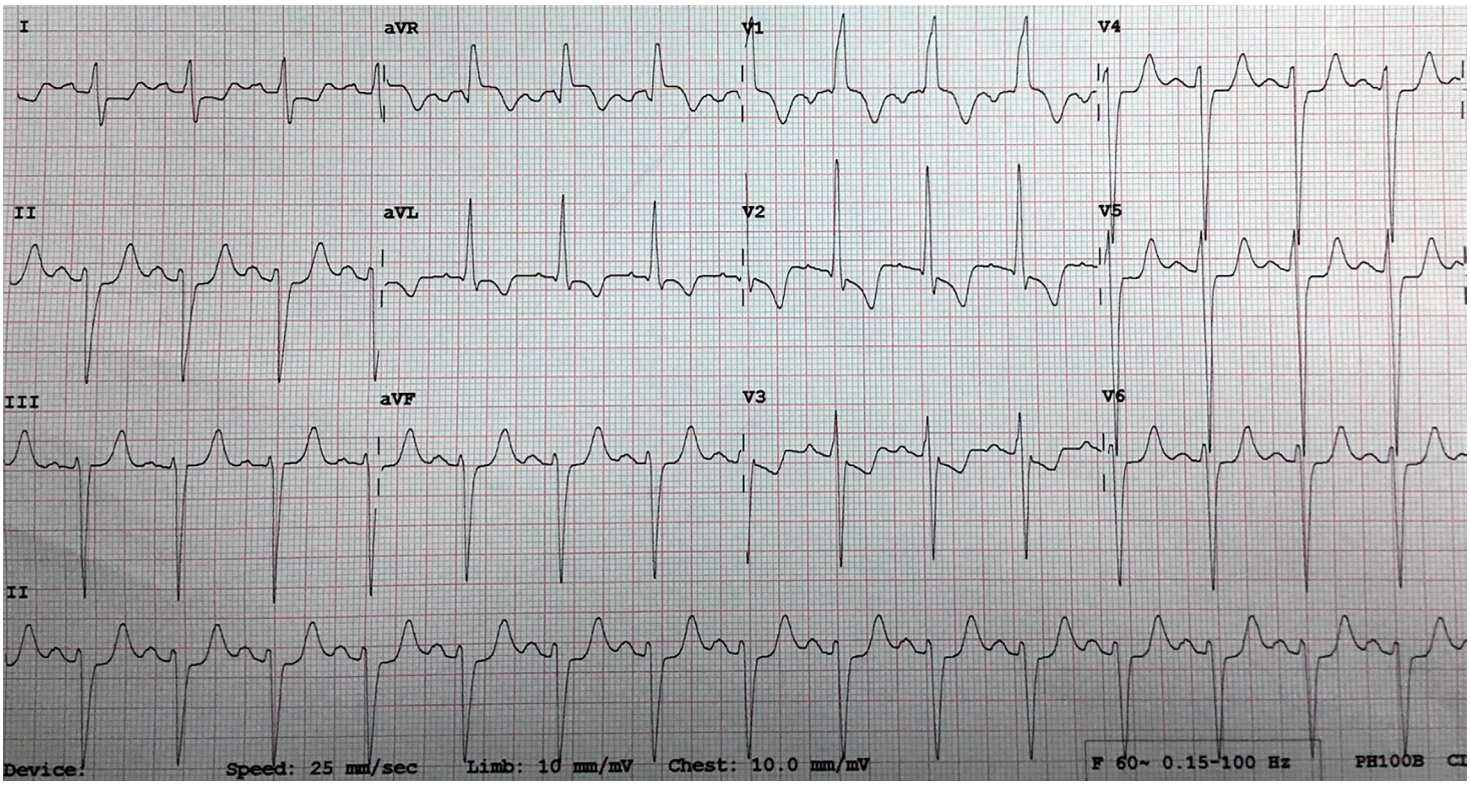

Figure 2: **ECG obtained immediately after the procedure.**

V1 LAE (Morris criteria + prolonged P duration = 120ms) + QRSd 120ms + ST-segment elevation followed by symmetric negative T-wave CRBBB + injury and ischemic. V2qRs pattern, prominent anterior QRS forces on right precordial leads V1-V2 "R-wave in crescendo" from V1 to V2 and decrescent from V2 to V6, prolonged R-wave peak time (> 40 ms) in V1-V2, R-wave voltage > 15mm and embryonic initial q wave in V1-V2 absence of q in I, V5-V6 consequence of absence of first septal vector. Conclusion: LAE + LVH + atypical LAFB + LSFB + RBBB (undescribed Trifascicular block: RBBB + left bifascicular block).

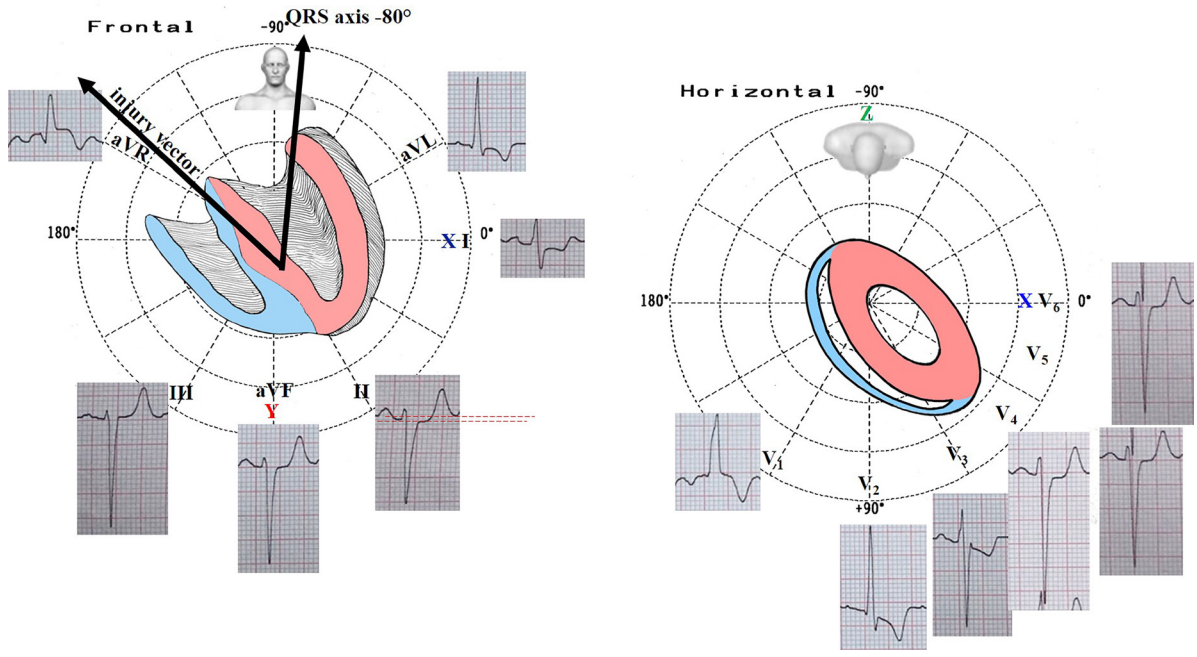

Figure 3: **Typical ECG/VCG of LSFB in the frontal and horizontal plane.**

Note the ST-segment elevation in the unipolar lead aVR and concomitant ST-segment depression in lead II. The current injury vector pointing to lead aVR and consequently moves away from bipolar II, indicates proximal critical obstruction of the LAD before its first septal perforator branch or LMCA artery obstruction. This is compatible with the alcohol injection in this branch. Additionally, symmetric ischemic T waves are observed in II, III and aVF. Extreme left axis deviation -80°, SIII>SII atypical LAFB (why atypical? Because the absence of initial q wave in I. In the presence of typical LAFB, the 10-20 initial QRS forces are directed to +120°, originating initial r wave in III and concomitantly q wave in I.

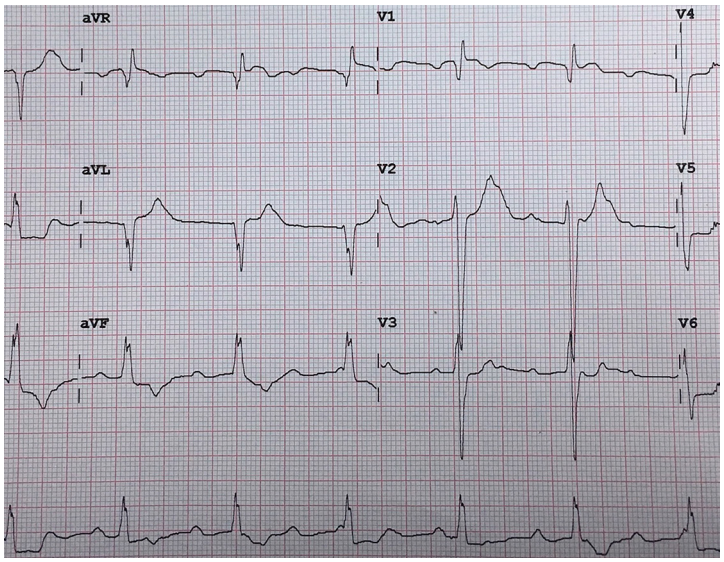

Figure 4: **ECG obtained one day after the procedure in the coronary care unit.**

LAE+ LVH+ second-degree atrioventricular block Mobitz type I + left posterior fascicular block: QRS axis + 120°+ rS pattern in I + qR pattern in III and II, RIII>RII, prolonged R-wave peak time in aVF>45 ms; + localized septal infarction secondary to the procedure QR pattern in V1. PAFs disappear: transient LSFB.

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Atypical Reasons for CRT Non-Response in a Pacing Induced Cardiomyopathy Patient

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Abstract

Pacing induced cardiomyopathy is a known complication of high percent right ventricular (RV) pacing. When treated with cardiac resynchronization therapy (CRT), most patients experience recovery of left ventricular (LV) systolic function.A small percentage of patients do not respond due to a number of factors.This case examines the management of a 30-year-old patient with pacing induced cardiomyopathy who was found to be a CRT non responder despite optimal LV lead position and whose LV ejection fraction normalized following RV lead revision.

Introduction

Cardiac Resynchronization Therapy (CRT)is standard of care for individuals suffering from dilated cardiomyopathy and heart failure with wide QRS duration.The role of right ventricular (RV) pacing alone has well -known deleterious effects on left ventricular (LV) function and volumes [1]. Pacing - induced cardiomyopathy (PCM) has been defined as LV ejection fraction < 45% in a patient with high percentage RV pacing and no other cardiac explanation for the reduction in systolic function. Reported incidence has ranged from 6% to 39% [2] with vast majority of them showing excellent response to CRT upgrade [2].Leclerc et al, in 2016, conducted a study randomly assigning 263 CRT patients to Right Ventricular Septal (RVS) vs. Right Ventricular Apical (RVA) pacing [2]. The results demonstrated that RVS pacing in CRT was non-inferior to RVA pacing at 6 months in reducing left ventricular end systolic volume (LVESV) [3]. The REVERSE trial found no difference in RV lead placement in CRT [4].While patients with reduced RV ejection fraction experience a slight improvement in response to CRT, the role of RV lead location in this scenario is not clear [5]. The REVERSE trial did not look at the detrimental effects of RV free wall placement. There is currently no clear data on the impact of RV free wall lead placement on effective CRT system.Stabile et al (2015) however, did find that patient outcomes after CRT implantation were strongly affected by both electrical and direct interlead distance [6].

Key Words

Cardiac Resynchronization Therapy (CRT), Left Ventricular (LV), CRT non-response.

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Case

A 32-year-old male with marfanoid syndrome and aortic root replacement as an adolescent developed high degree Atrio ventricular (AV) block at age 29 with subsequent dual chamber permanent pacemaker implantation.

LV ejection fraction at the time of dual chamber pacemaker implantation was 56%. Echocardiogram done 9 months after pacemaker implant showed deterioration of LV ejection fraction from 56 % to 31%. Goal Directed Medical Therapy (GDMT) was initiated and titrated to the maximum dosages including Valsartan-Sacubitril, Carvedilol and Spironolactone but LV ejection fraction did not improve and therefore the device was upgraded to a CRT-D [Figure 1]. At the time of upgrade his RV pacing lead was extracted easily, without complication, as it was no longer needed. It is not clear from the operative note what measures were taken at implant to assess RV and LV lead separation or right ventricular outflow tract placement. Miranda et al, (2012), also studied implant of the RV lead guided by maximal electrical separation (MES) comparing this to standard apical placement [7]. This study demonstrated a significant improved response to CRT compared to blind apical placement [7].

Repeat echocardiogram obtained 4 months after upgrade demonstrated an LV ejection fraction of 30%. Pacing and sensing thresholds were demonstrated at acceptable levels. The patient was having worsening heart failure symptoms with a deterioration now in NYHA functional class III-IV. Echocardiography revealed lack of septal activation with despite Bi-Ventricular pacing. It was suspected that his lack of septal activation was due to free wall placement of the RV lead. CT scan obtained supported free wall placement [Figure 1]. Given this scenario, a revision of the RV lead was completed 17

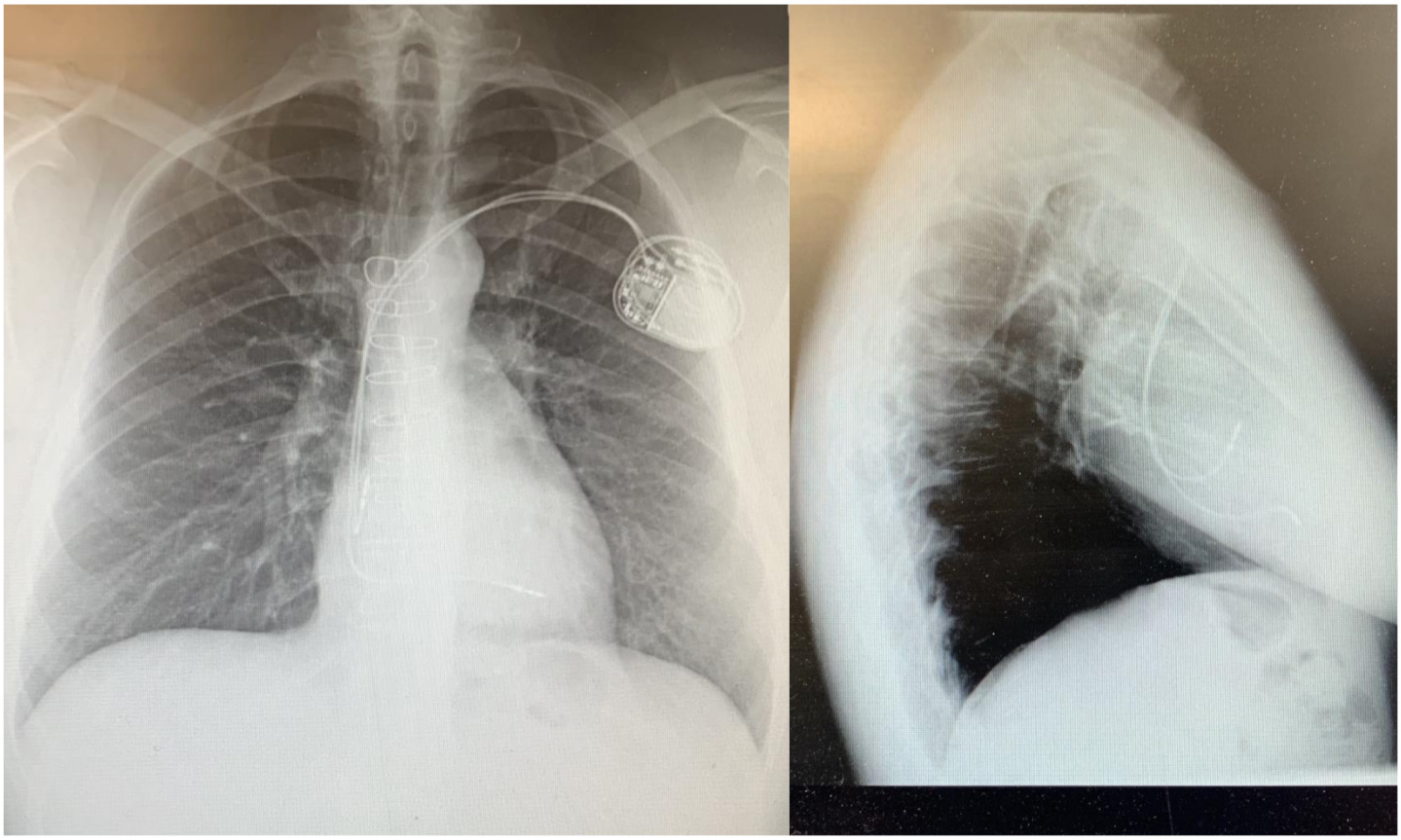

Figure 1: Chest X-ray of the initial pacemaker system with apparent RV apical lead placement.

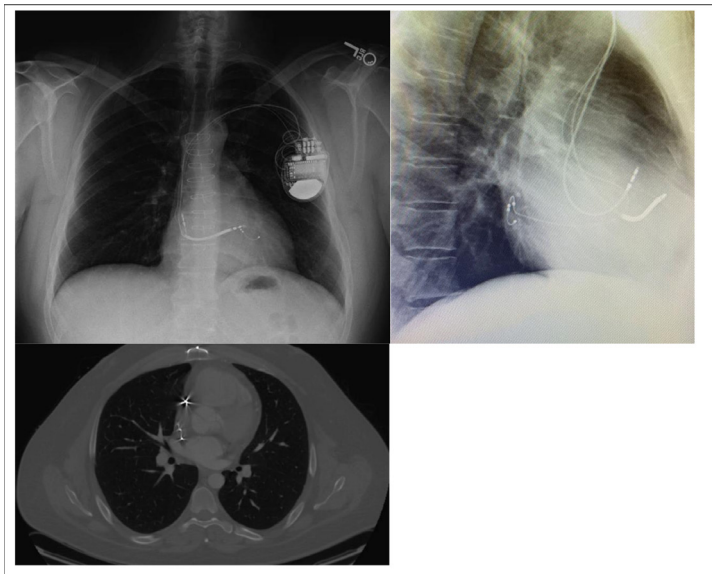

Figure 2: PA and Lateral Chest X-Ray and CT of the Chest following CRT-D upgrade of dual chamber pacemaker. Please note the anterior free wall location of the RV lead and minimal lead separation.

months after the initial CRT lead system placement.During the RV lead revision, the LV lead was in advertently repositioned and so it was also revised at this time[Figure 2]. The LV lead is in a more lateral position, however it is not significantly different from the initial CRT implant thus unlikely to provide a significant difference in systolic function. Three months after the lead revisions a repeat echocardiogram showed normalization of LV ejection fraction and septal wall activation [Figure 3]. The patient experienced a reduction in congestive symptoms and his functional class improved to NYHA functional Class I and he was able to resume normal activities.

Discussion

Non response to CRT therapy is mostly due to LV lead placement or the lack of ventricular synchrony. The REVERSE trial found no difference between septal or apical placement of RV lead in CRT response [4]. In our case, RV free wall lead placement at time of CRT-D upgrade resulted in inability to activate the septal wall, resulting in worsening LV ejection fraction, development of clinical heart failure and decline of functional status, with two acute hospital admissions requiring diuresis. Echocardiogram following initial CRT upgrade revealed mechanical dyssynchrony with akinesias of the entire septal wall. MRI did not indicate an infiltrative process and no perfusion defects were identified on nuclear stress testing. Revision of RV lead to a more apical location resulted in normal

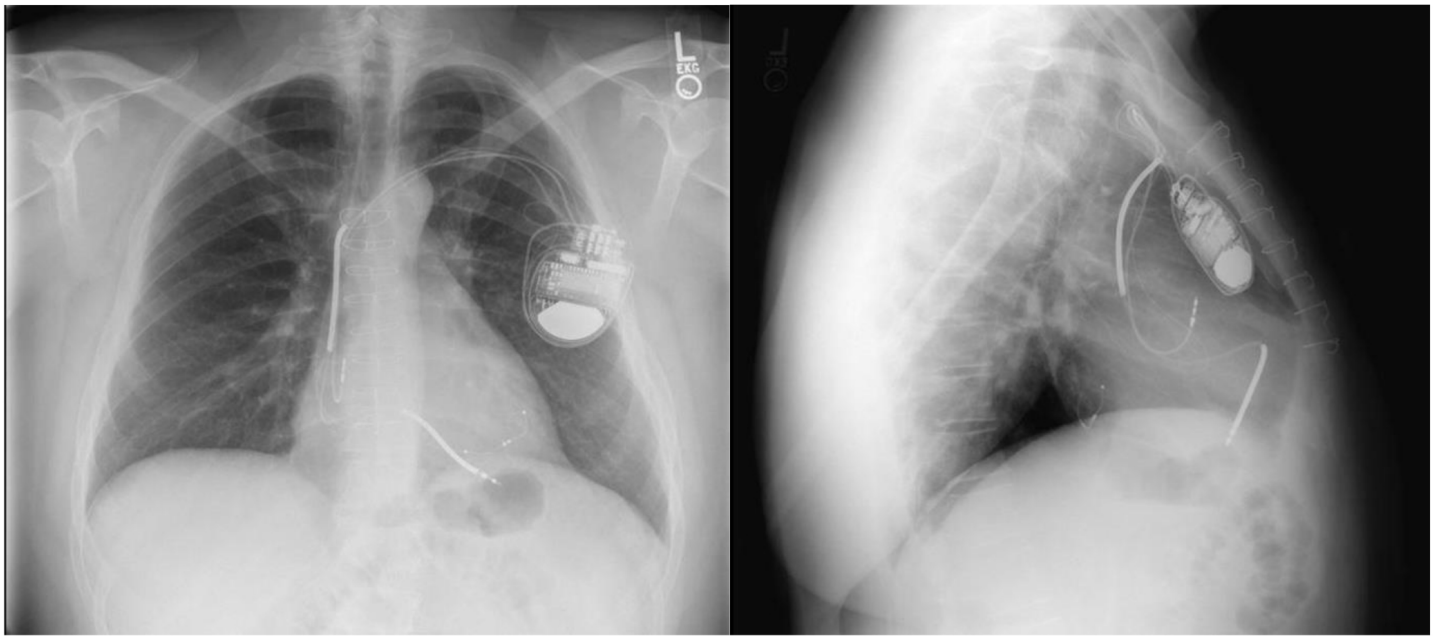

Figure 3: Post Redo CRT CXR with LV lead in a more lateral position and the RV lead in the apical position.

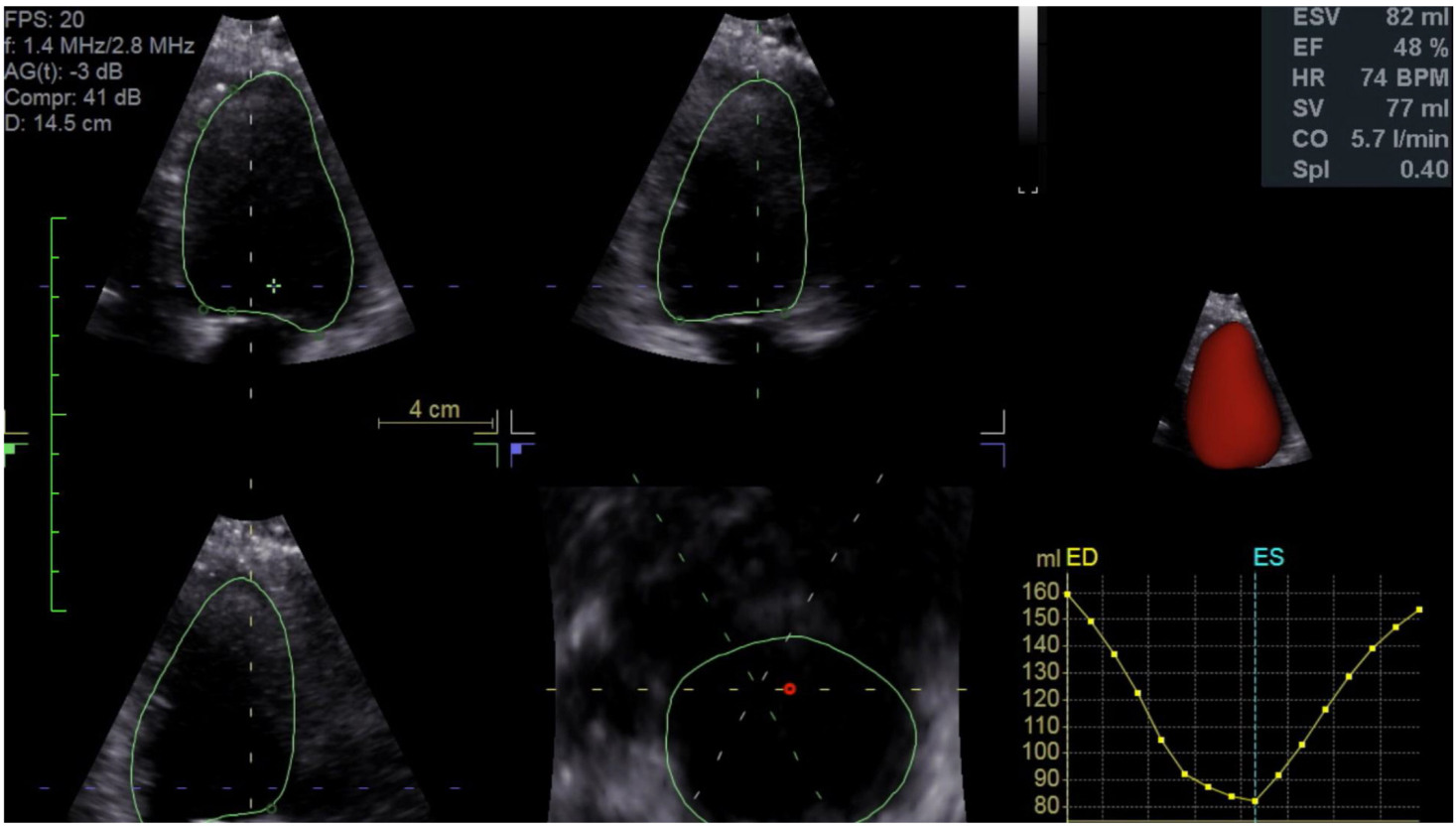

Figure 4: Echocardiogram 3 months after CRT redo reflecting normalized LV function.

septal activation. Improvement in symptoms were immediately seen,with change in functional status to NYHA Class I within the first month after lead revision. Ventricular synchrony was restored resulting in near normal systolic function. Our report thus suggests that RV lead placement on the free wall, in some patients, can result in lack of septal activation and non-response to CRT. Further studies are needed to elucidate this in detail.

Conclusion

We report a case study where RV free wall lead location resulted in septal akinesis and non-response to CRT in a patient with pacing induced cardiomyopathy. Ventricular function was restored to near normal with RV lead revision.

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Intra-Atrial Block: Definition and Relationship to Atrial Fibrillation and Other Adverse Outcomes

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Abstract

In 1916, Bachmann first reported on the inter-auricular time interval. However relatively little attention was paid to this ECG measurement for decades. Then, in 1956, Samuel Bradley and Henry JJ Marriott reported on intra-atrial block (IAB) in 4,500 ECGs.As defined by them, IAB was a P wave duration of 0.12 sec or longer. Since that time, others have defined IAB as 0.11 sec or longer or 0.12 sec or longer. Several authors have suggested subcategories, such as first-, second-, and third-degree patterns and some have defined specific intra-atrial and inter-atrial pathways. These are of electrocardiographic interest but have not been substantiated as related to different clinical outcomes. Many disorders have been associated with IAB. More importantly, however, IAB has been associated with several adverse outcomes, including sinus node dysfunction, atrial tachyarrhythmias – especially atrial fibrillation, thromboembolic events, and increased mortality. This brief review will detail the above to emphasize to ECG readers the importance of not overlooking IAB in their interpretations.

Introduction

Recently, in an ECG case in Circulation, Qin et al.[1] reported a 2:1 pattern of intra-atrial block (IAB) [a topic discussed in the literature much less frequently than other conduction abnormalities] as a cause of alternating P wave morphology. It was a beautiful example of normal sinus P waves alternating with widened and notched sinus P waves. However: (1)I was dismayed by the specific references chosen to define IAB and its patterns and incidence, since each reference related only to intra-atrial conduction impairment following a catheter ablation procedure, which was not a factor in their patient's history or care. (2) I was surprised that they used post-ablation intervals to define intra-atrial conduction in a non-ablated patient rather than information from the long history of reports regarding the definition and patterns of IAB in the absence of ablation. (3) They oversimplified the P wave variations that can occur with IAB. And, (4) I wondered why they did not also discuss the importance of IAB with respect to adverse outcomes – after all, it is more than just an ECG curiosity. This all suggested to me that a concise review of IAB would be timely.

Review

In 1916, Bachmann first reported on the inter-auricular time interval. [2] However relatively little attention was paid to this ECG measurement for decades. Then, in 1956, Samuel Bradley and Henry JJ Marriott reported on intra-atrial block in 4,500 ECGs.[3] As defined by them, IAB was a P wave duration of 0.12 sec or longer. Notching, as was seen by Qin et al.[1] occurred in ~10% of IAB. Moreover, Bradley and Marriott critically examined the even earlier literature that considered definitions of >0.10 sec, 0.11 sec, and 0.12 sec and concluded that there was good justification for adopting 0.11 sec as the upper limit of the normal P wave and for calling IAB as a sinus P wave of 0.12 sec or longer. In their 4,500 ECGs, the incidence of IAB was 4.5% -- "almost as high as that of atrioventricular or intraventricular block in the same series." More recently, Fauchier et al. [4] demonstrated that in patients with sinus node dysfunction, AV conduction disturbances, paroxysmal supraventricular tachycardias, and paroxysmal atrial fibrillation with slow ventricular responses, the incidence of IAB is even higher, being 26%, 20%, 16%, and 31% respectively. Others, including Antonio Bayes de Luna in 2015, agreed with the 0.12 sec definition for IAB, though some, including David Spodick and colleagues in 2014 and Williams and colleagues in 2015 defined IAB as a P wave of 0.11 sec or longer. [5,6,7]

Subsequent to the work of Bradley and Marriott, Jules Cohen and David Scherf detailed the patterns of complete intra-atrial and inter-atrial block,[8] which included intra-atrial and inter-atrial dissociation (separate rhythms within one atrium or between the two atria) and related atrial conduction impairment that protects atrial parasystolic foci. Moreover, Thomas James and others attempted to detail the pathways of preferential conduction within the right atrium from the sinus node to the AV node and between the right atrium and the left atrium [9-16] in which conduction delays would result in IAB and often associated alterations in P wave morphology. Intra-right atrial conduction, according to such investigators, [9-11] occurs primarily via three preferential pathways (anterior, middle, and posterior), although they have not been as convincingly identified histologically as are the intraventricular and His-Purkinje conduction tissues.

Key Words

Intra-atrial block, Inter-atrial block, atrial conduction, P wave duration Running Head, Intra-Atrial Block: Recognition and Significance.

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Right atrial to left atrial conduction appears to occur most often via Bachmann's bundle, though less frequently (and less well studied and characterized) it may occur via fibers in or around the fossa ovalis or coronary sinus. [12-14] Such left atrial breakthrough sites have been most recently confirmed in patients undergoing ablation for atrial fibrillation using magnetocardiography and electroanatomic mapping. Notably, IAB appears to be more frequent in patients with atrial fibrillation who are evaluated at the time of ablation than it is in patients without atrial fibrillation.Consider, however, that this data may reflect a selection bias as those patients with atrial fibrillation who are referred for ablation tend to be those whose atrial fibrillation has not been medication-responsive and thus may have more advanced altered atrial electrophysiology and/or more advanced atrial histopathology. They tend to have wider P waves than those patients without atrial fibrillation (see below).

To perhaps more precisely characterize IAB, Bayes de Luna and others [5,6,10,15-17] attempted to subdivide IAB into first-, second-, and third-degree patterns, analogous to the approach taken for AV conduction disturbances. In its simplest terms, first degree IAB is a widened P wave, with or without notching; second degree is abrupt and transient P wave widening, perhaps most often with delay in Bachmann's bundle, and third degree is IAB with loss of conduction across Bachmann's bundle. Figure 1 schematically shows normal intra- and inter-atrial conduction, IAB conduction, and IAB with block in Bachmann's bundle. [Not shown are possible delays in the inter-atrial connections via the coronary sinus or fossa ovalis regions.] Notably, several authors have suggested particular P wave alterations on ECGs or vectorcardiograms during sinus rhythm that are suggestive for specific locations of intra-atrial block [11,15,18-20], with those associated with delayed left atrial breakthrough most likely to be associated with risk for atrial fibrillation. [Readers who are interested in the specific P wave alterations are referred to these references for more detail.] See [Figure 2] for ECG examples of several patterns of IAB.

While IAB patterns are interesting electrocardiographically, subdividing IAB does not appear exceptionally helpful to me clinically, other than recognizing an increased association with atrial fibrillation when left atrial breakthrough is affected. Notably, the association of IAB (particularly when it is advanced as a consequence of delay in Bachmann's bundle as manifest by negative terminal forces in the inferior leads suggestive of retrograde left atrial activation) and atrial fibrillation has been termed Bayes syndrome. [11,15] Personally, I would think that inter-atrial block with independent right and left atrial rhythms or intra-atrial block with two separate atrial rhythms within the same chamber would be a better definition for third degree IAB [Figure 3]. Perhaps, first degree IAB could be subcategorized

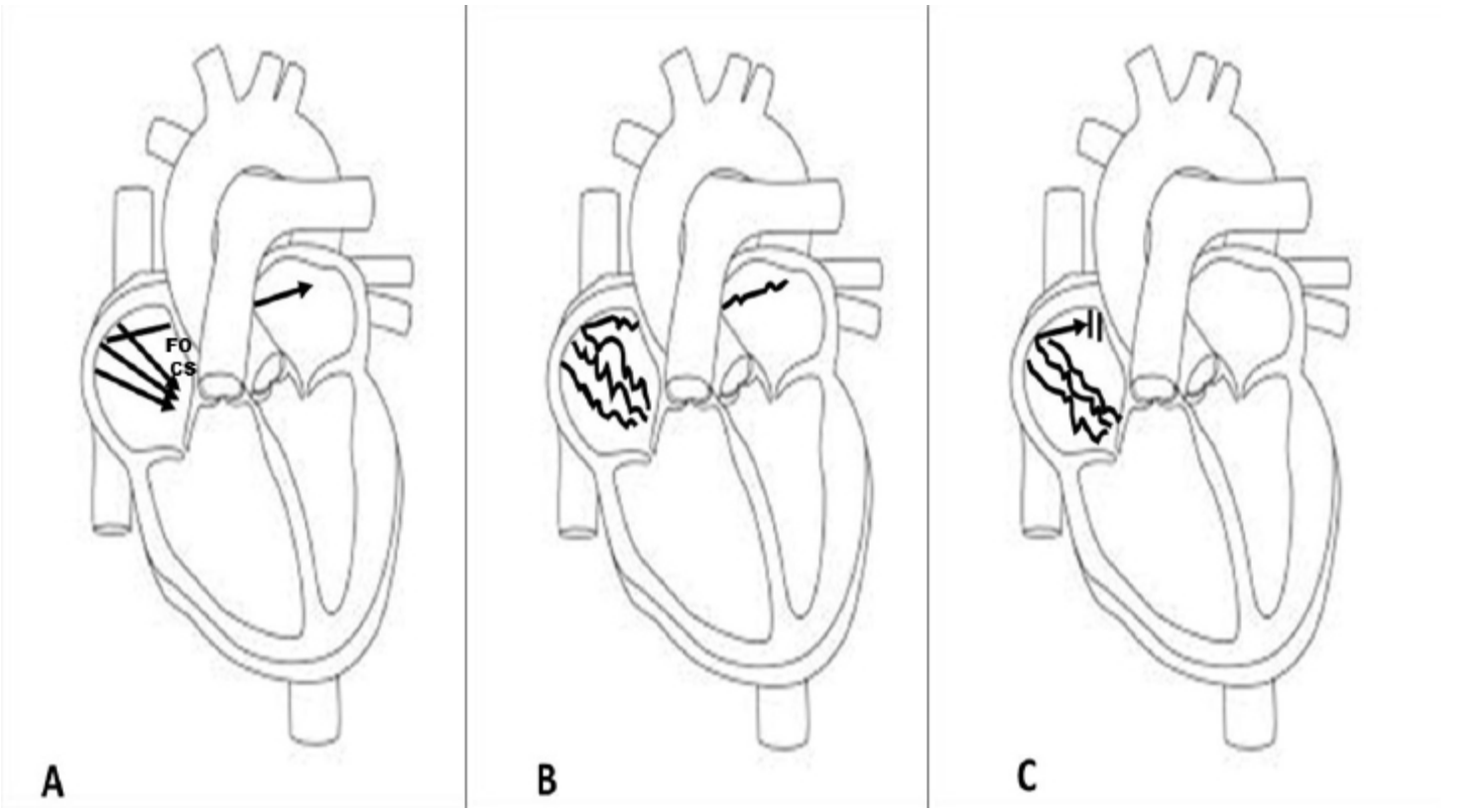

Figure 1: A schematic of normal intra and inter atrial conduction (solid arrows represent normal conduction velocity), panel A; slow intra and inter atrial conduction – represented by the squiggly lines, panel B; and slow intra atrial conduction with block across Bachmann's bundle, panel C. Conduction across the less frequently apparent coronary sinus (CS) and fossa ovalis (FO) fibers, which are likely used to achieve conduction to the left atrium in the setting of Bachmann's bundle block, is not illustrated although their approximate locations with respect to Bachmann's bundle is shown.

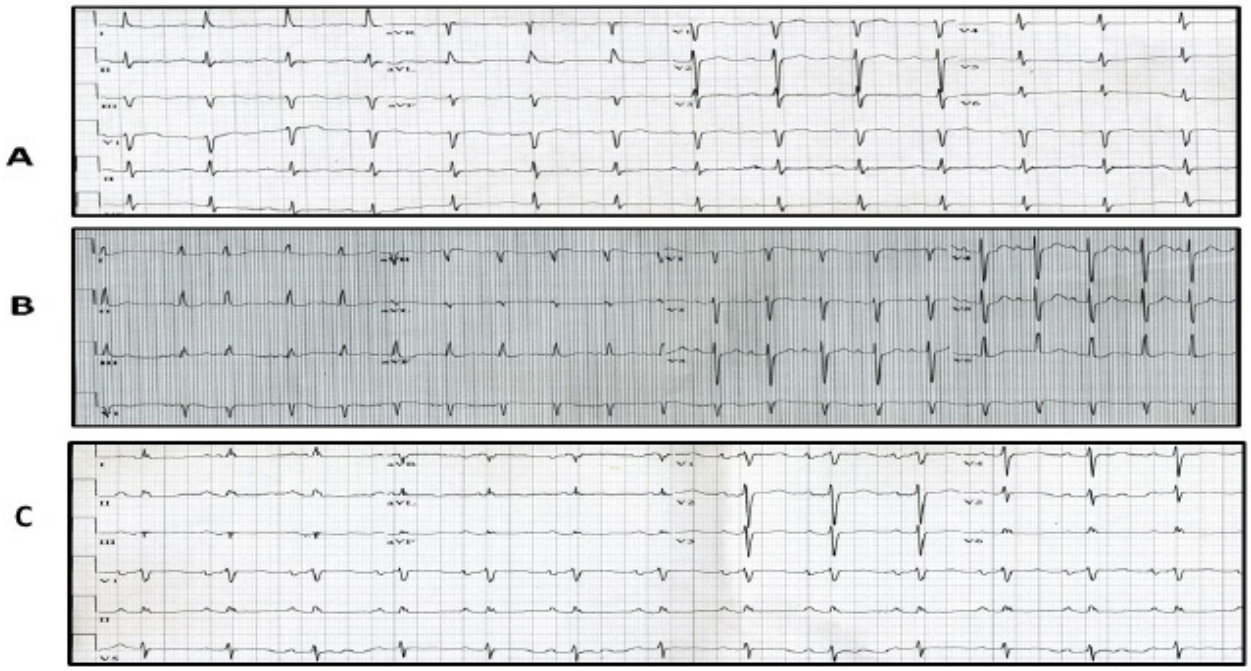

Figure 2: Three examples of IAB. Panel A shows a widened but smooth P wave. Panel B shows a widened and notched P wave (as well as some premature atrial complexes). Panel C shows a widened and notched P wave with the terminal forces being negative in the inferior leads. Panel A is most compatible with delay mainly in the right atrium. Panel B is most compatible with delay between the right and left atria, with the second part of the P wave (second notch) most likely representing delayed left atrial activation. Panel C is most suggestive of delay in Bachmann's bundle, with the terminal forces going away from the inferior leads and upwards towards the left atrium due to lower septal activation rather than conduction across Bachmann's bundle in the upper septum.

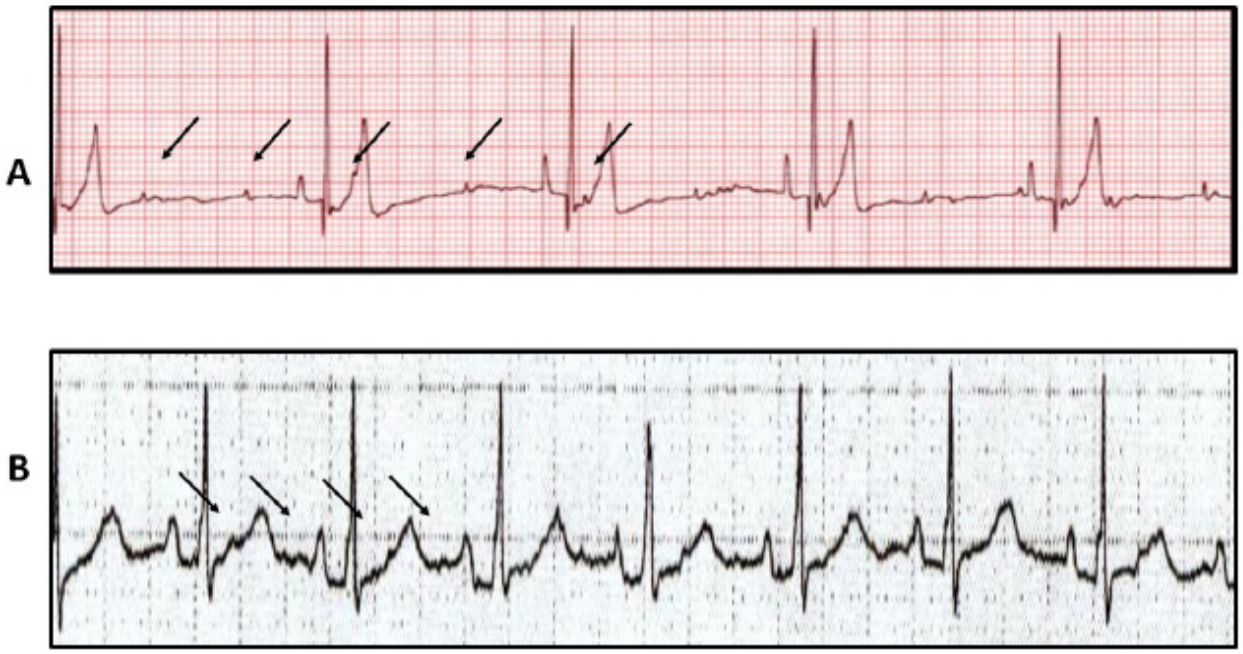

Figure 3: Two tracings showing types of atrial dissociation. Panel A shows right and left atrial dissociation with independent rhythms and therefore two sets of P waves marching through each other. Only the right atrial P wave (sinus rhythm) conducts to the ventricles and results in QRS complexes. Panel B shows a similar phenomenon but in this case the patient is post heart transplant with one set of P waves conducting to the ventricles that originate in the transplanted right atrium and the second set coming from the recipient's atrial rim. Arrows are place to indicate the non-conducted P waves.

by the presumed pathway(s) with delay or block. Importantly, with respect to Bayes syndrome, the block in Bachmann's bundle not only results in delay of left atrial activation but altered routes to left atrial activation, which could result in the potential for additional reentrant pathways within the atria (perhaps especially if Bachmann's bundle block is only unidirectional) thereby facilitating the development of atrial tachyarrhythmias.

Regardless of the site and degree of IAB (other than inter-atrial dissociation), but of importance because IAB widens the P wave and the measurement of the PR interval begins with the onset of the P wave, IAB can result in a lengthened PR interval through delay in impulse conduction from the sinus node, through the right atrium, to the AV node. In this circumstance, PR prolongation does not indicate any AV conduction delay, as it results from widening of the P wave and lengthening of the PA interval (as seen on intracardiac tracings) rather than prolonging the AH interval which is indicative of AV nodal delay. In contrast, if IAB is a consequence of right atrial to left atrial delay, but intra-right atrial conduction velocity is normal, then PR prolongation should not be noted. Importantly, IAB and sub-atrial conduction disturbances can coexist. Notably, Qin et al.[1] essentially ignored the contribution of the IAB, when present, to the prolonging of the associated PR interval in their report. In their case of 2:1 IAB, with the PR interval being normal when the P wave width was normal, the IAB-associated prolonged PR interval clearly did not indicate delay of AV conduction.

In addition to defining IAB, Bradley and Marriott [3] also explored the causes of P wave prolongation, as have others.[7,11] Reported causes include disorders that result in left atrial enlargement [including mitral stenosis and the P-mitrale pattern and many left ventricular disorders];Chagas disease; inflammatory and infiltrative disorders; age-related fibrosis; atrial septal structural abnormalities; and atrial ischemia (via impaired flow through Condorelli's artery – the left anterior atrial artery which supplies Bachmann's bundle among other atrial areas). Other causes include medications, such as quinidine and digitalis, as well as vagal stimulation. Recently, it has been shown that IAB may be provoked by adenosine; reduced by atropine;can be functional, occurring or stopping after refractory period changes associated with premature impulses; and may be associated with obstructive sleep apnea. [6,11,2-10,16,17,21,22,24] Sometimes the P wave morphology can offer a clue as to possible contributors to IAB or the site of delay. For example, a left atrial enlargement pattern would suggest left heart pathology. Negative terminal P wave forces in the inferior leads with a P wave otherwise compatible with sinus rhythm can suggest impairment of atrial impulse transmission across the upper atrial septum (e.g., Bachmann's bundle) resulting in lower transseptal conduction with resulting inferior to superior terminal P wave forces ([Figure 2], panel C). Because the interested reader can find substantial information regarding the electrophysiological, anatomic, and ultra-structural alterations that can underly IAB in other prior publications [6,7,15] I will not detail them in this brief review.However, it is of note that they do include cell loss, intercellular collagen deposition with the widest P waves being associated with the greatest amount of collagen deposition, [6,17] as well as excessive stretch of atrial myocardium. Of note, such changes can affect intercellular conduction and serve as a basis for reentrant circuits as well as impairment of function of atrial-associated tissues, such as the sinus node. Also, of note, IAB may be the only manifestation of an atrial disorder in some patients whereas in others when disease affects not only intra-atrial conduction but also myocyte function and therefore atrial contractility and possibly size, IAB is then part of an atrial cardiomyopathy. In some of the latter cases, progressive disease can ultimately result in atrial standstill with slow junctional escape rhythms. More frequently in others, the underlying atrial pathology as well as the associated atrial conduction impairments result in altered atrial electrophysiology and atrial tachyarrhythmias, such as atrial fibrillation. When the underlying disorders are associated with risk markers for thromboembolism in the presence of atrial fibrillation, such as hypertension, diabetes, heart failure, advanced age, then prophylactic oral anticoagulation is appropriate to consider. Thus, IAB should indicate the need for both an evaluation of any associated disorders and a closer follow up regarding atrial fibrillation (which in many patients has been shown to be subclinical but detectable by appropriate monitoring, prior to its first clinical presentation).

Lastly, in the era of transvenous catheter-based human electrophysiologic studies, confirmation of the above noted ECG-based interpretations has occurred. In 1977, our group demonstrated that IAB can be rate-related, as was shown in a case of simultaneous intra-atrial and intra-ventricular conduction defects that mimicked an intermittent trifascicular conduction disorder. [25] Others have shown that: (1) portions of the right atrium can be in sinus rhythm (protected by entrance block) while other portions and the left atrium can be in flutter-fibrillation; (2) similar phenomena can exist in the left atrium following ablation; (3) intra-atrial block may occur during atrial tachycardia though being absent during sinus rhythm; (4) intra- and inter-atrial dissociation can occur during atrial flutter or fibrillation,[26-33] and (5) second degree IAB can be produced with atrial stimulation at critical drive rates (in an era well before ablation) thus confirming rate-related potential.[34] In one patient, electrophysiologic testing of sinus node function in the small section of the right atrium that was in sinus rhythm revealed an underlying sinus node dysfunction, while the rest of the right atrium and the left atrium was in atrial flutter-fibrillation. [26]

Clinical Significance

Why should we care about IAB? After all, it is just widening of the P wave. Isn't this just cosmetic?To the contrary.

First, as noted earlier, IAB can mimic delayed AV conduction. Since the P wave onset initiates the measurement of the PR interval, IAB can result in PR prolongation, which may then be misinterpreted as delayed AV nodal and/or His-Purkinje conduction. Second,in patients with IAB, likely as a marker of atrial disease but also as an indicator of areas of delayed conduction in the atria that might sub serve reentry, there is an increased likelihood for development of atrial tachyarrhythmias, most frequently atrial fibrillation (AF) as well as for recurrences of AF following both cardioversion and ablation.This has been noted in multiple reports [5,6,11,17,35-41] and may be the most important associated consequence of IAB (as well as the reason IAB should be of interest to readers of this journal). Less

well studied is the relationship between IAB and the risk of post-ablation atrial tachycardias. Of note, but perhaps not of surprise, the risk for developing AF appears greatest when IAB is most pronounced, as measured by P wave width or P wave dispersion. [11,13-14,20,26-32,35-46] Relatedly, there have been reports of an increased risk for thromboembolism in patients with IAB—both stroke and peripheral. [6] Third, in our experience, not infrequently IAB also accompanies sinus node dysfunction, thus likely indicating pathology of both the sinus node and surrounding atrial tissue.Interestingly, in at least one report, in patients with sick sinus syndrome and paroxysmal atrial fibrillation in whom right atrial pacing was instituted as part of preventive treatment for recurrent AF, the presence of IAB during sinus rhythm was associated with a higher incidence of recurrent AF than when IAB was absent. [47] Accordingly, IAB may caution the clinician to be alert for symptoms compatible with sinus node dysfunction as well as atrial tachyarrhythmias; and, due to the latter, may signal a need for closer follow up by the treating physician. Moreover, IAB may be appropriate to consider in association with a patient's demographic and echocardiographic profile with respect to selection of patients to monitor for subclinical AF.Fourth, IAB has been epidemiologically associated with increased cardiovascular and total mortality. [6,48] Fifth, though rarely, severe IAB can result in cessation of atrial tachycardias that were previously present but dependent upon lesser but critical degrees of intra-atrial conduction delays. [49] Sixth, inter-atrial block can result in atrial dissociation with independent atrial rhythms that may be symptomatic and may confuse the interpretation of the standard ECG. [26,50-52]

With specific respect to intermittent IAB or varying degrees of IAB rather than consistent P wave widening, in 1974 MA Legato and MI Ferrer reported on the diagnosis, incidence, and implications of intermittent IAB.[53] These authors noted that with intermittent IAB: (1) the PR interval was significantly shorter when the P wave duration was normal but that the PR interval lengthened by a smaller increment than that which widened the P wave itself, suggesting that some of the P wave delay can occur after the onset of AV nodal activation; (2) intermittent IAB was not typically related to a change in sinus rate; and, (3) in 16 of their 56 study patients, intermittent IAB was the only defect on the ECG (18%) except for rare ectopy. In the other 40, while there were additional ECG abnormalities present, there was no consistent ECG finding that associated with the IAB. They also reported that the most attractive explanation for intermittent IAB are abnormalities in the specialized internodal tracts (e.g., per James et al) and/or inter-atrial tracts (e.g., Bachmann's bundle), with the latter being accompanied by alterations in the P wave morphology (such as a negative terminal component to the sinus P wave in the inferior leads). They supported their observations with literature involving lesions placed within specific atrial regions. In subjects with the most marked P wave widening (more than 30 msec), they invoked atrial myofibrillar blocks – in the working myocytes) beyond simple delay in the inter-nodal or inter-atrial tracts. However, as noted earlier, the most marked P wave widening may be related to more marked intercellular collagen deposition and not just myocyte alterations. Finally, in following their subjects, Legato and Ferrer reported that many of their patients developed non-intermittent IAB over several months to years as well as a variety of atrial arrhythmias, including permanent atrial fibrillation or slow non-sinus atrial rhythms "at an incidence greater than would be expected for a population of comparable age and background". [53] These follow up observations are compatible with those noted by others above and again suggest that IAB may be a harbinger of later AF.

Conclusion

IAB, defined by some as a P wave 0.11 sec or longer and by others as a P wave 0.12 sec or longer: is not uncommon, may take various ECG patterns, may be associated with sinus node dysfunction and its adverse outcomes, may be associated with underlying disorders in which there is an increased incidence of cardiovascular and all-cause mortality, and may be a marker of atrial disease with implications for atrial tachyarrhythmias, such as AF and its complications. Though it commonly is overlooked, IAB should not be missed when evaluating an electrocardiogram.

Conflict of Interest Disclosures

During the past 12 months Dr. Reiffel has served as an investigator for Janssen, an expert witness for Johnson & Johnson, and a consultant to Roivant. During the past 3 years, Dr. Reiffel has served as an investigator and consultant for Medtronic, Janssen, Gilead, and Sanofi; a consultant for Portola, Acesion, and InCardia Therapeutics; and a member of the speaker's bureau for Janssen and Boehringer Ingelheim. For this specific manuscript, Dr. Reiffel believes he has no conflict of interest.

Dr. Reiffel is the sole author of this paper, and therefore is responsible for the content and the preparation of the manuscript.

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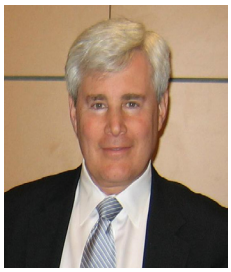

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