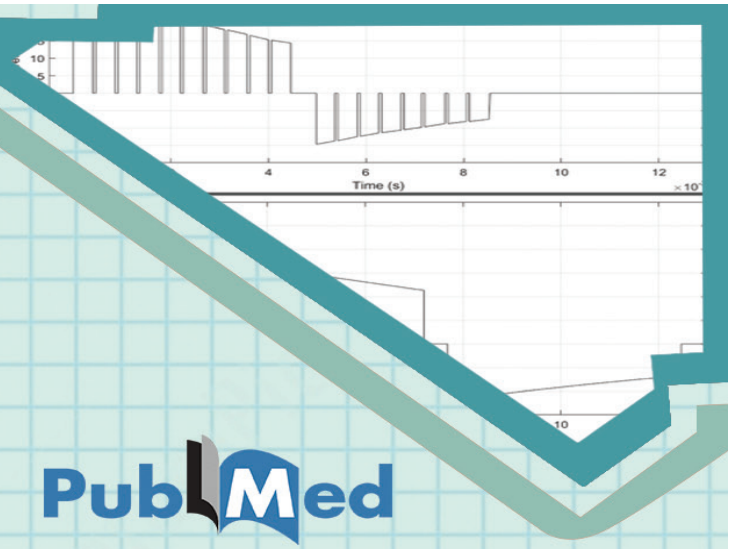
Oct - Nov 2019
Volume 12 - Issue 3



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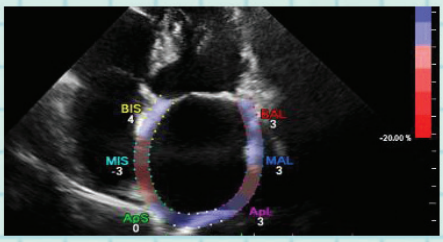
- Cardioversion of atrial fibrillation and flutter Comparative study of pulsed vs. low energy biphasic truncated exponential waveforms.
- The Choice of Antithrombotic Therapy in a Patient with New-Onset Atrial Fibrillation and High Coronary Thrombotic risk.
- Transient Left Atrial Appendage Inversion During Transcatheter Closure Device Placement Short Title LAA Inversion during Closure.
- Standardized Quantification of Vagal Denervation by Extracardiac Vagal Stimulation during Second Generation Cryoballoon ablation a Vein per Vein Analysis.
- Complete AV Block Induced by Right Coronary Artery Spasm Following Radiofrequency Ablation for Atrial Fibrillation.



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Contents

Oct - Nov 2019
Volume 12, Issue 3

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Happy Holidays !!

Journal of Atrial Fibrillation (JAFIB)

Oct - Nov 2019

Issue 3

Volume 12

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

Dear Colleagues

We thank you for your continued interest and patronage of the Journal of Atrial Fibrillation. Hope you had an amazing Holiday season. With 2019 coming to an end, it is important to reflect on some amazing science that has been generated in the field of electrophysiology especially Atrial fibrillation. In this issue of the Journal, we have several exciting articles ranging from atrial fibrosis and left atrial appendage leak closure. As always, we strive to bring high quality educational material to you. We encourage you to consider JAFIB to publish your work. If you are interested in contributing some high value review articles we will be happy to feature them in the upcoming issues of the journal.

We wish you a Happy and Prosperous New Year.

DJ Lakkireddy

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Standardized Quantification of Vagal Denervation by Extracardiac Vagal Stimulation During Second Generation Cryoballoon Ablation: a Vein per Vein Analysis

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Abstract

Aims: The purpose of this study was to evaluate the contribution in the acute loss in vagal innervation after ablation with the second generation cryoballoon (CB-A) in each distinct pulmonary vein (PV) by means of external cardiac vagal stimulation (ECVS) by positioning a catheter in the internal jugular vein in a cohort of 60 patients.

Methods: Sixty patients, 50 starting from the left superior pulmonary vein (LSPV) and 10 from the right superior pulmonary vein (RIPV) with symptomatic paroxysmal atrial fibrillation (PAF), having undergone ECVS before the first and after each PV ablation by means of CB-A ablation, were included.

Results: The ECVS performed pre-ablation provoked cardioinhibitory responses in all cases with mean pause duration of 10251.83 ms ± 2826.23 ms. At the end of the procedure, the vagal reactions (VR) were significantly diminished. Specifically, compared against the initial pause, responses were 8957.06 ± 2711.66 ms ($p < 0.01$) after left superior PV, 10017.36 ± 9127.0 ms ($p = 0.88$) after left inferior PV, 6020.16 ± 3780.709 ms ($p < 0.001$) after right inferior PV and 1687.5 ± 2183.7 ms ($p < 0.001$) after right superior PV. Noteworthy, if starting with ablation in the RSPV, VR was immediately reduced by 90.34%, 990.7 ± 379.78 ms ($p < 0.001$) as compared to baseline response.

Conclusions: Although not directly targeting the ganglion plexuses, AF ablation with the CB-A causes a significant acute loss in parasympathetic innervation. The RSPV showed to be associated with the most significant reduction of acute loss in parasympathetic innervation.

Introduction

The cardiac autonomic nervous system (CANS) might play a critical role in the onset and maintenance of atrial fibrillation [1, 2].Pulmonary vein isolation (PVI) has become the most popular invasive method in the treatment of paroxysmal atrial fibrillation (AF) after the discovery of triggers in the pulmonary veins [3]. According to the literature, modification of CANS activity might be an important and apparently desired collateral effect in the setting of PVI. In fact, the appearance of vagal responses (VR) during PVI might produce better long term outcomes [4–7]. Nevertheless, a detailed analysis of the direct effect of the parasympathetic innervation after ablation in each PVI is still unknown. With this goal in mind, we sought to evaluate the potential contribution of each PV in acute loss of vagal innervation during cryoballoon ablation by using external cardiac vagal stimulation (ECVS) in 60 patients.

Key Words

Vagal Stimulation, Cardiac Autonomic Nervous System, Ganglionated Plexi, Atrial Fibrillation, Pulmonary Vein Isolation, Second-Generation Cryoballoon.

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Methods

Patient population

Sixty consecutive patients who suffered from drug-refractory symptomatic paroxysmal atrial fibrillation (PAF) underwent PVI by means of second-generation CB. After isolation of each PV, a systematic evaluation was conducted to evaluate their potential contribution of loss in vagal innervation by using ECVS, retrospectively. The exclusion criteria were any contraindications for the procedure, including the presence of an intracavitary thrombus, uncontrolled heart failure, contraindications to general anaesthesia and prior AF ablation. All patients signed informed consent for the procedure. The ethical committee of our institution approved the study. The protocol was carried out in accordance with the ethical principles for medical research involving human subjects established by the Declaration of Helsinki, protecting the privacy of all participants as well as the confidentiality of their personal information.

Preprocedural management

A transthoracic echocardiogram was performed within 1 week prior to ablation enabling assessment of structural heart disease. To exclude the presence of thrombi, trans-oesophageal echocardiography

was performed the day before the procedure. All patients underwent a pre-procedural computed tomography scan to assess detailed left atrial (LA) and PV anatomy. All antiarrhythmic drugs (AAD) were discontinued at least 3 days before ablation, apart from amiodarone that was stopped 1 month before. Procedures were performed under general anesthesia and atropine was prescribed.

Procedure

The heart rate, blood pressure, oximetry, plethysmography, patient and room temperature, capnography and respiratory gases were monitored continuously throughout the procedure. If patients were in AF at the beginning of the procedure, an external cardioversion was executed to restore sinus rhythm. Then through the right femoral vein, a quadripolar catheter was advanced to the right internal jugular vein in the region of the jugular foramen, being directed medially, to perform ECVS.Once correct position was achieved, a direct current stimulation with square wave pulses of 50 microseconds in duration at a frequency of 50 Hz, and amplitude (adapted according to patient characteristics, 0.5 to 1 V/kg limited to 70 V) between 50 to 70 V was delivered through a conventional catheter in order to observe the patient basal VR. Short stimulations and minor modifications were performed to look for the optimal position corresponding to the highest response of sudden cardioinhibition. After having identified the ideal stimulating position, 5 s of stimulation was delivered.The catheter was held in this position for vagal stimulation during all the procedure. Immediately after achieving isolation in each PV, ECVS was repetated. All ECVS responses were recorded as was the duration and type of vagal response induced in each following stimulation. Then, through a single transseptal puncture, an inner-lumen mapping catheter (Achieve®, Medtronic©) was advanced to each PV ostium through a steerable 15 Fr sheath (FlexCath Advance®, Medtronic©, Minneapolis, MN, USA). Baseline electrical information was gathered in each PV ostium. A 28-mm Cryoballoon Advance (CB-A) (Arctic Front AdvanceTM, Medtronic©) was advanced, inflated, and positioned at each PV ostium. Optimal vessel occlusion was defined by selective contrast injection showing total contrast retention with no backflow into the left atrium. The ablation sequence in the first 50 patient was treating the left superior PV (LSPV) first, followed by the left inferior PV (LIPV), right inferior PV (RIPV), and right superior PV (RSPV). In the last 10 patients, the sequence was RSPV, RIPV, LIPV, and LSPV. Once vessel occlusion was deemed satisfactory, delivery of cryoenergy to allow freezing was commenced. Standard cryothermal applications lasted 180 s. Our target temperature was −40 °C within the first 60 s. If the temperature did not attain this value, an extra freeze was delivered. Successful PVI was defined as an absence of all PV potentials or their dissociation from an atrial activity. During the entire procedure, activated clotting time was maintained over 250 s by supplementing heparin infusion as required.

Phrenic nerve monitoring

Prior to ablation of the right-sided PVs, a standard decapolar catheter was placed in the superior vena cava cranial to the RSPV, or in the right subclavian vein in order to pace the right phrenic nerve during ablation. Phrenic nerve pacing started once the temperature reached −20 °C in order to avoid balloon dislodgement due to diaphragmatic contraction in the first phase of cryoenergy application. Pacing was continued throughout the entire duration of cryoenergy delivery. In cases of phrenic nerve palsy, the freeze was immediately aborted with a "double stop" technique and recovery was observed. If recovery wasn't achieved in 15 minutes, the procedure was aborted and phrenic nerve was tested in the next day with "sniff test".

Post-procedural management

After completion of the procedure, the patients were continuously monitored via telemetry for at least 18 hours. Before discharge, a transthoracic echocardiogram was performed in all patients in order to exclude post-procedural complications. Patients were discharged on the following day and were instructed to continue AAD and anticoagulation therapy for at least 3 months.

Statistical analysis

Categorical variables are expressed as absolute and relative frequencies. Continuous variables were assessed for parametric distribution using Kolmogorov-Smirnov test. Continuous variables with parametric distribution were reported as mean ± standard deviation. Continuous variables with non-parametric distribution and discrete variables were reported as median and interquartile range. Correlations were assessed using Pearson's or Spearman's test, accordingly. Differences among all VR groups, including initial response and following each PV ablation, were assessed by repeated measures one-way ANOVA if all distributions were found parametric or Friedman's test if at least one distribution was found non-parametric. Differences between initial VR and VR after each PV ablation were assessed by paired Student's t test if distributions were found parametric or Wilcoxon matched-pairs test if at least one distribution was found non-parametric. A two-tailed p value of less than 0.05 was considered significant. All statistical analyses were performed with IBM SPSS Statistics for Windows, Version 24.0. (SPSS Inc., Chicago, IL, USA).

Results

Baseline characteristics

Patients were included from the 12th of March 2018 to the 7th of May 2018. No patient was excluded based on anatomical findings. Baseline clinical characteristics are shown in [Table 1]

Procedural characteristics

In all cases, all PVs were successfully isolated with the CB-A solely. The total procedural and fluoroscopy times were 73.8± 15.74 min and 21.01± 7.92 minutes, respectively.

Vagal Reactions Following Ablation in DistinctPulmonary Vein

The meanprobationn pause duration was 10251.83 ms ± 2826.23 m. External cardiac vagalstimulation wass performed following each pulmonary vein ablation. In the first 50 patients after ablation in the LSPV, the mean pause was 8957.06 ± 2711.66 ms ($p = 0.001$). After ablation of the LIPV, RIPV and RSPV, the mean pause was 10017.36 ± 9127.0 ms ($p = 0.88$), 6020.16 ± 3780.709 ms ($p < 0.001$) and 1687.5±2183.7 ms ($p < 0.001$) respectively. The duration of

the pause in response to ECVS significantly differed with respect to baseline after ablation in the LSPV -1367.553 ±2564.9 ms (p = 0.001), LIPV -214.222 ±9729.510 (p = 0.88), RIPV -4196.735 ±3725.82 ms (p < 0.001) and RSPV -8443.12 ±3656.0 ms(p < 0.001). Additionally, significant differences in pause duration were seen if comparing responses between LSPV and baseline -1367.55±2564.90 ms (p = 0.001), between LIPV and LSPV 1249.12 ±10209.55 (p = 0.42), between RIPV and LIPV-3922.67 ±10084.19 ms (p = 0.01) and between RSPV and RIPV -4312.29 ±4118.39 ms (p < 0.001).

Noteworthy, after the ablation of the RSPV, we noticed a significant reduction of vagal response to ECVS if compared to all other veins [Figure 1]. In order to confirm the hypothesis that the RSPV was responsible for an important acute VR reduction, due to the vicinity with the right superior ganglionated plexi and right inferior ganglionated plexi, in the last 10 patients the ablation procedure started in the RSPV. Interestingly, if starting with ablation in the RSPV, VR was reduced by 90.34%, 990.7 ± 379.78 ms (p < 0.001) if compared to baseline response.

Table 1: Baseline characteristics of the study population (n = 60)

	N=60
Age (years)	59.37 +/- 8.57
Male gender (%)	36 (60)
Hypertension (%)	29 (48)
Diabetes mellitus (%)	12 (20)
Heart failure (%)	4 (6)
Coronary artery disease (%)	9 (15)
LVEF (%)	57.43 ± 5.15
LA diameter (mm)	44.08 ± 4.85

LA = left atrium; LVEF = left ventricular ejection fraction.

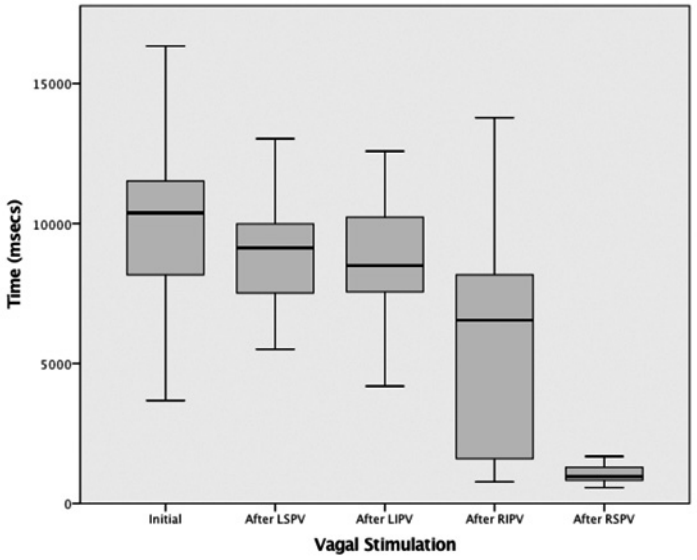

Figure 1: Vagal response to extracardiac vagal stimulation at the beginning and after each pulmonary vein ablation in the first 50 patients.

We did not detect predictors of higher response to ECVS, both in the baseline clinical characteristics of the patient population, as age or sex (P = n.s.), nor in any procedural parameter.

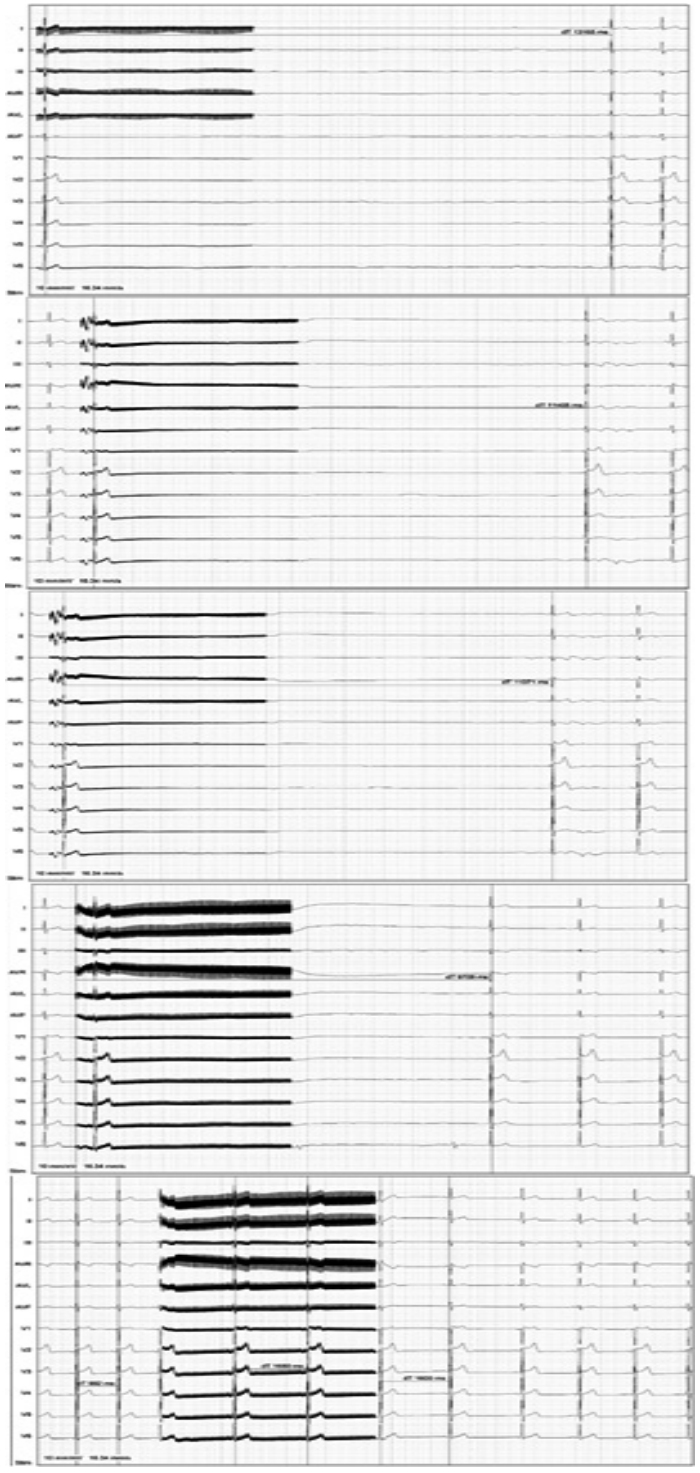

Figure 2: Initial vagal response to the extracardiac vagal stimulation before ablation and after each pulmonary vein ablation starting from the LSPV, LIPV, RIPV and RSPV. The interesting here is the gradual decrees of the sinus suppression to the extracardiac vagal stimulation.

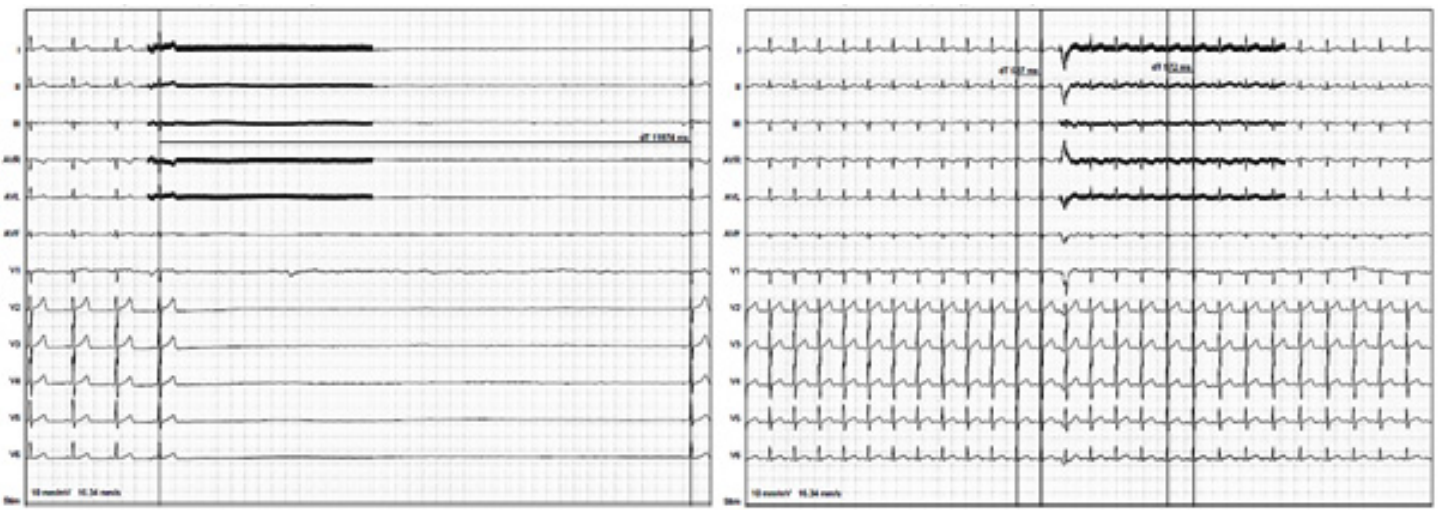

Figure 3: A vagal reaction to the extracardiac vagal stimulation before ablation (left ECG) and after solely the ablation of the right superior pulmonary vein (right ECG), the vagal response is almost abolished.

Complications

Transient phrenic nerve palsy was observed in 2 patients (3.3%) phrenic nerve function recovered in both patients before the end of the procedure.

Discussion

The ganglionated plexi, as well as the PV ostia, are richly innervated by both the sympathetic and parasympathetic autonomic systems [1, 8]. As described by Tolga et al, there is still no consensus among the authors on the anatomical location and number of the GPs.[9] A recent publication by our group showed that surprisingly the CB-ablation can modify acutely the parasympathetic tone during PVI. [10] Although ablation was performed only in the left atrium and not bi-atrial as reported by Pachon et al. [11] and Tolga et al. [12], in our case series acute modification of parasympathetic innervation was obtained in all patients. This might be explained by the extensive antral ablation created by the second generation cryoballoon, but this should not be accepted as a usual response. Because, in PVs with larger ostium, CB application will not cause atrial ablation effect.

It has been shown that following CB application, large portion of the left atrium is ablated [13, 14].This extensive ablation in the LA and the modulation of the GPs might importantly contribute to the success of the CB-A, since the elimination or decrease of the VR might suggest an acute transmural lesion. Therefore, in order to improve outcomes in patients with AF, ablation of the GP has been proposed as an adjunctive complementary method to conventional PVI [15, 16].

Anatomically, the cardiac nervous system can be subdivided into Extrinsic Cardiac Nervous System (ECNS), which contains fibers that mediate connections between the heart to the brain and spinal cord and the Intrinsic Cardiac Nervous System (ICNS), composed primarily by autonomic nervous fibers, which is an interconnected neural system consisting of epicardial ganglionated plexi and an extensive network of atrial intramural microganglia.[17]

During ablation, parasympathetic, sympathetic and the sensory fibers destroyed. The critical difference between them is that the parasympathetic postganglionic neuronal cells are found in the GPs [18] and in the cardiac wall [19]. Therefore, axons are short in length, and the ablation of these structures makes the parasympathetic reinnervation less probable, as the neuron body is eliminated [20]. This might enable long-term modulation of these ganglia from the endocardial surface [21].

On the other hand, the sensory and sympathetic postganglionic cells are far from the heart and are preserved whereas the sympathetic and sensory fibers eliminated by ablation have the capacity of recovery similar to that observed in post-transplantation patients [22].

A stepwise ECVS following ablation of each PV in the first 50 patients led to a producible reduction in VR [Figure 2].

Importantly, ablation in the RSPV produced the most impressive inhibitory responses to ECVS resulting in the vein producing the most marked loss of parasympathetic innervation. This might be explained by the proximity of 2 major GPs to the ostium of the RSPV and LA, the right superior ganglionated plexi and right inferior ganglionated plexi. The same region has the richest nerve density in comparison to the other PV-LA connection [23]. The CB-A wide antral ablation around this specific vein might largely include both GPs in the lesions' extension.

This observation is in accordance with finding of a previous study. In the latter, the authors compared the occurrence of spontaneous VR between 2 different strategies during CB-A procedure. The first consisted in starting ablation of left sided veins and successively approaching the septal PVs. In the second strategy, the operator

approached the RSPV as first. Interestingly, if left sided veins were ablated first, spontaneous VR could be observed in 35.9 % patients. Conversely, only 1 patient out 42 experienced a VR in the other group. Of note, in this patient, ablation was stopped after 60 seconds due to right phrenic nerve injury [5].

The main difference between our study and the above mentioned paper by Myazaki and colleagues is that in our procedural protocol, VR reactions were voluntarily provoked by ECVS and therefore could be quantified in a standardized fashion.

The left lower GP is usually less richly innervated by parasympathetic fibers. In addition, if analysing anatomical findings, it is the farthest from the venous ostia of all. It usually is found at the inferior portion of the posterior wall of the left atrium, or>2cm away from the LIPV ostium [7, 8, 23]. These observations might explain the absence of significant changes after the ablation in the LIPV since the lesion might only partially reach the GP or not affect it at all [13].

Limitations

In this study, we solely stimulated the right vagal nerve causing sinus node suppression. Although both vagal nerves act on both the sinus node and the AV node, stimulation of the left vagal nerve produces a higher response on the AV node, whereas the stimulation on the right side produces a higher response on the sinus node. This study was conducted on a limited cohort of patients. Future studies enrolling larger patient populations are warranted in order to confirm our findings.

Acknowledgements

CdA receives compensation for teaching purposes and proctoring from AF solutions, Medtronic, Abbott, Biotronik, Atricure and research grants on behalf of the center from Biotronik, Medtronic, St Jude Medical Abbot, Livanova, Boston Scientific Biosense Webster. GBC receives compensation for teaching purposes and proctoring from AF solutions Medtronic and Biotronik.Pedro Brugada receives and speakers fees from Biotronik, Medtronic.

Conclusion

Although not directly targeting the ganglion plexuses, AF ablation with the second-generation CB causes a significant acute loss in parasympathetic innervation. The RSPV showed to be associated to the most significant reduction of acute loss of parasympathetic innervation.

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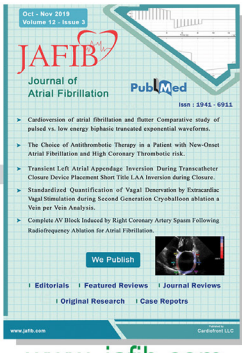

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Intensity and Distribution of Patchy Late Gadolinium Enhancement in Left Atrium in Patients With Atrial Fibrillation

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Abstract

Purpose: Late gadolinium enhancement (LGE) cardiac magnetic resonance imaging (MRI) studies were performed on healthy individuals to establish signal intensity thresholds for reproducible left atrial (LA) patchy LGE detection. Using established criteria, differences in LA patchy LGE between healthy volunteers (HV) and patients with atrial fibrillation (AF) or hypertension were analyzed.

Methods: Fifty-three patents with AF (mean age 56 years, 60% men), 25 patients with hypertension and no history of AF (mean age 54 years, 40% men), and 28 HV (mean age 50 years, 52% men) were enrolled in an observational, non-interventional, case-control prospective study. LA patchy LGE quantification was performed using LGE MRI (1.5 T scanner, voxel size 1.25x1.25x2.5 mm) and the custom-built software based on estimation of LA voxel image intensity ratio and comparison with threshold value obtained from HV data.

Results: Based on analysis of healthy individuals' data, the optimal threshold value for the left atrial patchy LGE quantification was determined at 1.38. Patients with AF had a higher extent of LA patchy LGE (9.1 [1.72; 18.58] %) than patients with hypertension (3.81 [0.57; 9.51] %) and HV (0.78 [0.05; 3.5] %). The predominant location of LA patchy LGE in AF was in the pulmonary vein ostia region, in hypertension – LA posterior wall, and in HV – lower part of LA posterior wall. In AF patients, the extent of LA patchy LGE correlated with LA end-diastolic volume (r=0.37) and LA ejection fraction (r=-0.4), in HV – with age (r=0.66) and LA end-diastolic volume (r=0.4).

Conclusions: AF and hypertension are associated with higher extent and different location of LA patchy LGE compared to changes caused by natural aging. The extent of LA patchy enhancement correlates with LA dilatation.

Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia in the general population [1]. Data from animal and human studies demonstrated that excessive myocardial fibrosis in the left atrium (LA) [2-4] can exacerbate electrical inhomogeneity of the myocardium and contribute to the progression of AF [5,6]. Due to an important clinical role of LA structural changes in AF, a robust noninvasive method for their assessment is needed for better comprehension and treatment of AF [6].

Late gadolinium enhancement (LGE) magnetic resonance imaging (MRI) identifies pathological changes in myocardium associated with cardiomyocyte necrosis and edema, scarring or fibrosis [7]. Recently, the ability of high resolution LGE MRI to quantify fibrotic changes in thin LA myocardium as patchy enhancement has been demonstrated [8,9]. Previous studies have revealed 10-40% incidence of LA patchy LGE/fibrosis in patients with AF and investigated its potential diagnostic and prognostic usefulness for interventional treatment of AF [10-12].

Because of the complex anatomy and histology of LA, the fibrosis quantification techniques based on LGE MRI threshold determination vary, and a preferable approach has not yet been established [9,13,14]. This insufficiency may be due to very limited data availability regarding the validation of LGE MRI findings at histopathological level [13-15]. This limitation sets a complex problem of establishing a type of "reference myocardium" for LA fibrosis quantification using LGE MRI.

The main hypothesis of the study was that HV, especially young, have minor changes in LA and their imaging results can be used as a ground-truth for LA patchy LGE quantification. It was also hypothesized that patients with cardiovascular disease with and without AF may have differences in the amount and distribution

Key Words

Left atrium, Structural remodeling, Atrial fibrillation, Hypertension, Aging, Hypertension, Late gadolinium magnetic resonance imaging.

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of LA patchy LGE. In the current study, the signal intensity (SI) characteristics of LGE in LA and patchy LGE myocardium were assessed quantitatively in HV, patients with AF, and patients with hypertension and with no history of AF.

Methods

Study design

This was an observational, non-interventional, case-control prospective study and its protocol was approved by the local ethics committee in compliance with Declaration of Helsinki. All patients gave written informed consent. The study was conducted during 2016-2017 at the National Medical Research Center of Cardiology of the Ministry of Healthcare of the Russian Federation.

To be included in the study patients must have been diagnosed with AF documented by electrocardiogram (ECG) and have sinus rhythm at the time of inclusion in the study. AF was categorized as either paroxysmal (lasts less than 7 days) or persistent (lasts more than 7 days and converted to sinus rhythm). In patients who had no hypertension as well as no signs of cardiovascular disease or other disease included in the list of exclusion criteria, AF was stratified as "lone AF". Patients with previously diagnosed hypertension (three blood pressure measurements ≥ 140/90mmHg on three different days in a 3-month period, or 1 measurement of ≥ 180/110mmHg) and without history of arrhythmia were also enrolled in the study.

Patients were excluded from the study cohort if they had claustrophobia, pregnancy, clinical instability, metallic implants, implanted pacemakers or defibrillators, rheumatic heart disease, acute and chronic inflammatory diseases, diabetes, heart failure, ischemic heart disease, cardiomyopathies, valvular and congenital heart disease, chronic kidney and hepatic diseases, and hyperthyroidism.

Sixty patients with AF and 30 patents with hypertension and no history of AF underwent clinical examination by cardiologist and met criteria for inclusion in the study. The examination included blood count test, biochemical blood test, thyroid stimulating hormone test, urine analysis, 12-ECG, echocardiography, 24-hour ECG monitoring, stress-testing, coronary angiography, if indicated, and cardiac MRI including LGE MRI. Because of inferior quality of LGE images, seven patients with AF and five patients with hypertension were later excluded from the study.

Twenty eight HV (HV group) (11 women, 17 men), who were not known to suffer from any significant illnesses relevant to the proposed study, whose body composition measurements, such as weight, were within normal ranges and whose mental state was such that they were able to understand and give valid consent to the study, were also enrolled in the study. All HV gave an informed consent and underwent the same examination and MRI protocol as patients in other groups.

Cardiac magnetic resonance protocol

Cardiac MR was performed on a 1.5-Tesla scanner (Magnetom Avanto, Siemens Medical Solutions, Germany) using a five-channel phased-array surface coil. Preliminary, patients with persistent AF were converted to sinus rhythm. Cine-MRI was performed using standard steady state free precession (SSFP) sequences in short breath-hold. Image acquisition was performed in four- and two-chamber view and a stack of short-axis slices was obtained to cover the whole LV and LA. The scan parameters were as follows: repetition time (TR) = 3.4 ms, echo time (TE) = 1.5 ms, flip angle = 73°, slice thickness = 6 mm, maximum field of view (FOV) = 400 mm, matrix 256×256 mm.

LGE MRI was performed 15-20 min after contrast agent intravenous injection (gadoversetamide (OptiMark, Libel-Flarsheim Company, USA), at a dose of 0.15 mmol per kg of body weight). For image acquisition, 3D IR GRE MR-pulse sequence with isotropic voxel and fat saturation was used. Imaging protocol was described earlier by Oakes et al. [9]. The parameters for image acquisition were: TR = 610-1100 ms, TE = 2.44 ms, flip angle = 22°, slice thickness = 2.5 mm, maximum field of view (FOV) = 400 mm with voxel size of 1.25×1.25×2.5 mm (reconstructed to 0.625×0.625×2.5 mm), inversion time (TI) of 270 to 380 ms and parallel imaging with GRAPPA technique with R 2. Study was performed during free breathing using breath synchronization. ECG-gating was used for image acquisition during LA diastole phase. Acquisition time of LGE MRI was from 5 to 15 minutes. All subjects tolerated the study well.

Cine-MRI analysis

LA volumes and ejection fraction (EF) were determined from 2-chamber view across the LA short axis cine-MRI images using Circle/cvi42 (2013 Circle Cardiovascular Imaging Inc.). An experienced operator manually defined endocardial contours of LA excluding the LA appendage. Phase systole and phase diastole were marked manually. Based on these data the software calculated LA end-diastolic volume (EDV), end-systolic volume (ESV) and ejection fraction (EF).

LGE image analysis

Only validated images were considered for further quantitative analysis. Validation of successful high resolution LGE images was the following: feasible visualization of heart chambers and vessels, esophagus, absence of blurring, absence/minimal artifacts, correct fat suppression, correct TI, high SI of aorta or mitral valve [Figure 1 A, B].

LGE MRI image analysis included LA myocardium semiautomatic segmentation, characterization of LA myocardium SI, and LA patchy LGE quantification. LA myocardium segmentation was performed by a specially trained operator using ImageJ 1.46r (NIH, USA). LA endocardial border was defined manually. LA epicardial border was reconstructed automatically parallel to endocardial border based on specified individual LA wall thickness (1.5-3 mm). In order to reflect the individual anatomy of LA wall epicardial border was corrected manually. Regions of mitral annulus, descending aorta, esophagus and artifacts were thoroughly excluded from the segmentation [Figure 1 F-H]. The blood pool located in the LA cavity was segmented as a region surrounded by the LA endocardial border [Figure 1B]. Additional specially trained operator verified and corrected the

obtained LA borders (Supplement).

The evaluation of LA wall SI comprised automatic estimation of the histogram representing the SI of the entire LA wall myocardium voxels [Figure 1B]. The typical shape of the histogram curve was close to Gaussian curve. Thus, mean LA SI and maximum LA SI was estimated on the histogram using Gaussian tools. The histogram of blood voxel SI was reconstructed automatically, and mean blood SI was estimated automatically.

To overcome disadvantages of manual operator-based calculations of the extent of LA patchy LGE, a LGE Heart Analyzer software package was developed and written in MATLAB (Mathworks Inc., USA). This software requires the layers of both segmented LA myocardium and blood to be uploaded in DICOM format. Then it automatically estimates voxel intensity histogram, MIR and voxels with IIR above a manually set threshold value and calculates the extent of LA patchy LGE. Using CardioViz 3D v. 1.4.0 platform (Asclepios Research Project, Inria Sophia Antipoli) LGE Heart Analyzer also reconstructs a three-dimensional model of LA with mapped patchy LGE.

Statistical analysis

Continuous data are expressed as median (25th percentile – 75th percentile), and categorical variables are presented as absolute numbers (percentage). For intergroup comparison, a Mann-Whitney rank sum test and/or Kruskal-Wallis test followed by Dunn's test were used. The associations of LA patchy LGE with quantitative indicators were assessed using Spearman correlation. By Bland-Altman plots, inter- and intra-observer agreements in LA segmentation were represented as mean difference and corresponding 95% confidence interval (1.96 SD). Receiver operating characteristic (ROC) analysis was performed to differentiate between HV and patients with AF based on quantitative assessment of LGE in LA (MIR values) by calculating areas under the curve (AUC) and optimal cutoff values from the ROC curves, using the Youden index. The DeLong method was used to compare different AUCs. For all tests, the significance level was set to $p \leq 0.05$. All statistical analyses were conducted using SigmaPlot v.10 (Systat Software Inc.).

Results

A total of 78 patients and 28 HV were enrolled the observational, non-interventional, case-control prospective study. 53 patients (21 women, 32 men) had AF and 25 patients had hypertension (15 women, 20 men) without a history of arrhythmias. Their baseline characteristics are presented in [Table 1].

AF was accompanied by hypertension in 25 patients. The other 28 patients had "lone AF". Forty-five AF patients received antiarrhythmic drugs, and 28 oral anticoagulants if indicated according to individual CHA2DS2Vasc score. Patients who had hypertension (45) took effective antihypertensive medications for at least 6 months and achieved 0 grade of hypertension.

The were no significant differences between the groups in age, gender, smoking, left ventricle ejection fraction and indexed mass.

Table 1: Baseline characteristics of patients and healthy volunteers

	Atrial fibrillation n=53		Hypertension n=25	Healthy volunteers n=28	Kruskal-Wallis test (p)
	AF_{lone} n=28	$AF_{+hypertension}$ n=25			
Age, years	52 [41; 57]	57 [51; 62]			0.053
	56 [44.5; 60.5]		54 [50.5; 56]	48 [34; 53.5]	0.07
Men, n (%)	32 (60.4)		10 (40)	17 (60,7)	0.1
	18 (64.3)	13 (52)			0.055
Women, n (%)	21 (39.6)		15 (60)	11 (39,3)	0.1
	10 (35.7)	12 (48)			0.09
Smoking, n (%)	12 (22.6)		5 (25)	11 (39,3)	0.06
Body mass index, (kg/m²)	28 [25.6; 32.3]		28.9 [25; 31,9]	24.5 [22,3; 26]	0.01
Left ventricle ejection fraction, %	61.3 [58.4; 76.4]		62.8 [60; 73.1]	60.5 [60.3; 78.1]	0.8
Left ventricle indexed mass, g/m²	58.3 [48; 66.2]		61 [52.3; 66.7]	58 [51.6; 65.9]	0.4
Hypertension					
- grade 1, n (%)	-	1 (4)	2 (8)	-	0.06
- grade 2, n (%)	-	10 (40)	10 (40)	-	0.2
- grade 3, n (%)	-	14 (56)	13 (52)	-	0.06

AF – Atrial fibrillation

Table 2: Values of maximum intensity ratio in study groups

	HV	AF	P (vs HV)	Hypertension	P (vs HV)
MIR 2 SD	1.43 [1.24; 1.59]	1.69 [1.5; 1.92]	<0.001	1.54 [1.47; 1.89]	<0.001
MIR 3 SD	1.63 [1.5; 1.74]	1.93 [1.71; 2.24]	<0.001	1.85 [1.68; 2.12]	0.003
MIR 4 SD	1.87 [1.65; 2.08]	2.17 [1.93; 2.54]	<0.001	2.07 [1.83; 2.23]	0.02

AF - atrial fibrillation, HV - healthy volunteers, MIR - maximum intensity ratio, SD – standard deviation

Group of healthy volunteers had significantly lower body mass index.

Introduction of maximum intensity ratio indicator

Quantitative characterization of LGE in LA myocardium was performed based on image intensity ratio indicator (IIR was calculated for each voxel of LA wall as myocardial voxel SI divided by blood SI) [16]. Maximum intensity ratio (MIR) indicator was introduced in order to quantitatively assess the SI of the most enhanced regions in LA wall that represent a patchy LGE. MIR was calculated using Gaussian tools as maximum LA wall SI (at 2 standard deviations (SD), 3 SD and 4 SD) divided by mean blood SI [Figure 2].

The values of MIR at 2 SD, 3 SD and 4 SD were significantly lower in HV than in AF or hypertension without AF groups [Table 2].

Table 3: Age-related differences in left atrium in healthy volunteers

	HV, age < 40 n=11	HV, age >40 n=17	P (vs HV age < 40)
Left atrial end-diastolic volume, ml	45 [37; 46]	70 [50; 80]	0.04*
Left atrial indexed volume, ml/m²	30.5 [19.1; 30.5]	37 [29.6; 41.8]	0.05*
MIR 2 SD	1.22 [1.2; 1.28]	1.45 [1.4; 1.6]	0.01*
MIR 3 SD	1.39 [1.35; 1.54]	1.66 [1.58; 1.75]	0.013*
MIR 4 SD	1.55 [1.5; 1.71]	1.88 [1.82; 2.13]	0.05*

HV – healthy volunteers, MIR - maximum intensity ratio, SD – standard deviation
*Statistically significant difference
The values of MIR indicator also correlated with LA EDV (r=0.5, r=0.4, r=0.45, 2 SD, 3 SD and 4 SD, respectively).

Age-related differences in the intensity of LGE of the left atrial myocardium in healthy volunteers

Positive correlation between the age of HV and MIR indicator values (r=0.66; r=0.54; r=0.6, 2 SD, 3 SD and 4 SD, respectively) was observed in this study. Quantitative analysis of this relationship demonstrated that MIR values among the subgroup of HV over the age of 40 were significantly higher than the same indicators in the subgroup under the age of 40 [Table 3].

Estimation of the threshold for left atrial patchy LGE quantification

In order to assess capability of MIR for distinguishing between HV and patients with AF the ROC-analysis was performed [Figure 3]. It was determined that MIR calculated at 2 SD gives the best differentiation between HV and patients with AF (AUC=0.847)

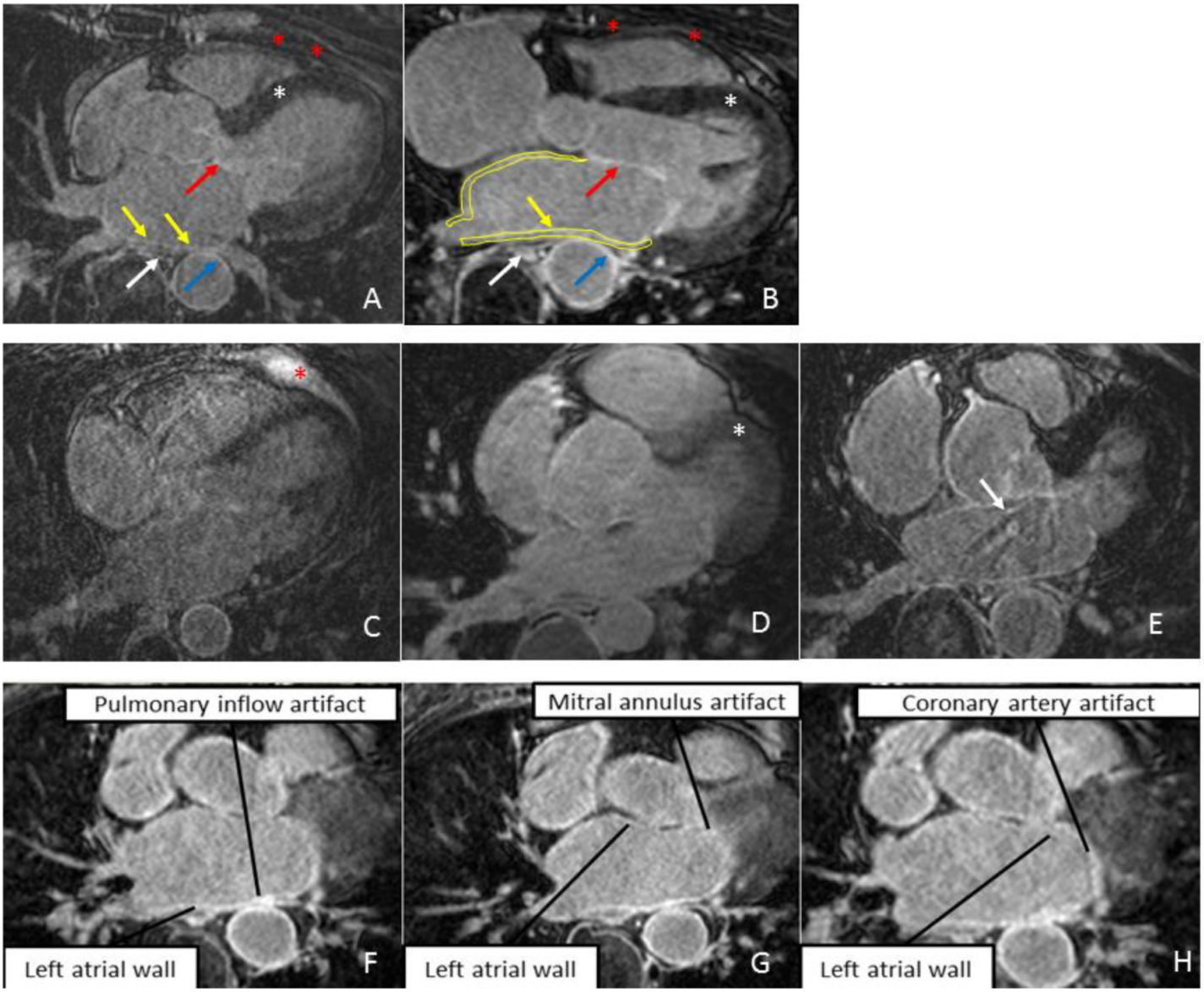


Figure 1: Feasible images of the left atrium (A, B). Left atrial wall (yellow arrows, yellow line); esophagus (white line); late gadolinium enhancement (LGE) in mitral valve (red arrows), in aorta (blue arrows); correct inversion time (white asterisks); correct fat suppression (red asterisks). Common artifacts and structures: image blurring (C, D); unsatisfactory fat suppression (C, red asterisk); navigation artifacts (E, white asterisk), blood flow artifact (F), mitral annulus (G) and coronary artery (H) must be differentiated from left atrial wall.

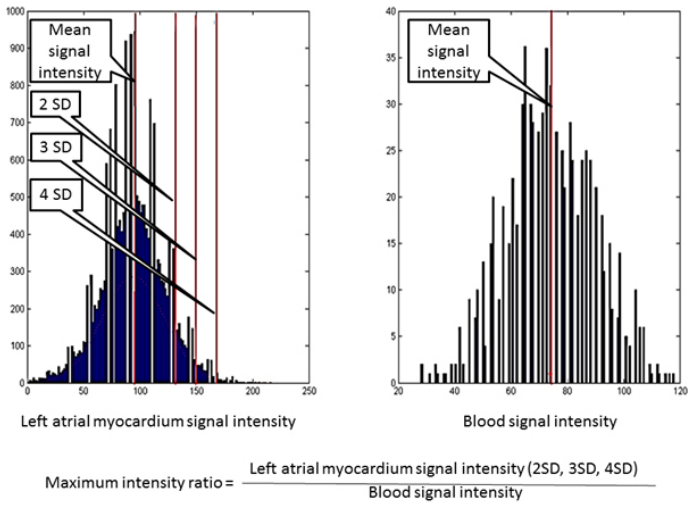


Figure 2: **Quantitative assessment of left atrial and blood signal intensity. Calculation of maximum intensity ratio indicator.**

compared with MIR at 3 SD (AUC 0.824) and 4 SD (0.769). MIR in HV group was considered as ground-truth data for patchy LGE quantification. According to Youden index the threshold value for LA patchy LGE was determined as 1.6 (sensitivity 66%, specificity 91%).

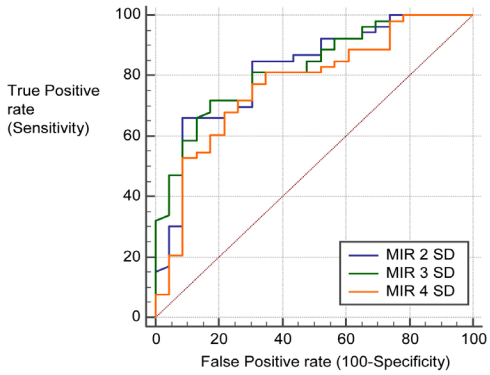
In order to increase the sensitivity of MIR indicator-based threshold ROC-analysis was performed for the subgroup of HV under the age of 40 (n=11) and patients with AF [Figure 4].

According to ROC-analysis the criterion value 1.38 (sensitivity 94%, specificity 98%) corresponding with Youden index was applied as a threshold parameter for LA patchy LGE quantification [Figure 5]. Voxels with IIR exceeding the threshold value were considered as pathologically enhanced, i.e. represented patchy LGE. The extent of LA patchy LGE was expressed as a number of voxels identified as enhanced over the total number of voxels within the endocardial and epicardial boundaries. LA patchy LGE quantification was performed automatically with manually set threshold using LGE Heart Analyzer software package.

Left atrial patchy LGE extent in patients with atrial fibrillation, hypertension and in healthy volunteers

LA patchy LGE was detected in 35.7% of HV (10 cases) [Table 4]. All of these study subjects were over the age of 40. The average extent of LA patchy LGE in this group was 0.78%. The extent of LA patchy LGE in HV correlated with the age (r=0.66) and LA EDV (r=0.4). The highest value of LA patchy LGE among HV (17%) was registered in a 57-year old male with LA EDV 111 ml. No LA patchy enhancement was found in study subjects under the age of 40.

LA patchy LGE was detected in 84.9% of patients with AF (46 cases). The extent of LA patchy LGE in patients with AF was significantly higher than in HV (9.1 [1.72; 18.58] % vs. 0.78 [0.05; 3.5] %, p=0.05, respectively). The highest value of LA patchy LGE (73%) in the AF group was registered in a 64-year old male (LA EDV 75 ml) with frequent paroxysms of AF.



Sample size			81
Positive group			53 (65.4%)
Negative group			28 (34.6%)
Variable	AUC	SE [a]	95% CI [b]
MIR 2 SD	0.847	0.0544	0.711 to 0.896
MIR 3 SD	0.824	0.0490	0.720 to 0.902
MIR 4 SD	0.769	0.0605	0.659 to 0.858

[a] DeLong et al., 1988
[b] Binomial exact

Youden index J for MIR 2 SD curve	0.5734
Associated criterion	>1.612
Sensitivity	66.04
Specificity	91.30

Figure 3: **Receiver Operator Characteristic (ROC) Analysis to differentiate patients with atrial fibrillation from healthy volunteers using maximum intensity ratio indicator. Comparison of differentiation abilities of three ROC-curves of a maximum intensity ratio (MIR) at 2 (blue), 3 (green) and 4 (red) SD performed using area under the curve (AUC) (see table). MIR at 2 SD indicator curve resulted in the highest AUC with 0.847. SD – standard deviation**

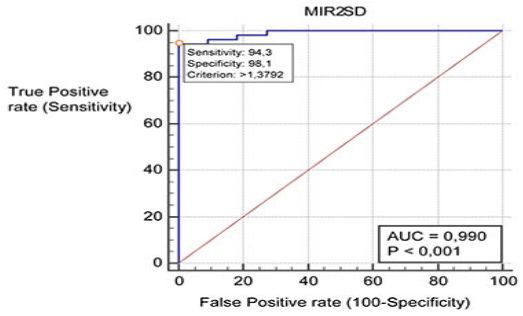
There was no correlation between the type of AF, age, gender, smoking, body mass index and the extent of LA patchy LGE. The extent of patchy LGE in patients with AF correlated with LA EDV (r=0.37) and LA EF (r=-0.4). 25 patients with AF and concomitant hypertension trended toward the higher extent of patchy LGE (9.1 [1.72; 18.58] %) than 28 patients with "lone AF" (4.37 [0.82; 16.03]%).

In the group with hypertension and no history of AF, LA patchy LGE was detected in 72% of patients (18 subjects). The extent of LA patchy LGE in patients with hypertension was intermediate between that of patients from the AF group and HV (3.81 [0.57; 9.51] %). In this group, the highest value of LA patchy LGE (23%) was detected in a 59-year old female (LA EDV 88 ml).

Left atrial patchy LGE location in patients with atrial fibrillation, hypertension, and healthy volunteers

In patients with AF, the predominant location of patchy LGE was in the pulmonary vein region (24 subjects, 52.2%) [Figure 6A, B]. In other cases, patchy LGE was located uniformly in all LA walls [Figure 6 E, F] (15 subjects, 32.6%) or in the LA posterior wall (7 subjects, 11.2%) [Figure 6 C].

In patients with hypertension, patchy LGE was predominately located uniformly in all LA walls (8 subjects, 44.4%) [Figure 6 E, F]. In all other cases patchy LGE was distributed in the pulmonary vein region (5 subjects, 27.7%), in the LA posterior wall (3 subjects,



Sample size	64
Positive group	53 (82.8%)
Negative group	11 (17.2%)
Area under the ROC curve (AUC)	0.990
Standard Error [a]	0.00864
95% Confidence interval [b]	0.925 to 1.000
z statistic	56.674
Significance level P (Area=0.5)	<0.0001

[a] DeLong et al., 1988
[b] Binomial exact

Youden index J	0.9434
Associated criterion	>1.38
Sensitivity	94.34
Specificity	98.10

Figure 4: **Receiver Operator Characteristic (ROC) Analysis to differentiate patients with atrial fibrillation from healthy volunteers at the age under 40 years using maximum intensity ratio indicator (MIR) at 2 SD. MIR at 2 SD indicator curve resulted in AUC 0.990 with the threshold value 1.38 (sensitivity 94%, specificity 98%).**

16.7%), or the in lower part of the LA wall (2 subjects, 11.2%).

In HV mild patchy LGE was located predominately in the lower part of the LA adjacent to the mitral valve (9 subjects, 90%) [Figure 6D] or in the pulmonary vein region (1 subject, 10%).

Discussion

The present study evaluated healthy individuals as a reference cohort for LA patchy LGE quantification and demonstrated the differences in LGE of the LA myocardium between HV, patients with AF, and patients with hypertension and no history of AF.

Since Peters et al. [8] and Oakes et al. [9] independently pioneered successful visualization of the LA myocardium using LGE MRI, various approaches for LA patchy LGE/fibrosis quantification have been proposed and thoroughly reviewed [13,14]. Insufficient data regarding the peculiarities of LA fibrosis in subjects with and without AF limit usefulness of fibrosis quantification and interpretation in routine clinical practice.

Sites of inflammation, interstitial and replacement fibrosis or amyloid deposits typically patchy and non-uniform were elucidated in LA myocardium in association with AF in animal and clinical studies [2-4]. It was hypothesized that these patches can be detected using high resolution LGE MRI. Several studies demonstrated validation of LGE in left ventricle myocardium using myocardial biopsy samples [17]. However, only one study reported validation of LGE in LA myocardium using myocardial biopsy samples in AF [15]. As the present study had no histological validation due to ethical

Table 4: **Mechanical function and quantitative characteristics of late gadolinium enhancement of the left atrium in study groups**

	Atrial fibrillation n=53	AF_{lone} n=28	$AF_{+hypertension}$ n=25	Hypertension n=25	Healthy volunteers n=28
Left atrial end-diastolic volume, ml	79 [65.5; 86.6]*	75 [65.7; 84.3]*	81 [64.7; 87.9]*	71 [54; 88.5]	66.5 [56; 78.5]
Left atrial indexed volume, ml/m²	38.8 [29.5; 43.7]	35.8 [30.5; 44.1]	39.4 [28.4; 42.9]	36.7 [32.4; 44.25]	35.5 [24.6; 38.5]
Left atrial ejection fraction, %	44.5 [34.5, 54.5]*	42 [36.7; 52.2]*	45 [35.6; 50.9]*	54.5 [47.5, 58.5]	56.1 [49; 63.2]
MIR 2 SD	1.69 [1.5; 1.92]*	1.62 [1.3; 1.81]*	2.08 [1.98; 2.27]*	1.54 [1.47; 1.89]*	1.43 [1.24; 1.59]
The extent of LA patchy LGE, %	9.1 [1.72; 18.58]*	4.37 [0.82; 16.30]	10.9 [6.94 19.37]*	3.81 [0.57; 9.51]	0.78 [0.05; 3.5]
Maximal patchy LGE, %	70	36	70	23	17

AF – atrial fibrillation, LA – left atrium, MIR – maximum intensity ratio, LGE – left gadolinium enhancement, * p<0.05 vs healthy volunteers

aspects we used term "patchy LGE" instead of "fibrosis".

SI normalization of the image is advantageous for the assessment of LGE in LA using IIR [16]. In the current study, IIR-approach was modified by proposing a fixed indicator MIR. It quantitatively reflects the SI of the most enhanced regions in the LA myocardium. Our results demonstrate that patients with AF and hypertension have significantly higher values of MIR than HV. This observation may reflect the presence of fibrosis or inflammation in the LA myocardium as it was described in histopathological studies [3,6]. Moreover, ROC-analysis has shown that applying MIR indicator at 2 SD allows distinguishing the patients with AF from HV.

In the current study, we evaluated the largest group of HV of different ages (28 persons, 26-59 years of age) so far described in the literature. Our results show that the intensity of LGE in HV (MIR) correlates well with age, and 40 years seems to be the critical age for the development of LA structural changes. These data agree with studies that describe age-related changes of the LA myocardium which may be the result of increase of stiffness of LV in healthy population [18]. LA age-related structural changes in some healthy persons may be an additional risk factor for AF development [1,19].

Our data demonstrate that the subgroup of HV aged under 40 years has low intensity of LGE in the LA myocardium (low values of MIR). This justifies using young HV's MIR as a threshold for LA patchy LGE quantification and expands previously reported data [20]. The threshold value derived from ROC-analysis (1.38) is close to the value reported by Benito et al. (1.2) [20], who also used healthy persons as a reference cohort for LA fibrosis quantification. The minor difference in the threshold values may be due to dissimilarity in techniques of LA wall and blood pool segmentation. In our study, the use of the whole group of HV as a reference cohort gave a higher threshold for fibrosis quantification – 1.6. This data well

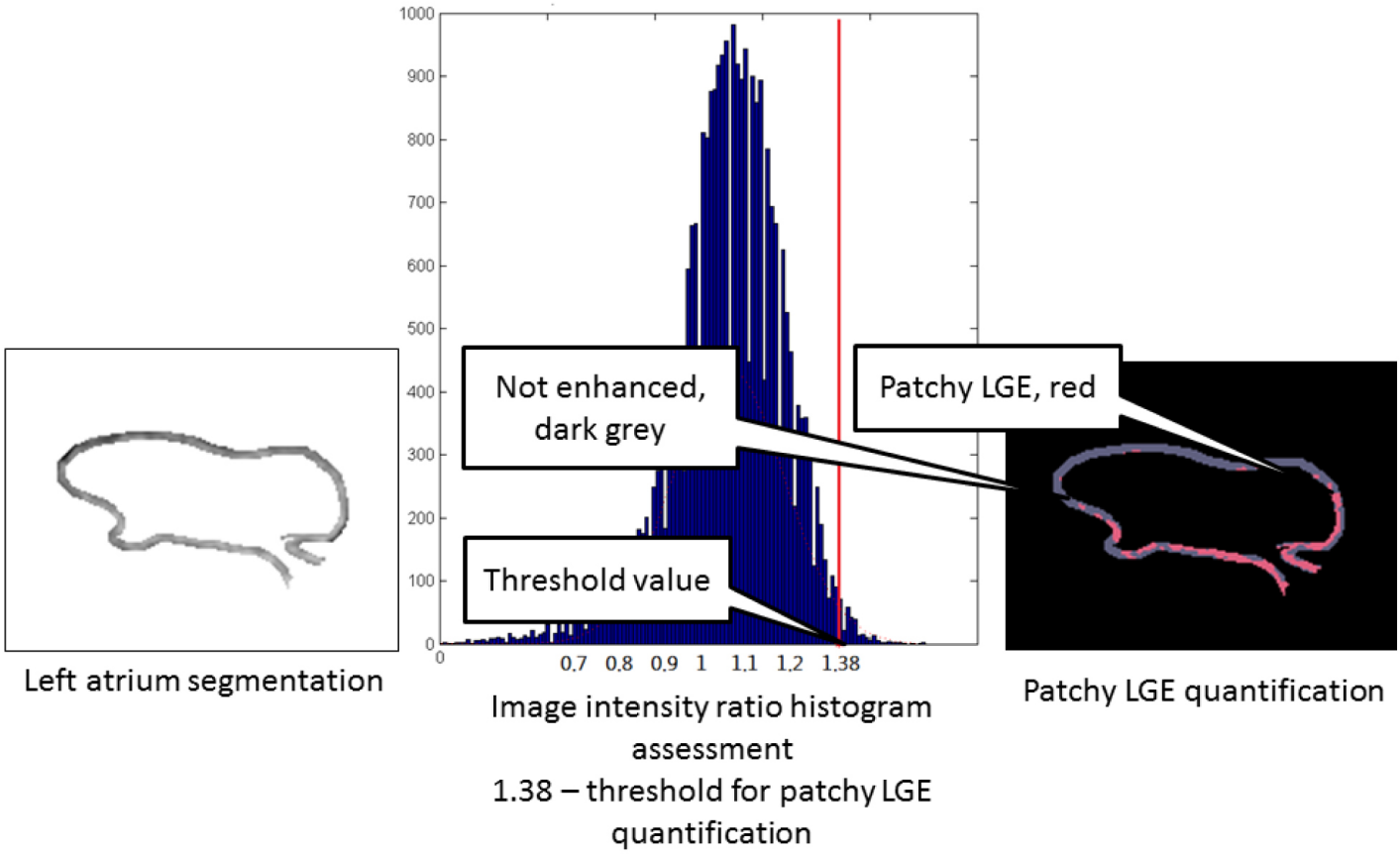


Figure 5: **Left atrial patchy late gadolinium enhancement quantification algorithm based on comparison of left atrial voxel image intensity ratio with threshold value obtained from healthy volunteer's data.**

agrees with Khurram et al, who offered to use the threshold of 1.6 for denser fibrosis and 0.97 – for less dense fibrosis according to electro-anatomical mapping [16]. Our results suggest that the use of lower threshold (1.38 vs. 1.6) value increases sensitivity of fibrosis quantification.

Patients with AF and especially those with hypertension demonstrated the highest extent of patchy LGE in LA (up to 70%). Patients with "lone AF" had only non-significant trend to lower extent of LA patchy enhancement than patients with AF and hypertension, which is in agreement with the results of Mahnkopf et al. [10]. We demonstrated that the predominant location of patchy LGE was in pulmonary vein and posterior wall regions. This may be explained using data of Hunter et al., who have demonstrated that pulmonary vein ostia regions and LA posterior wall undergo sufficient wall stress associated with AF [21]. Thus, formation of inflammation or fibrosis in these areas might be a result of stretch-induced activation of fibroblasts and myofibroblasts [22]. The extent of LA patchy LGE correlated with LA dilatation and LA EF decrease that is in agreement with the results of Kuppahally et al. [23]. These findings also support the idea that LA dilatation and wall stress are associated with structural changes in myocardium.

In seven patients with "lone AF", LA patchy LGE was not elucidated. These findings may reflect an initial stage of LA damage in association with AF. However, no data regarding the relationship between the minimal LA damage and clinical data were obtained in these persons.

The data regarding the relationship between the extent of LA patchy LGE/fibrosis and the type and persistency of AF are still controversial [9,10,24]. No correlation between the extent of LA patchy LGE and type of AF was found in the current study. This agrees well with the previous reports [10,11]. To reveal the relationship between LA patchy enhancement and AF clinical course it is necessary to set up complex prospective studies, including estimation of individual AF-burden.

It should be mentioned specifically that patients with no history of AF or even healthy persons may also demonstrate LA patchy LGE [25]. We have demonstrated minor LA patchy LGE only in HV aged over 40 years. In general, the mean extent of LA patchy LGE in HV was significantly lower than in patients with AF that is in agreement with the previous reports [26,20]. The extent of LA patchy enhancement

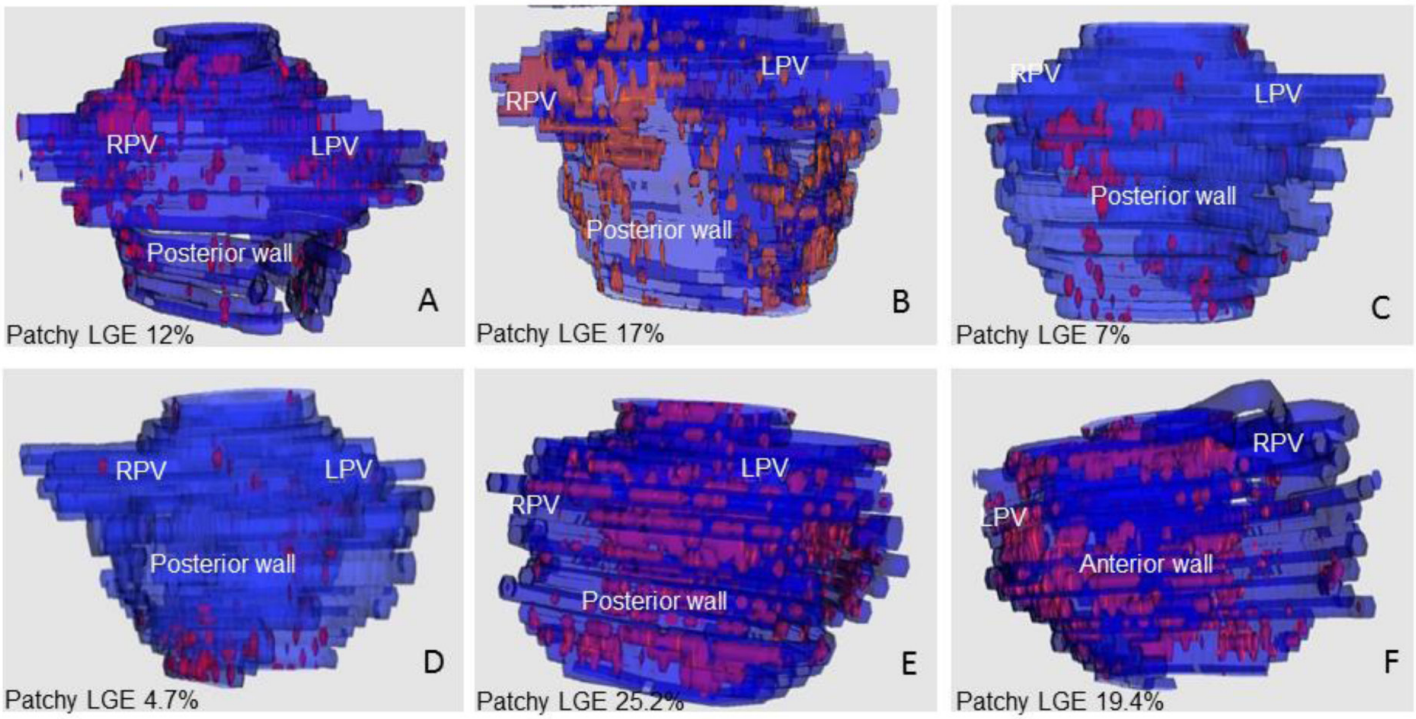


Figure 6: **Predominant locations of left atrial patchy late gadolinium enhancement. Blue color marks healthy myocardium, red color marks fibrotic patches. Pulmonary vein ostia region (A, B), seen predominately in patients with AF; posterior wall (C), seen in patients with atrial fibrillation or hypertension; inner part of the posterior wall, in a healthy volunteer (D); uniform distribution (E, F), characteristic for hypertension or atrial fibrillation. LGE – late gadolinium enhancement, RPV – right pulmonary veins ostia region, LPV – left pulmonary veins ostia region. In the left lower corner of each image the extent of patchy late gadolinium enhancement (LGE) is represented.**

in HV correlated with age and LA dilatation, and thus may represent age-related changes in LA. The predominant location of patchy LGE in HV adjacent to the mitral valve may reflect age-related changes in this area (calcification of posterior mitral annulus [27]), however, this needs further investigation on a larger group of healthy individuals.

In the current study, the extent of LA patchy LGE in patients with hypertension and no history of AF was intermediate between that of patients with AF and HV. Patients with hypertension demonstrated LA patchy LGE mainly located uniformly in all LA walls unlike the patients with AF. These changes may be a result of both LA wall stress related to elevated blood pressure and renin-angiotensin-aldosterone system activation [28]. Absence of correlation between the extent of patchy LGE in hypertension and clinical data was an unexpected finding of our study. We can only assume that lack of correlation between the extent of patchy LGE and initial grade of hypertension or LA volume may be due to the effective antihypertensive treatment.

In general, these observations support the idea that LA patchy LGE itself is not a specific phenomenon for AF. Evaluation of LA patchy LGE/fibrosis in cardiovascular diseases without the history of AF may reveal the new peculiarities of LA structure in AF.

Conclusion

AF, hypertension or natural aging may be associated with LA structural changes according to high resolution LGE MRI. Quantitative assessment of SI in the LA myocardium using indicator MIR at 2 SD revealed that young HV demonstrate low intensity of LGE in LA myocardium and, thus, are feasible as ground-truth for LA patchy LGE quantification. AF and hypertension seem to be associated with higher extent and different localization of LA patchy LGE than natural aging. The clinical relevance of LA patchy enhancement in persons with and without AF is currently unclear. The mechanisms of patchy structural changes in different locations of LA need further longitudinal studies.

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A Meta-Regression Analysis of Atrial Fibrillation Ablation in Patients with Systolic Heart Failure

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Abstract

Background: Meta-analyses of randomized controlled trials comparing atrial fibrillation (AF) ablation to medical therapy in patients with heart failure (HF) reported improvement in left ventricular ejection fraction (LVEF), quality of life using the Minnesota Living with HF Questionnaire (MLWHFQ), and 6-minute walk test (6MWT). Nonetheless, there was significant heterogeneity not accounted for suggesting that not all HF patients derive the same effect from AF ablation.

Objectives: To evaluate if baseline LVEF or the etiology of the cardiomyopathy would moderate the efficacy of AF ablation.

Methods: We performed random effects meta-regression using the mean baseline LVEF and total percentage of patients with non-ischemic cardiomyopathy (NICMP) in the placebo arms as moderator variables.

Results: Six trials with a total of 687 patients were included. The baseline LVEF in the control arm of trials ranged from 25% - 42.9%, and the percentage of patients with NICMP within each trial varied from 35% to 100%. When baseline LVEF was used as the moderator variable, no significant change in heterogeneity was observed for any of the outcomes of interest (R2 0.00 – 0.02). However, when controlling for NICMP, heterogeneity dropped substantially for the outcomes of LVEF (I2 44.7%, R2 0.91), and MLWHFQ (I2 0.00%, R2 1.00) but not 6MWT (I2 67.4%, R2 0.00). This indicates that improvement in LVEF and MLWHFQ was greater in the AF ablation group when more patients with NICMP were included in the trials.

Conclusions: In patients with systolic HF, AF ablation may be more beneficial in patients with NICMP.

Introduction

Atrial fibrillation (AF) and heart failure (HF) are two common conditions that often coexist and can predispose each to one another.[1-3] Guidelines do not provide a clear consensus regarding the best approach for management of AF in patients with HF. Multiple randomized controlled trials (RCTs) examined the role of catheter ablation in AF patients with HF and demonstrated improvement in left ventricular function (LVEF) and quality of life.[2-8] Recently, several meta-analyses[9-11] have analyzed these trials and reported improvement in the pooled outcome of LVEF, 6-minute walk distance and quality of life. However, wide variation for the difference in each of these outcome measures was noted between trials suggesting that not all HF patients with AF derive the same effect from ablation and there is a need to better understand which patients with HF are most likely to benefit from AF ablation.

Key Words

Atrial fibrillation, Heart failure, Non-ischemic, Cardiomyopathy.

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When conducting meta-analyses, some variation in treatment effect between trials is expected due to differences in study quality (e.g. potential bias in design, acquisition and adjudication of specific data elements) which may become evident when performing bias assessment with validated instruments such as the Cochrane Bias Assessment tool. In other cases, variation may be related to differences in patient sampling, the application of the intervention and management strategies in the control groups. This may be intentional on the part of investigators and meant to address gaps or areas of uncertainty. In each of the cases above, differences in trial-level effects may be expected and intuitively understood and contribute to the overall understanding of an interventions effect. However, in other cases, variation may not be easily explained by these factors and, when this is the case, confidence in the generalizability of a summary effect measure should decrease and the evidence-based community should seek to understand the source of variability in efforts to better target the intervention to those most likely to benefit or not.

A method to understand the source of variability in clinical trials is to perform meta-regression analyses where the treatment effect of the trial is measured against one or more moderator variables. Intuitively, this approach is not that different from performing

regression analyses of single datasets to determine how the presence of baseline covariates contributes to the outcome of interest. Similarly, meta-regression of clinical trials seeks to understand how differences in covariates among the study groups of individual clinical trials contribute to the observed treatment effects.

We hypothesized that the wide variation in the treatment effects of AF ablation for HF patients observed in the published clinical trials is due to differences in the patient populations of the individual trials and that understanding this may contribute to better application of AF ablation in HF patients. Specifically, we hypothesized that baseline LVEF and the etiology of the cardiomyopathy (i.e. ischemic versus non-ischemic) would moderate the efficacy of ablation on outcomes of LVEF improvement, 6-minute walk distance and quality of life. To test this hypothesis, we conducted a meta-regression analysis of several covariates, which we felt could contribute to the heterogeneity of effects observed between trials.

Methods

Data collection and extraction

We searched Medline, Google Scholar, the Cochrane Central Register for RCTs, and ClinicalTrials.gov for studies that examined AF catheter ablation in patients with HF (latest search date: Dec 1, 2018). Three authors (M.R., M.M. and A.F.) drafted the study protocol which was then revised by all coauthors. Two authors (M.R. and M.M.) independently reviewed all articles and abstracts for inclusion, and independently extracted information on patient's characteristics, study design, intervention, follow-up, and outcomes in a standardized manner. Discrepancies were discussed and resolved by consensus.

Trials that randomized patients with AF and systolic HF to catheter ablation versus medical therapy were included.

Outcome and quality assessment

The primary outcomes of interest were LVEF, Minnesota Living with Heart Failure Questionnaire (MLWHFQ) scores, and 6-minute walk distance. We used the Cochrane Risk of Bias table and the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) system, to report risk of bias and quality of study outcomes in each study, respectively.

Statistical analysis

The primary analyses were performed using RevMan version 5.3 (The Nordic Cochrane Center, The Cochrane Collaboration; Copenhagen, Denmark). We used the inverse variance random effects model to calculate the pooled mean difference in the outcomes of interest. Sensitivity analysis was performed as following: (i) comparing trials that randomized patients to AF catheter ablation vs. rate control, (ii) comparing AF catheter ablation to medical therapy in patients with persistent AF only, and (iii) individually eliminating studies to detect if any is the cause of heterogeneity.

To examine whether baseline LVEF or etiology of cardiomyopathy contributed to the heterogeneity in the outcomes, we performed random effects meta-regression using comprehensive Meta-Analysis Version 3, Borenstein, M., Hedges, L., Higgins, J., & Rothstein, H. Biostat, Englewood, NJ 2013. For these regression analyses, the mean baseline LVEF and total percentage of patients with non-ischemic cardiomyopathy in the placebo arms of trials were used as moderator variables.

We created meta-regression linear prediction graphs by plotting the moderator variable on the x-axis and treatment effect measure on the y-axis. The bubbles were plotted in proportion to the contribution of each study to the regression model.

The following parameters were used to test the model of heterogeneity: (i) Tau^2 which is the estimate of the true variance among studies, (ii) I^2 which represents the percentage of variability in the effect risk estimate among studies due to heterogeneity rather than chance (with I^2 <25% considered as low, I^2 >75% considered as high, and in between [25% to 75%] as intermediate), and (iii) R^2 which represents the proportion of between-study variance explained by the moderator.

A two-sided p-value of <0.05 was considered to be statistically significant.

Results

Qualitative Synthesis

We included six trials in our analysis, [Figure 1]. A total of 687 patients were included (342 patients randomized to catheter ablation and 345 patients randomized to medical therapy alone). The mean age in the trials ranged from 55 to 64 years, and the mean follow-up time ranged from six months to 38 months. The average baseline LVEF was 33.2% in the ablation arm and 34.0% in the control arm. Non-ischemic cardiomyopathy was present in 199 (58.2%) patients in the ablation arm and 170 (49.3%) patients in the control arm. 297 (86.8%) patients in the ablation arm and 286 (83.0%) in the control arm, had persistent AF. Further patients' characteristics are shown in [Table 1].

Risks of bias and quality assessment

Study limitations and biases (per Cochrane and GRADE criteria) are summarized in [Table 2]. Randomization was performed using random number generation in all trials. None of the trials tested AF ablation against a sham procedure and thus patients and their treating physicians were not blinded. This creates performance and outcomes assessment bias. Therefore, our confidence in the outcome assessment is moderate. Assessment of LVEF was blinded in four trials.[2, 3, 5, 6]

All studies appropriately described crossovers and dropouts. Crossover occurred in two patients in the study by Jones et. al.[3] and in 46 patients in the CASTLE AF trial.[8] Loss to follow-up was most prevalent in the CASTLE AF trial (33 [9.1%] patients). Further details on interventions and follow up are provided in [Table 3].

Evaluation of the funnel plots revealed no evidence of publication bias.

Table 1: Characteristics of patients included in the studies

	MacDonald		Jones		Hunter		Di Biase		Prabhu		Marrouche	
	Ablation arm	Rate control	Ablation arm	Rate control	Ablation arm	Rate control	Ablation arm	Amiod-arone	Ablation arm	rate control	Ablation arm	Medical therapy
Mean age (yrs)	62.3 ± 6.7	64.4 ± 8.3	64 ± 10	62 ± 9	55 ± 12	60 ± 10	62 ± 10	60 ± 11	59 ± 11	62 ± 9.4	64	64
Female gender	23%	21%	19%	8%	4%	4%	25%	27%	6%	12%	13%	16%
No. of patients	22	19	26	26	26	24	102	101	33	33	179	184
Follow up (months)	9.7	6.9	12	12	12	6	24	24	6	6	37.6 ± 20.4	37.4 ± 17.7
Persistent AF	100%	100%	100%	100%	96%	88%	100%	100%	100%	100%	70%	65%
NYHA class	II & III	II & III	II & III	II & III	II & III	II & III	II & III	II & III	≥II	≥II	I-IV	I-IV
ICMP	50%	47%	38%	27%	23%	29%	62%	65%	0%	0%	40%	52%
NICMP	50%	53%	62%	73%	77%	71%	38%	35%	100%	100%	60%	48%
LVEF %	36.1 ± 11.9	42.9 ± 9.6	22 ± 8	25 ± 7	31.8 ± 7.7	33.7 ± 12.1	29 ± 5	30 ± 8	32 ± 9.4	34 ± 7.8	32.5	31.5
LA diameter (mm)	N/A	N/A	50 ± 6	47 ± 7	52 ± 11	50 ± 10	47 ± 4	48 ± 5	48 ± 6	47 ± 8	48	49.5
6 min walk distance (meters)	317.5 ± 125.8	351.8 ± 117.1	416 ± 78	411 ± 109	N/A	N/A	348 ± 111	350 ± 130	491 ± 147	489 ± 132	N/A	N/A
Quality of life	55.8 ± 19.8	59.2 ± 22.4	42 ± 23	49 ± 21	N/A	N/A	52 ± 24	50 ± 27	N/A	N/A	N/A	N/A
Diabetes Mellitus	32%	21%	N/A	N/A	N/A	N/A	22%	24%	4%	5%	24%	36%
HTN	64%	58%	N/A	N/A	30%	33%	45%	48%	13%	12%	72%	74%
CAD	50%	53%	42%	50%	N/A	N/A	62%	65%	N/A	N/A	27%*	36%*

AF: Atrial fibrillation, CAD: Coronary artery disease, HTN: Hypertension, ICMP: Ischemic cardiomyopathy, NICMP: Non-ischemic cardiomyopathy, N/A: Not available.
*History of myocardial infarction.

Outcomes

LVEF: Data for difference in change in LVEF was available from all six trials. Compared to medical therapy alone, AF catheter ablation was associated with a significant increase in LVEF (mean difference 6.4%; 95% CI: 2.8 – 10.0; P< 0.001), [Figure 2]. In a sensitivity analysis when including only trials that had a blinded assessment of LVEF, AF catheter ablation was not associated with a statistically significant increase in LVEF (mean difference 5.3%; 95% CI: -0.6 – 11.2; P= 0.08). The heterogeneity test was significant (Tau^2= 16.2; df= 5; P< 0.001, I^2= 91%), and it did not improve on sensitivity analysis.

When baseline LVEF of the placebo group was used as the moderator variable, we observed no significant change in heterogeneity (Tau^2= 15.9; df= 4; P< 0.001, I^2= 91.1%, R^2= 0.02). However, when percentage of patients with non-ischemic cardiomyopathy in the placebo group was used as the moderator variable, heterogeneity dropped significantly and a strong linear relationship was observed such that as the percentage of patients with non-ischemic cardiomyopathy increased in the trials, the difference in change in LVEF was greater with ablation (Tau^2= 1.5; df= 4, I^2= 44.7%; P= 0.12, R^2: 0.91), [Figure 2]. This means that most of the variation observed in the treatment effect of the difference in change in LVEF between the ablation and control groups from the original meta-analysis could be explained by the percentage of patients in the trials who had non-ischemic cardiomyopathy.

Quality of life based on MLWHFQ scores: Four trials reported data on MLWHFQ. There was a significant improvement in the MLWHFQ scores in the AF catheter ablation group when compared to the medical therapy group (mean difference -8.0; 95% CI: -14.3 – -1.7; P= 0.01), [Figure 3]. There was moderate heterogeneity (Tau^2= 14.1, df= 3; P= 0.22, I^2 = 33%).

Baseline LVEF was not related to the observed treatment effects (Tau^2= 35.6; df= 2; P= 0.11, I^2= 54.4%, R2= 0.00). On the other hand, when the percentage of patients with non-ischemic cardiomyopathy was used as the moderator variable, heterogeneity dropped to zero and a strong linear relationship was observed such that as the percentage of patients with non-ischemic cardiomyopathy increased in the trials, improvement in MLWHFQ scores was greater with ablation (Tau^2= 0.0; df= 2; P= 0.41, I^2= 0.0%, R^2= 1.00), [Figure 3]. This means that nearly all of the variation observed in the treatment effect of mean difference in change in MLWHFQ scores between the ablation and control groups from the original meta-analysis could be explained by the percentage of patients in the trials who had non-ischemic cardiomyopathy.

6-minute walk distance in meters: Data on 6-minute walk distance were reported in five trials. The mean increase in 6-minute walk distance was higher in the AF catheter ablation group compared to the medical therapy group (mean difference 24.2; 95% CI: 5.7 – 42.7; P= 0.01), [Figure 4]. Heterogeneity was significant (Tau^2=

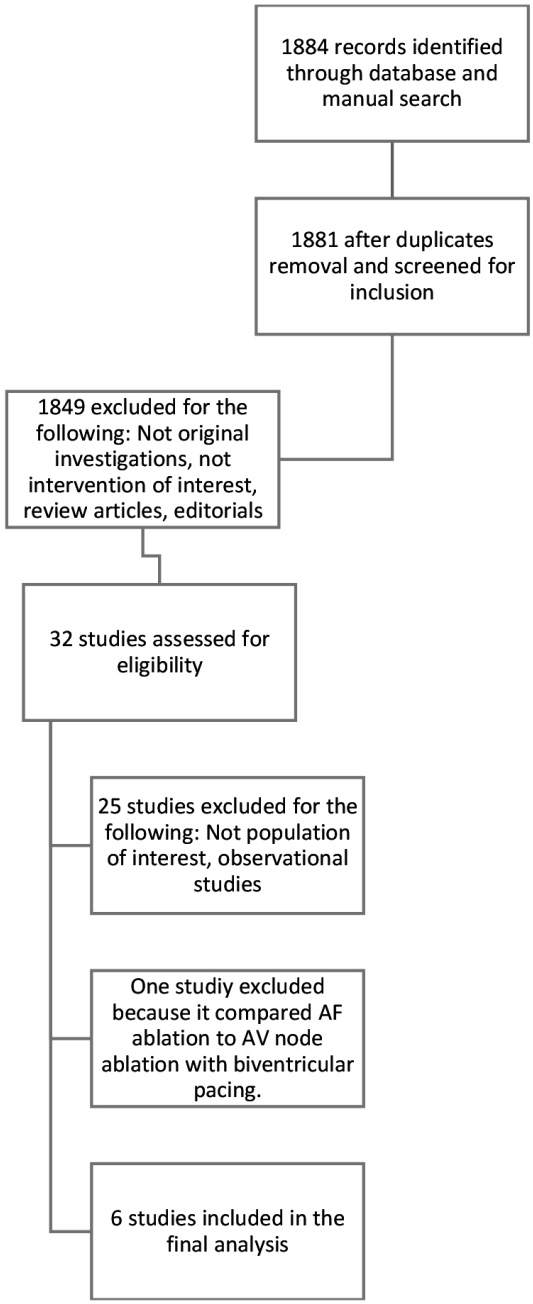

Figure 1: PRISMA diagram showing search strategy results.

235.9; df= 4, P= 0.01, I^2= 70%). On sensitivity analysis, most of the heterogeneity was driven by the AATAC and CASTLE AF trials[6,8], and when excluded from the analysis, the heterogeneity became low (I2: 0.0%) without significant change in the point estimate, P< 0.05).

Controlling for baseline LVEF didn't result in significant change in heterogeneity (Tau^2= 289.0; df= 3; P= 0.005, I^2= 77.0%, R^2= 0.00). Similarly, we didn't observe significant change in heterogeneity when the percentage of patients with non-ischemic cardiomyopathy was used as the moderator variable (Tau^2= 228.2; df= 3; P = 0.03, I^2= 67.4%, R^2 = 0.00), [Figure 4]. This means that the variation observed in the treatment effect of mean difference in change in 6-minute walk distances between the ablation and control groups from the original meta-analysis could not be explained by the percentage of patients in the trials who had non-ischemic cardiomyopathy.

Cardiovascular mortality, heart failure hospitalizations, and stroke: With the exception of the AATAC[6] and CASTLE AF trials,[8] the

Table 2: Risk of bias assessment

Bias	Study	Judgement	Support for judgement
Random sequence generation (selection bias)			
	MacDonald 2011	Low risk	Computer generated
	Jones 2013	Low risk	Computer generated
	Hunter 2014	Low risk	Random number generator
	Di Biase 2016	Low risk	Computer generated
	Prabhu 2017	Low risk	Computer generated
	Marrouche 2018	Low risk	Computer generated
Allocation concealment (selection bias)			
	MacDonald 2011	Low risk	Computer generated randomization
	Jones 2013	Low risk	Computer generated randomization
	Hunter 2014	Low risk	Random number generator
	Di Biase 2016	Low risk	Computer generated randomization
	Prabhu 2017	Low risk	Computer generated randomization
	Marrouche 2018	Low risk	Computer generated randomization
Blinding of participants and personnel (performance bias)			
	MacDonald 2011	High risk	No blinding
	Jones 2013	High risk	No blinding
	Hunter 2014	High risk	No blinding
	Di Biase 2016	High risk	No blinding
	Prabhu 2017	High risk	No blinding
	Marrouche 2018	High risk	No blinding
Blinding of outcome assessment (detection bias)			
	MacDonald 2011	Moderate risk	Only scans analysis was blinded
	Jones 2013	Low risk	People conducting cardiopulmonary exercise test and imaging analysis were blinded
	Hunter 2014	Moderate risk	Only echocardiogram analysis was blinded
	Di Biase 2016	Moderate risk	Only echocardiogram analysis was blinded
	Prabhu 2017	High risk	No blinding
	Marrouche 2018	High risk	No blinding
Incomplete outcome data addressed (attrition bias)			
	MacDonald 2011	Low risk	No significant attrition
	Jones 2013	Low risk	No significant attrition
	Hunter 2014	Low risk	No significant attrition
	Di Biase 2016	Low risk	No significant attrition
	Prabhu 2017	Low risk	No significant attrition
	Marrouche 2018	Low risk	No significant attrition
Selective reporting (reporting bias)			
	MacDonald 2011	Low risk	
	Jones 2013	Low risk	
	Hunter 2014	Low risk	
	Di Biase 2016	Low risk	
	Prabhu 2017	Low risk	
	Marrouche 2018	Low risk	

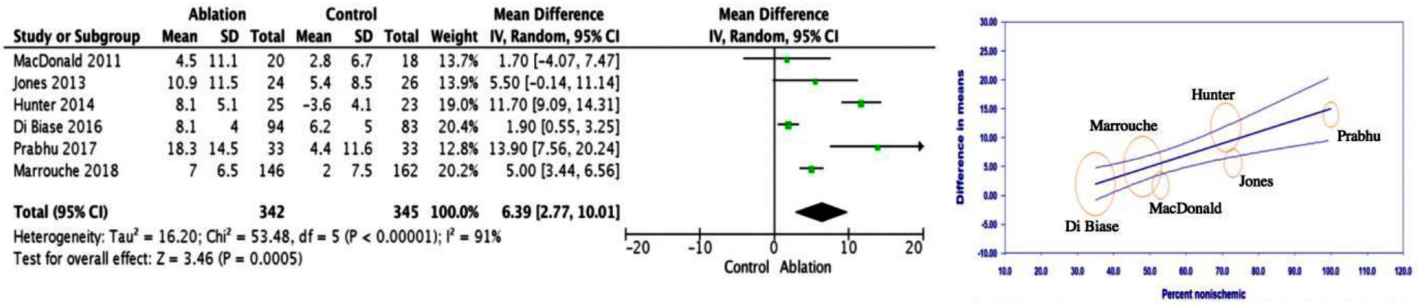

Figure 2: Change in LVEF, meta-analysis (left) and meta-regression (right) results.

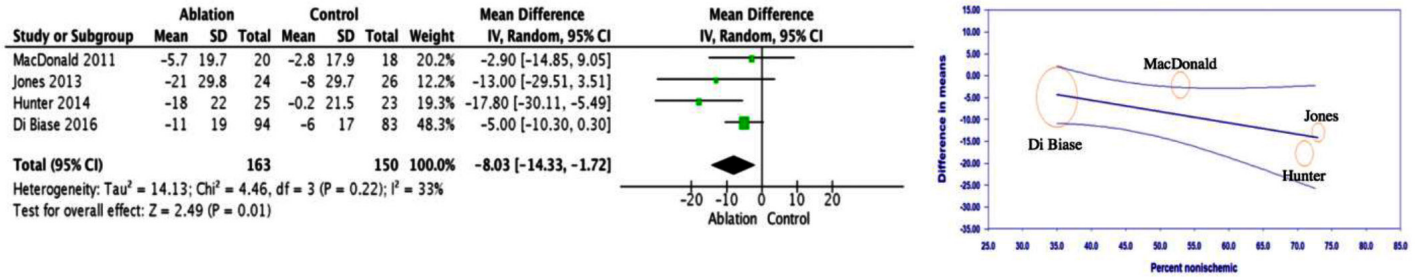

Figure 3: Change in MLWHFQ, meta-analysis (left) and meta-regression (right) results.

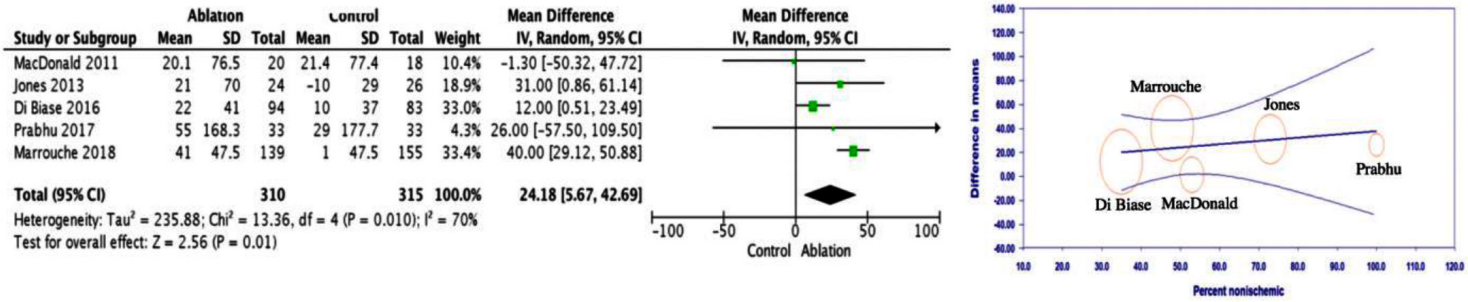

Figure 4: Change in 6MWT, meta-analysis (left) and meta-regression (right) results.

Table 3: Intervention and follow-up

	MacDonald	Jones	Hunter	Di Biase	Prabhu	Marrouche
Ablation strategy	PVI ± Linear lesions and sources of complex fractionated electrograms ± Cardioversion ± cavotricuspid isthmus ablation	PVI ± Linear lesions ± left atrial complex fractionated electrograms ± Cardioversion ± cavotricuspid isthmus ablation.	PVI with ablation of complex or fractionated electrograms ± Linear lesions ± Cavotricuspid isthmus ablation	PVI, and left atrial posterior wall isolation ± SVC isolation ± Linear lesions ± left atrial complex fractionated electrograms ± cardioversion	PVI, left posterior wall isolation ± cardioversion	PVI, Additional ablation lesions were made at the discretion of the operators
Frequency of monitoring (months)	3 & 6	3,6 & 12	1, 3 & 6	3, 6, 12 & 24	3 & 6	3, 6, 12, 24, 36, 48 & 60
Method of assessing rhythm on follow up	24h Holter monitor	48h Holter monitor ± existing implantable devices	48h Holter monitor	ECG, and existing implantable devices	24h Holter monitor and ILR	Existing implantable devices
Repeat ablation	6 (28.6%)	5 (19.2%)	14 (53.8%)	1.4 ± 0.6 per person	Repeat procedure was allowed (frequency not given)	37 (24.5%)
Crossover	None	2	None	None	None	46
Loss to follow up	3	None	1	None	1	33
AAD on follow up	Oral amiodarone for 3 months in all patients post ablation.	AAD stopped post ablation unless indicated by other reasons	AAD stopped post ablation unless indicated by other reasons	AAD allowed for 3 months after the first ablation	12 patients post ablation	48 patients in the ablation arm and 64 in the control arm.

remaining trials were not designed nor powered to detect a difference in cardiovascular mortality or HF hospitalizations.

Unplanned hospitalizations and death were significantly higher in the amiodarone arm in the AATAC trial[6] (58 [57%] vs. 32 [31%]; P < 0.001) and (18 [18%] vs. 8 [8%]; P= 0.037), respectively.

In the CASTLE AF trial,[8] cardiovascular mortality and HF hospitalizations were significantly higher in the medical treatment arm (41 [22.3%] vs. 20 [11.2%]; P= 0.008) and (66 [37.9%] vs. 37 [23.7%] P= 0.004), respectively. Stroke occurred at higher rates in the medical treatment arm, however, this didn't reach statistical significance (11 [6.0%] vs. 5 [2.8%]; P= 0.14).

Discussion

In this meta-regression analysis of randomized controlled trials, it appears that patients with non-ischemic cardiomyopathy benefit more from AF catheter ablation compared to those with ischemic cardiomyopathy. This can be inferred from the regression analyses showing that the difference in change in LVEF and MLWHFQ scores was greater and in favor of the AF ablation group when more patients with non-ischemic cardiomyopathy were included in the trials. Each of these outcomes was found to have a strong linear relationship with the regression line, R^2 values ranging from 0.91 – 1.0 when the percentage of patients with non-ischemic cardiomyopathy was plotted on the x-axis and treatment effect was plotted on the y-axis, [Figures 2-3]. On the contrary, the regression line for 6MWT was flat, indicating that the improvement in 6MWT was not affected by the percentage of patients with non-ischemic cardiomyopathy included in the trials. This is not surprising as the heterogeneity for 6MWT was driven by the AATAC and CASTLE AF trials,[6, 8] and when excluded from the analysis, the heterogeneity dropped significantly (I^2: 0.0%). On the other hand, it does not appear that baseline LVEF was related to the efficacy of ablation in these trials for any of the outcomes assessed.

Multiple meta-analysis of RCTs[9, 10, 12] and observational studies[13] reported improvement in LVEF, 6-minute walk distance and quality of life when catheter ablation is used as a treatment strategy in patients with AF and systolic HF. Nonetheless, there was significant heterogeneity in the outcome measures that was unaccounted for. While the results of the pooled outcomes of this analysis are similar to previously published reports, this is the first meta-regression of RCTs to examine the source of heterogeneity among studies that we are aware of.

The greater benefit of AF catheter ablation seen in patients with non-ischemic cardiomyopathy may not be surprising if many of these patients have tachycardia induced cardiomyopathy that would be expected to improve with restoration of sinus rhythm. Conversely, restoration of sinus rhythm may be less likely to improve cardiac function and related outcomes when cardiomyopathy is due to ischemia. The results of this analysis support previous report by Ling et al[14] who performed AF ablation in 16 patients with cardiomyopathy and no late-gadolinium enhancement on cardiac magnetic resonance imaging. At six months follow-up, LVEF improved from 40% ± 10% to 60% ± 6% in the 15 patients who maintained sinus rhythm post ablation.

These results are novel and interesting and should be viewed as hypothesis generating. There are important limitations to this meta-regression analysis. First, each of the associations derived from the separate regressions are limited by the small number of trials. Second, the overall quality of the individual trials was assessed as moderate only due to the potential for performance and ascertainment bias. Third, the meta-regression was performed based on the mean percentage of non-ischemic cardiomyopathy in each study. An individual level meta-analysis would more accurately address our questions. Nonetheless, these data are not available for the authors. Despite this limitation, we still find bio-plausibility in the regression results. For the regression analysis of difference in change in LVEF, where significant heterogeneity in this outcome was not reduced by sensitivity testing, the percentage of patients with non-ischemic cardiomyopathy in each trial varied from a low of 35% to a high of 100%. This is a significant spread of cardiomyopathy percentage over the trials, which could plausibly affect outcomes of the intervention. Also, the difference in change in mean LVEF between trials ranged from nearly 0% to 15%. This spread is outside the range of typical inter-reader variability using echocardiography and enough to be considered clinically meaningful. Furthermore, when visually examining the regression plot there is no single trial that significantly deviates from the regression line intercept and its 95% confidence interval bounds. If on the other hand, the spread in non-ischemic cardiomyopathy percentage across trials ranged from 40-50% and mean LVEF difference from 0-5% it would be less credible to assert that a true relationship existed and even more so if one or more trials deviated significantly from the regression line.

Conflicts of interest

None.

Funding

None.

Disclosure

None.

Conclusion

In patients with systolic HF, AF catheter ablation appears to be more beneficial in patients with non-ischemic cardiomyopathy. More studies are needed to specifically examine this group of patients and test this hypothesis.

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Cardioversion of Atrial Fibrillation and Flutter: Comparative Study of Pulsed vs. Low Energy Biphasic Truncated Exponential Waveforms

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Abstract

Background: Despite the widespread use of biphasic waveforms for cardioversion and defibrillation, the efficacy and safety of shocks has only been compared in a few studies.

Methods: This retrospective study aims at comparing the efficacy and safety of biphasic truncated exponential (BTE) pulsed energy (PE) waveform with a BTE low energy (LE) waveform for cardioversion of atrial fibrillation (AF) and atrial flutter (AFL). The treatment energies were following an escalating protocol for PE waveform (120-200-200J in AF and 30-120-200J in AFL) and LE waveform (100-200-200J in AF and 30-100-200J in AFL). The protocol was stopped at successful cardioversion (sinus rhythm at 1 minute post-shock), otherwise after the 3rd shock. If the 3rd BTE shock failed, a monophasic shock of 360J was delivered.

Results: From May 2008 to November 2017, 193 patients (153 PE, 40 LE) were included in the study. Both groups significantly differed in a few characteristics, including chest circumference ($p<0.05$). After adjustment, the success rate was not significantly different for the two waveforms (94.5% PE vs 92.5% LE, Odds Ratio [95% Confidence Interval] = 0.25 [0.03–2.2]).There was no difference in safety: post-shock changes in Hsc-TnI levels were similar ($p=0.25$). The efficient cumulative energy was particularly related with BSA ($\beta = 131.5$, $p=0.05$), AF/AFL duration ($\beta = 0.24$, $p=0.01$) and gender ($\beta = 61.8$, $p=0.05$).

Conclusions: The major clinical implications of this study concern the high success rate of cardioversion with both biphasic pulses and no superiority of LE over PE waveform with an excellent safety profile without post-shock myocardial injuries.

Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia (Chugh, 2010) and is the major risk factor for death, stroke, heart failure and coronary artery disease (Lip, 2016). It affects about 2-3% of the population in Europe (Zoni-Berisso, 2014).

According to the ESC Guidelines (Kirchhof, 2016), electrical cardioversion (ECV) is administered as a standard intervention for restoration of sinus rhythm in AF. In the short-term, ECV restores sinus rhythm quicker and more effectively than pharmacological cardioversion. AF is also associated with shorter hospitalization duration, although it includes risks from patient sedation.

Until the 90's, direct transthoracic current was delivered using external defibrillators with monophasic waveforms. During the last decades, new biphasic waveforms were designed and their superiority in efficacy and safety was explicitly demonstrated (Gurevitz, 2005; Inácio, 2016; Koster, 2004; Krasteva, 2001; Mittal, 2000; Page, 2002). Various biphasic waveforms became an industry standard: rectilinear biphasic (RB), biphasic truncated exponential (BTE) with high energy (HE), low energy (LE) and pulsed energy (PE).

The BTE technologies can differ in various design characteristics, such as capacitors, tilts, pulse durations or charge voltages and energies. The PE is the most recent designed waveform. Advanced PE defibrillators deliver a BTE waveform with an alternately turned on and off current. Although the initial peak currents are high, PE achieves therapeutic effect with low average current and almost complete utilization of the charged energy (Krasteva, 2001).

This original study is carried out to compare the efficacy and safety of PE and LE waveforms in elective ECV.

Key Words

Cardioversion, Atrial fibrillation, Biphasic waveforms, Pulsed energy, Low energy.

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Material and Methods

Study population

This is a retrospective and monocentric trial, evaluating the results

of external transthoracic cardioversion using PE and LE waveforms. The clinical study takes place in the Intensive Cardiology Care Unit (ICCU), Cardiology Clinic of the National Heart Hospital (NHH), Sofia, Bulgaria, following the standard hospital procedures during ECV accepted in the NHH, and approved by the NHH local ethical committee.

Between May 2008 and November 2017, a total number of 820 patients undergo ECV in the ICCU-NHH, among them 729 are subjected to elective ECV of persistent AF or atrial flutter (AFL) with BTE defibrillators. The patient allocation is summarized in the CONSORT flow diagram [Figure 1].

Patients <18 years, pregnant, presenting other arrhythmias than AF or AFL, with a spontaneous heart rate (HR) <60 bpm, presenting a digitalis intoxication, conduction disturbances (patients without pacemaker) or an impossibility to sustained sinus rhythm irrespective to anti-arrhythmic therapy and frequent ECV are excluded. Asymptomatic patients with long duration of AF or AFL (>1 year); thyroid dysfunction; thrombosis in cardiac cavities; spontaneous echo contrast >2 degree; large atrial size >50 mm (parasternal long axis view) and small chance for sustained sinus rhythm; patients with planned cardiac operation in the next 3 months; patients with embolic event in the last 3 months are not eligible.

The inclusion criteria for elective ECV consider: symptomatic AF/AFL with duration <12 months; symptomatic first detected AF/AFL; persistent AF/AFL after successful causal therapy; rare recurrences of AF/AFL with long periods of sinus rhythm; impossibility to reach a sustained normal ventricular rate in AF/AFL; embolic events irrespective of proper anticoagulant therapy.

Patient preparation and ECV procedure

Standardized indications and procedures are applied as established in the ICCU-NHH. On the day of the cardioversion before the procedure, each patient signs a written informed consent form. In addition, patients have a transesophageal echocardiogram to evaluate the dimensions of the left atrium and ventricle, the ejection fraction of the left ventricle, the echo contrast and thrombosis. All therapy, including antiarrhythmic and anticoagulation drugs up to five days before ECV has been collected in medical records and reported in the study.

The patients are shaved before placement of the standard self-adhesive defibrillation pads in antero-lateral position. Afterwards, the patients are premedicated with 0.5 mg Atropine sc 15-30 min before ECV at the discretion of the attending physician with prophylactic considerations against post ECV bradycardia. The use of atropine is influenced mainly by the heart rate before ECV, treatment with combination of antiarrhythmic drugs and history of bradycardia in the particular patient without documented conductive disorders (the latter is excluding criteria if unprotected by pacemaker). The anesthesia is conducted by an anesthesiologist with slow intravenous injection of Propofol, adjusted individually to reach deep sedation (Cook's scale points < 7).

During the ECV intervention, the patient is shocked following the energy protocols described in [Figure 2]. The time-interval between consecutive shocks is respected to be at least 1 min. During the follow-up period of 24 hours in the Cardiology Clinic, vital signs and ECG are measured, as well as potential complications are recorded. Furthermore, 8 to 12 hours after the ECV intervention, blood samples are collected to analyze the high sensitive cardiac Troponin I (Hsc-TnI).

Protocol and study designs

Devices

PE shocks are delivered with an external semi-automatic defibrillator (Multipulse Biowave®, Defigard DG4000, Schiller Médical, Wissembourg, France). Otherwise, LE waveform is generated using another external defibrillator (HeartStart XL, Philips Medical Systems, 3000 Minuteman Road, Andover, MA USA). Both devices are embedding an impedance compensation technology, which adapts the pulse duration for proper delivery of the selected energy. The waveforms generated by both defibrillators are illustrated in [Figure 2].

For each patient, the choice of the device used is left to the appreciation of the physician.

Escalating energy protocols

The protocol for selection of the treatment energies is part of the standard hospital procedure for elective cardioversion of AFL and AF. A protocol with escalating energies has been primary established in order to limit the energy of the shocks delivered to the «good» responders of the treatment. Because AFL is known to be easier to convert than AF (Gallagher, 2001), two different escalating energy protocols are used for AF and AFL patients, as indicated in [Figure 2]. In both protocols, a stack of three shocks are preset. If the third shock is inefficient, a fourth shock is administered using a monophasic waveform at 360J.

The choice of escalating protocols with different energy levels for PE (DG4000) and LE (HeartStart XL) is due to the different manually selectable energy settings available in both devices:

- DG4000 offers 11 energy settings: 2J, 4J, 8J, 15J, 30J, 50J, 70J, 90J, 120J, 150J, 200J
- HeartStart XL offers 12 energy settings: 2J, 3J, 5J, 7J, 10J, 20J, 30J, 50J, 70J, 100J, 150J and 200J.

The choice of minimal energy (30J) and maximal energy (200J) is corresponding in both devices, however, the energy level just in the middle range (115J) is provided by the closet selectable energy setting in DG4000 (120J) and HeartStart XL (100J).

End points

The primary efficacy endpoint corresponds to the success at the end of the ECV intervention, further denoted as cumulative success rate. Success is defined as the restoration of sinus rhythm for at least 1 minute after the shock.

The secondary efficacy endpoints are considered to be : the cumulative energy (the accumulated energy by the stacked shocks,

estimated as the cumulative energy setting, as well as the true delivered cumulative energy) and the number of delivered shocks.

The safety is evaluated by the troponin level change after ECV. The absolute Hsc-TnI values before and 8-12 hours after the ECV, as well as their normalized difference are compared.

Statistical analysis

Standardized Statistical analysis is performed with RStudio, version 3.5 (RStudio, Inc., Boston, USA).

According to the sample size of LE group (N=40), for a power of 80% to detect a difference of at least 15% in cumulative success rate with a risk alpha of 0.05 and bilateral test, the sample size of the PE group should be over 143 patients. Continuous data are expressed as mean value ± standard deviation (SD) and categorical data are expressed in percentages. Baseline characteristics are compared using χ^2 test or a Fisher's exact test for discrete variables and Mann-Whitney U test for continuous variables. All efficacy endpoints are compared adjusting both groups on baseline characteristics. Multivariate analysis of patients' baseline characteristics is performed with multivariate linear and logistic regressions. A first model (Model 1) is built using classical risk factors according to the literature (Kirchhof, 2016; Lip, 2016): age, gender, BMI, diabetes, renal failure and AF/AFL duration. A second model (Model 2) is designed using the same risk factors in combination with the baseline characteristics, which appear statistically different between PE and LE groups ($p < 0.05$). The significance of both models is estimated with the odds ratio (OR) and its 95% confidence interval (CI). Linear regression is evaluated with the β coefficient, giving the direction of the factor (X) effect on the variable to be explained (Y) : $Y=a+bX$. Safety is evaluated using the Student's paired t-test. All tests of statistical significance are 2 tailed and a p-value < 0.05 is considered significant.

Results

Patient characteristics

Among the 820 patients initially enrolled, 193 are allocated and treated with an escalating energy protocol [Figure 1]. Among those, 153 (79.3%) are treated with PE waveform and 40 (20.7%) with LE waveform. The major proportion of patients in PE group is mainly due to the more frequent use of the PE defibrillator in ICCU-NHH. [Table 1] summarizes the major baseline characteristics of both groups, which are properly matched for 68 variables, including age, gender, weight, height, BMI, BSA, etc. A few differences between both groups are found seen in 7 variables, including chest circumference, left ventricular tele diastolic dimension (LV tdd), valvular heart disease, ASA classes, the calcium channel blocker (CCB) administration and the diastolic blood pressure.

The patients from the PE group have a better ASA class and higher values of chest circumference and LV tdd compared to the LE group. Conversely, the patients from the LE group have a higher rate of valvular disease and CCB. These differences are taken into account when both groups were compared in respect of efficacy and safety.

Table 1: Baseline characteristics of patients included in the study. Continuous data are expressed as mean value ± SD and categorical data are expressed as % (number n)

BASELINE CHARACTERISTICS	PE N = 153	LE N = 40	p-value
AGE (years)	59.7 ± 11.0	59.4 ± 11.8	0.93
MEN (%)	70.6 (108)	62.5 (25)	0.43
WEIGHT (kg)	89.3 ± 15.9	85.5 ± 16.3	0.12
HEIGHT (cm)	174.3 ± 9.05	172.9 ± 8.61	0.49
BMI (kg/m2)	29.3 ± 4.40	28.5 ± 4.68	0.20
BMI > 25 (%)	83.7 (128)	72.5 (29)	0.07
BSA (m^2)	2.05 ± 0.22	1.98 ± 0.20	0.06
LEAN BW (kg)	62.2 ± 11.0	59.4 ± 9.86	0.17
FAT BW (kg)	27.1 ± 10.3	26.0 ± 10.0	0.41
CIRCUMFERENCE (cm)	105.4 ± 11.1	100.6 ± 9.00	0.01*
FIRST ECV (%)	78.4 (120)	75.0 (30)	0.80
STRUCT HEART DISEASE (%)	90.2 (138)	95.0 (38)	0.53
HEART FAILURE (%)	35.3 (54)	47.5 (19)	0.09
DIABETES (%)	14.4 (22)	10.0 (4)	0.68
THYROID NORMAL (%)	37.9 (58)	35.0 (14)	0.66
TSH	1.79 ± 1.22	2.37 ± 0.99	0.06
TSH NORMAL (%)	41.8 (64)	35.0 (14)	0.79
COPD (%)	1.31 (2)	2.50 (1)	0.43
RENAL FAILURE (%)	24.2 (37)	22.5 (9)	0.53
GFR (ml/min)	217.5 ± 111.0	234.6 ± 123.6	0.43
AF/AFL DURATION (days)	120.6 ± 119.8	165.6 ± 277.0	0.99
PREVIOUS HF (%)	13.1 (20)	20.0 (8)	0.39
NOW HF (%)	3.27 (5)	0.00 (0)	-
HB (G/L)	141.9 ± 13.5	139.8 ± 15.1	0.31
HT (%)	42.1 ± 4.08	42.4 ± 4.80	0.64
WBC (109/L)	7.49 ± 1.86	7.17 ± 1.74	0.26
GLU (mmol/L)	6.23 ± 1.90	6.45± 2.90	0.61
UREA (mmol/L)	6.64 ± 2.24	6.65 ± 2.23	0.91
CREAT (mmol/L)	98.8 ± 18.4	92.0 ± 15.4	0.05
K (MMOL/L)	4.31 ± 0.41	4.31 ± 0.37	0.77
NA (MMOL/L)	139.0 ± 2.97	139.3 ± 2.56	0.93
AST (U/L)	26.9 ± 18.0	20.3 ± 4.24	0.22
ALT (U/L)	30.5 ± 20.9	23.1 ± 9.76	0.15
CK (U/L) MB (U/L)	123.3 ± 171.6 13.4 ± 7.99	90.6 ± 48.9 13.1 ± 6.66	0.08 0.74
TN (U/L)	0.03 ± 0.08	0.03 ± 0.02	0.95
TEE (%)	97.4 (149)	100.0 (40)	0.58
ECHOCONTRAST (%)	20.3 (31)	25.0 (10)	0.77
LA (MM)	50.8 ± 8.17	50.3 ± 6.95	0.90
NORMAL LA <50MM (%)	70 (45.8)	17 (42.5)	0.86
LV TSD (mm)	34.0 ± 7.14	32.6 ± 6.67	0.31
NORMAL LV TSD <36mm (%)	51.6 (79)	57.5 (23)	0.59
LV TDD (MM)	51.1 ± 6.32	48.6 ± 5.47	0.04*
NORMAL LV TDD <57mm (%)	71.9 (110)	85.0 (34)	0.18
LV TSV (ML)	47.4 ± 22.6	44.5 ± 16.0	0.95

NORMAL LV TSV <50ml (%)	61.4 (94)	57.5 (23)	0.48
LV TDV	101.7 ± 33.1	102.1 ± 26.3	0.62
NORMAL LV TDV <140ml (%)	81.1 (124)	82.5 (33)	0.55
EF (%)	55.7 ± 8.55	56.4 ± 8.17	0.34
NORMAL EF > 50% (%)	69.9 (107)	70.0 (28)	1.00
ASA CLASS			0.02*
CLASS 1	1.96 (3)	7.50 (3)	
CLASS 2	64.7 (99)	35.0 (14)	
CLASS 3	30.7 (47)	50.0 (20)	
CLASS 4	2.60 (4)	7.50 (3)	
FIRST DIAGNOSIS			
AH (%)	55.6 (85)	47.5 (19)	0.46
CAD (%)	7.84 (12)	2.50 (1)	0.31
CMP (%)	6.54 (10)	7.50 (3)	0.73
VALVE (%)	18.3 (28)	40.0 (16)	0.01*
NONE (%)	11.8 (18)	2.50 (1)	0.13
ANESTHETIC			
PROPOFOL DOSIS (mg)	117.4 ± 32.0	122.5 ± 40.8	0.64
ANTICOAGULATION			
SINTROM (%)	89.5 (137)	90.0 (36)	1.00
HEPARIN (%)	7.19 (11)	10.0 (4)	0.52
NOAC (%)	3.27 (5)	0.00 (0)	0.59
ANTIARRHYTMIC DRUGS			
AMIODARONE (%)	69.9 (107)	67.5 (27)	0.92
BETA BLOCKER (%)	45.1 (69)	45.0 (18)	1.00
CCB (%)	6 (3.92)	7 (17.5)	0.01*
DIGITALIS (%)	3.27 (5)	5.00 (2)	0.64
PROPAFENONE (%)	11.8 (18)	2.50 (1)	0.13
NUMBER DRUGS	1.34 ± 0.49	1.38 ± 0.54	0.85
ACE INHIBITOR/ARB (%)	64.7 (99)	60.0 (24)	0.74
ATROPIN BEFORE (%)	34.6 (53)	37.5 (15)	0.83
HR BEFORE (bpm)	93.6 ± 20.0	96.5 ± 19.7	0.32
SYSTOLIC BP (mmHg)	133.7 ± 16.5	132.4 ± 13.3	0.55
DIASTOLIC BP (mmHg)	85.1 ± 12.3	81.5 ± 11.1	0.04*

Note: *: p<0.05 marks significant differences.
BMI: body mass index, BSA: body surface area, BW: body weight, HF: heart failure, TSH: thyroid stimulating hormone, COPD: Chronic obstructive pulmonary disease, GFR: glomerular filtration rate, TEE: transesophageal echocardiogram, LA: left atrium, LV: left ventricle, TSD: telesystolic diameter,TDD: telediastolic diameter,TSV: telesystolic volume,TDD: telediastolic volume, EF: ejection fraction, ASA: the American Society of Anesthesiologists physical status classification system, AH: arterial hypertension, CAD: coronary artery disease, CMP: cardiomyopathy, Valve: valvular heart disease, CCB: calcium channel blocker, HR: heart rate, BP: blood pressure.

Cardioversion results

Efficacy

The results of the cumulative success rates achieved after each shock are summarized in [Table 2]. They indicate that after the final 3rd shock of the BTE stack, the cumulative success rates are very high and insignificantly different for both groups (PE and LE): 146 (95.4%) patients from PE group are converted against 37 (92.5%) from LE group (p = 0.90), considering AF and AFL patients together. The same insignificant differences of the cumulative success rates are observed for the treatment of AF and AFL patients separately with both PE and LE stacks. Moreover, the total number of delivered shocks with both devices do not differ: 1.63±0.83 (PE) vs. 1.70±0.88 (LE), p = 0.67. Finally, the cumulative success rate is not found to be

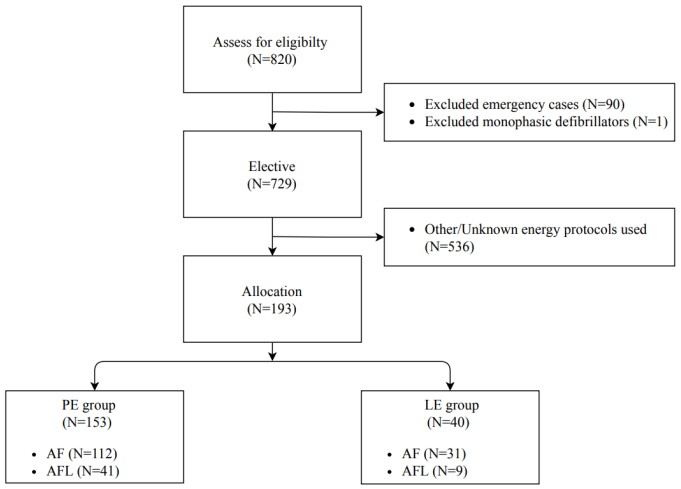
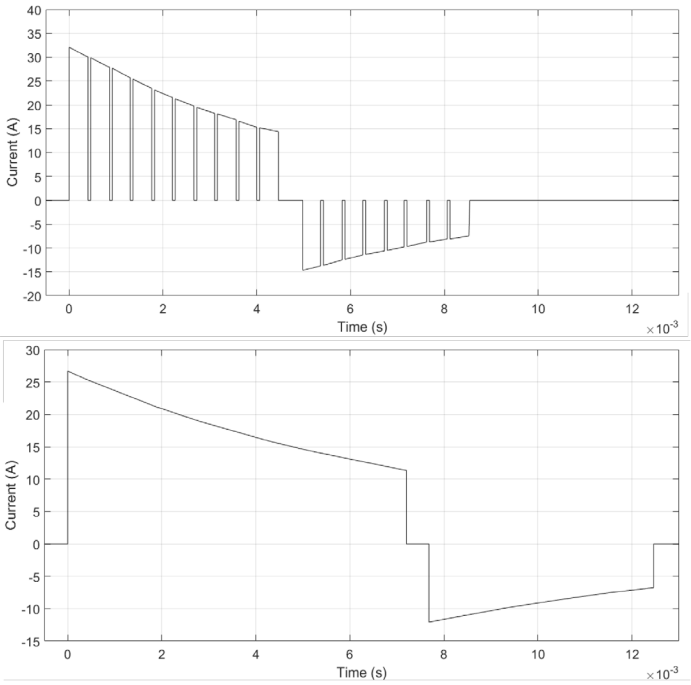


Figure 1: CONSORT flow diagram showing the patient allocation groups.



Rhythm	Group 1 DG4000 (PE)	Group 2 HeartStart XL (LE)
AF	120J-200J-200J	100J-200J-200J
AFL	30J-120J-200J	30J-100J-200J

Figure 2: Waveforms of PE (top trace) and LE (bottom trace) recorded during ECV interventions with energy setting of 200J and a patient impedance of 75Ω. Below, the escalating energy protocol applied at 1st-2nd-3rd shocks for both waveforms.

Table 2: Number of patients shocked (PS) and cumulative success rate (CSR) at each ECV shock for patients (AF+AFL) grouped to BTE waveforms (PE and LE). The values are reported as % (number of patients N). The last shock delivered is a monophasic shock (MS). Both groups (PE and LE) are compared with Model 1 and Model 2, reporting their respective OR [95% CI].

Shock number	Energy Setting PE (J)	Energy Setting LE (J)	Outcome	PE (N=153)	LE (N=40)	Model 1 OR [95% CI]	Model 2 OR [95% CI]
1	120	100	PS	100% (153)	100% (40)	-	-
			CSR	54.9% (84)	52.5% (21)	0.78 [0.37–1.6]	0.56 [0.21–1.5]
2	200	200	PS	45.1% (69)	47.5% (19)	0.98 [0.43–2.1]	1.11 [0.39–3.0]
			CSR	86.3% (132)	82.5% (33)	0.57 [0.22–1.6]	0.35 [0.09–1.5]
3	200	200	PS	13.7% (21)	17.5% (7)	1.83 [0.52–5.8]	2.30 [0.48–9.9]
			CSR	95.4% (146)	92.5% (37)	0.35 [0.07–1.9]	0.25 [0.03–2.2]
4(MS)	360	360	PS*	4.5% (7)	5.0% (2)	-	-
			CSR	97.8% (149)	92.5% (37)	0.23 [0.04–1.4]	0.13 [0.09–1.8]

*OR were not assessed for PS 4 due to the too small sample size.

associated with any confounding factors in both regression models (i.e. age, gender, BMI, diabetes, renal failure and AF/AFL duration, baseline characteristics, etc.).

[Figure 3] compares the cumulative success rates of PE and LE groups, depicted in function of the cumulative energy setting after each shock. Although there are disparities in the protocols of both PE and LE groups, we do not notice any significant differences in the distributions of both types of cumulative energies (reported as median values [interquartile range]): cumulative energy setting (120J [120-320J] for PE vs. 100J [100-300] J for LE, p = 0.93) and cumulative delivered energy (122J [119-320J] for PE vs. 134J [103-315J] for LE, p = 0.34).

Overall, only 9 (4.7%) patients are not converted with BTE shocks and received monophasic shocks [Table 2]. Among them, 7 (4.5%) are treated with PE waveform and 2 (5.0%) with LE waveform. Sinus rhythm has been restored only for 3 (2.0%) patients from the PE group using monophasic shocks. This difference between both groups conversion after 3 BTE shocks is not significant (OR [95% CI] = 0.25 [0.03–2.2]). In addition, there is no difference in baseline characteristics between successfully and unsuccessfully converted patients. However, all unsuccessful patients present a structural heart disease.

Cumulative energy setting differs with patient characteristics. Using a multivariate linear regression, six variables are found to be significantly associated with efficient cumulative energy setting: AF/AFL duration, gender, BSA, LVtdd, valvular disease and chronic respiratory disease. The efficient cumulative energy is higher for men (β = 61.8, p =0.05), increases with the AF/AFL duration (β = 0.24, p=0.01), BSA (β = 131.5, p=0.05), LVtdd (β = 6.0, p=0.02) and the presence of chronic respiratory disease (β = 136.5, p = 0.01), while decreases with the presence of valvular disease (β = - 65.8, p=0.05).

The safety of each waveform is evaluated, comparing Hs-cTnI before and after ECV [Table 3]. No difference between both groups is found in Hs-cTnI levels before and after ECV, or in their normalized ratio (p>0.05).

Table 3: Hs-cTnI levels before and after ECV

Troponin levels	PE (N = 153)	LE (N=40)	p
Hs-cTnI before ECV (µmol/L)	0.026±0.077	0.027±0.019	0.87
Hs-cTnI after ECV (µmol/L)	0.034±0.087	0.029±0.019	0.49
(Hs-cTnI before - Hs-cTnI after)/(Hs-cTnI before)	0.539±1.582	0.304±0.922	0.25

Discussion

This is the first clinical trial, which compares PE and LE waveforms. Using the cumulative success rate as the primary endpoint; the superiority of the LE waveform could not be demonstrated in the present study.

The lack of difference in efficacy between both devices is in accordance with previous comparisons between biphasic waveforms. In fact, no difference in cardioversion efficacy was reported in other studies comparing RB vs. HE waveforms (Alatawi, 2005; Kim, 2004; Neal, 2005) or RB and LE waveforms (Deakin, 2013). Only one study (Schmidt, 2017) comparing the success rate of HE and PE waveforms showed a difference (89% vs. 67%). The lower success rate obtained with the PE waveform could be explained by the use of a defective device as mentioned by this research team (Schmidt, 2017).

The success rates of both BTE waveforms estimated in this work are in accordance with previously published results. A study comparing RB and LE shocks (Deakin, 2013) reported a cumulative success rate of 90.9% for LE waveform. This study also used an escalating protocol with a comparable final energy (200J) and the same definition of success (1 minute post-cardioversion). This success rate is not statistically different to our results (p = 0.76).

PE, LE and HE are BTE waveforms using the same impedance compensation method (varying the pulse duration). However, these waveforms differ in various design characteristics, including charging

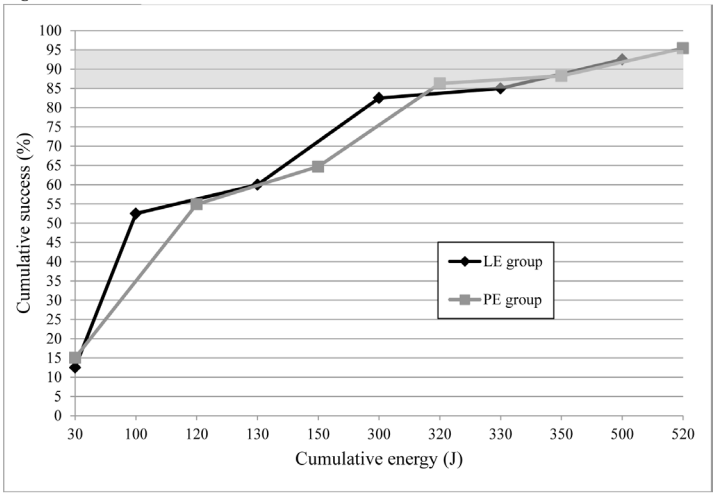


Figure 3: **Cumulative success rate versus cumulative selected energy for patients treated with PE waveform (N=153) and patients treated with LE waveform (N=40). Results for AF and AFL patients are combined.**

voltage (lowest for HE, highest for PE) and charging capacitor (lowest for PE, highest for HE). One study (Anantharaman, 2017) considered that HE and LE shocks differed only by the selected energy levels and by the pulse duration. To compare both groups, the same defibrillator was used. However, the type of the shock (HE, LE or PE) was defined by the waveform characteristics.

In this work, there was no difference in safety: Hs-cTnI levels were not different in both PE and LE groups. These results agree with previous studies, showing no difference in Hs-cTnI levels after ECV between both BTE waveforms (Neal, 2003; Schmidt, 2017). Furthermore, no elevation of Hs-cTnI after the procedure was found according to the literature (Neal, 2003; Schmidt, 2017; Glover, 2008; Vikenes, 2000; Allan, 1997; Bonnefoy, 1997).

In conclusion, we observed a high success rate with both biphasic pulses and no superiority of LE over PE with an excellent safety profile without myocardial injuries.

Limitations

To interpret the findings, limitations must be considered. Ideally, this study should have been randomized. Despite its retrospective nature, both groups are rather similar in baseline characteristics. Skin burns information has not been collected during the study.

In addition, with the small sample size only a power of 80% can be reached. But, the results [Table 2] show a similarity and it is unlikely that a better outcome with a higher power can be attained.

Finally, the energies used in the escalating energy protocol do no match due to slight differences in the energy settings available in both devices. Thus, the energy of the first shock (AF patients) or second shock (AFL patients) is different: 100J for LE waveform and 120J for PE waveform. However, cumulative delivered energies were similar.

Conclusion

This study aimed to compare PE (Pulsed Energy) and LE (Low Energy) waveforms in respect of efficacy and safety. The difference in observed efficacy of the PE vs. LE did not reach statistical significance. No difference in safety between both waveforms was also highlighted.

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Assessment of Left Atrial Function in Patients with Paroxysmal, Persistent, and Permanent Atrial Fibrillation Using Two-Dimensional Strain.

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Abstract

Background and purpose: Atrial fibrillation (AF) has a progressive nature, leading to structural, functional, and electrical changes in the left atrium (LA). Enhanced response to treatment in patients with AF can be achieved through improved knowledge of atrial structure and a better understanding of its function. The aim of this study was to assess LA strain and its determinants in patients with paroxysmal (PAF), persistent (PsAF), and permanent AF (PmAF).

Methods: Fifty-eight patients with registered non-valvular AF were divided into 3 groups depending on the type of AF. The participants underwent transthoracic echocardiography to assess the anatomy and function of heart chambers. Left atrial longitudinal strain (LALS) was measured in four-chamber projections using two-dimensional speckle tracking echocardiography.

Results: Patients with PAF had higher LALS (15.7±12.0) when compared to those with PsAF (4.3±7.9) and PmAF (5.8±7.8, all P=0.003). Multiple linear regression showed that the independent predictors of LALS were diastolic blood pressure (β=0.95, R^2=0.88) in the PAF group; left atrial area (β=-0.56) and creatinine (β=-0.63, R^2=0.58) in the PsAF group; AF duration (β=0.89) in the PmAF group (R^2=0.72).

Conclusions: LA strain has different determinants depending on AF type. LA size, renal function, and AF duration determine LALS in long-lasting AF. LA strain is a simple and accurate technique to estimate LA dysfunction in patients with long-lasting AF.

Introduction

Atrial fibrillation (AF) is one of the most common cardiac arrhythmias in clinical practice. AF has a progressive nature, leading to structural, functional, and electrical changes in the left atrium. Previous studies have shown that AF begins as paroxysmal in nature, progresses over time, then becomes chronic as the end result [1]. This arrhythmia is characterized by disorganized atrial muscular activation without effective atrial contraction. During AF, the atrial pump function is lost due to asynchronous atrial contraction [2].

Cardiac imaging plays a critical role in the assessment of AF and helps to determine treatment options. Additionally, it helps to identify states that predispose to the development and progression of AF. Cardiac imaging enables early identification of left ventricular (LV) dysfunction or valvular heart disease [3]. It also complements the clinical evaluation, provides AF prognosis, and supports the decision-making process with regard to rhythm strategy (rate control or rhythm control). All of these features make echocardiography the most commonly used imaging technique in the evaluation of AF patients [3-4]. Development of new echocardiographic techniques, such as two-dimensional echocardiographic speckle tracking (STE), have improved the detailed assessment of myocardial properties. Global longitudinal strain, evaluated by STE, is a well-validated parameter used to quantify LV longitudinal function [5] in sinus rhythm and in AF [4, 6-7]. Recently, this technique has also been used in the assessment of regional and global left atrial (LA) function [8-10] with good reproducibility [11]. The latest European Association of Cardiovascular Imaging (EACVI)/ European Heart Rhythm Association (EHRA) Expert Consensus Document considers LA strain as a promising method which can be used for indirect measurement of atrial function in AF [6]. The EACVI/ American Society of Echocardiography and Industry Task Force have recently published a document which standardizes LA strain measurements [12].

LA strain measurement has prognostic implications in AF patients [13-14]. Widespread clinical adoption of this approach will require the definition of normal reference ranges in AF patients [15]. Recently, reference ranges for LA strain have been determined in healthy subjects [15-16].

Key Words

Atrial Fibrillation, Echocardiography, Left Atrial Strain, Left Atrial Function, Speckle-Tracking.

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To the best of our knowledge, there have been no reports on LA strain in different types of AF. The aim of this study was to analyze left atrial longitudinal strain (LALS) and estimate its determinants in patients with paroxysmal (PAF), persistent (PsAF), and permanent (PmAF) AF.

Material and Methods

Study patients

Fifty-eight consecutive patients with documented non-valvular AF, admitted to our department between January and July 2017, were enrolled in a prospective study. According to current practice guidelines, we divided patients into 3 groups depending of AF type. Patients with PAF had self-terminating AF episodes lasting up to 7 days. Those with episodes lasting longer than 7 days or requiring cardioversion for termination were in the PsAF group. PmAF was defined as AF which was chronic and accepted by the patient and physician [17].

Exclusion criteria were as follows: left ventricular ejection fraction (LVEF) <30%, severe valvular heart defect, prosthetic heart valves, unstable coronary artery disease (unstable angina pectoris or acute myocardial infarction within the last 30 days), uncontrolled hypertension (≥ 160/100mmHg), stroke (<3 months), recent thromboembolic event (<3 months), congenital heart disease, and chronic kidney disease of stage 4 or more.

We used a standardized questionnaire to collect patient demographic data and information about cardiovascular risk factors and current treatment [18]. The CHA_2DS_2-VASc score was used for evaluation of risk of stroke or systemic embolism [19]. Bleeding risk was estimated using the HAS-BLED score [17].

Standard echocardiographic evaluation

All patients underwent transthoracic echocardiography using a Philips EPIQ 7 ultrasound machine with synchronous electrocardiogram recording. The measurements were averaged from 3 consecutive cardiac cycles in AF patients while in sinus rhythm and from 5 consecutive cardiac cycles during AF.

LA anatomy was evaluated according to EACVI and EHRA guidelines [6,20-21]. We measured LA anteroposterior diameter (LA AP) using the parasternal long-axis window. LA length, width, area (LAA), and volume (LAV) were determined in the apical 4-chamber (A4C) and apical 2-chamber views. LAV was calculated using the biplane area-length method. Right atrial (RA) longitudinal and short-axis diameters, area, and volume were measured in the A4C view. Measurements were indexed to body surface area (BSA).

LVEF was measured using the biplane Simpson method. LV diastolic function was evaluated by E-velocity deceleration time (EDT), E-wave velocity, e'-velocity, and E/e' ratio. Tricuspid annular plane systolic excursion and peak systolic velocity of the tricuspid annulus were measured to assess right ventricular (RV) function.

Speckle tracking echocardiography

LA strain was measured using two-dimensional STE [12]. Care was taken to obtain true apical images. Five consecutive A4C cardiac cycles were stored with a frame rate of at least 60 frames per second in cine-loop format and then analyzed offline. LA endocardial border was manually traced in A4C, thus delineating a region of interest (ROI). After visually verifying the quality of tracking and eventual manual adjustment of the ROI, the software automatically calculated the average of 7 LA segments and generated time-longitudinal strain curves. Examples of the technique are shown in [Figure 1].

Intra-observer and inter-observer variability

Inter-observer variability for all measurements was studied in a group of 10 randomly selected subjects. Images were analyzed by 2 independent investigators who were unaware of each other's measurements. Inter-observer variability was determined by repeating the offline measurement of LALS in 10 patients 1 week apart. Variability values were calculated as the absolute difference between corresponding measurements in terms of mean percentage.

Statistical analysis

The study was powered to have an 80% chance of detecting a 40% difference in LALS between groups at p = 0.05, and was based on a previous study [22]. In order to demonstrate such a difference in LALS or greater, 12 patients were required in each group. Continuous variables were described as mean ± standard deviation or median and interquartile range as appropriate. The Shapiro-Wilk test was used to verify the normality of distribution. Homogeneity of variance was verified using Cochran's test. Means were compared by univariate analysis of variance followed by the Tukey-Kramer test, whereas medians were assessed by the Kruskal–Wallis test and test for multiple comparisons of mean rank. Categorical variables were presented as percentages and compared using the chi-square

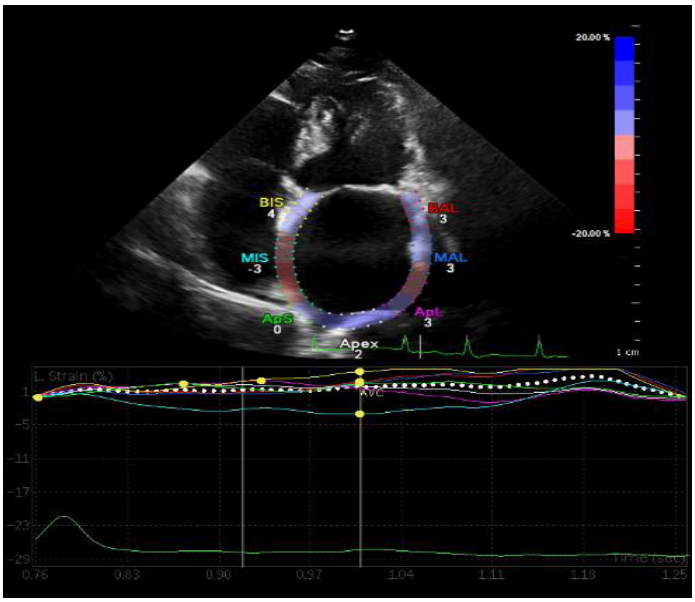

Figure 1: **Left atrial longitudinal strain curves.**

Two-dimensional strain by speckle tracking echocardiography demonstrating left atrial longitudinal strain curves and strain numeric values from the apical four-chamber view. A single cardiac cycle is tracked, the wall of the LA is divided into 7 segments (septal and lateral wall are divided into: basal, mid and apical segments, and apex) which are color coded. The dashed curve represents the average atrial longitudinal strain along the cardiac cycle. Abbreviations: AVC, aortic valve closure.

Table 1: General characteristics of the study population

	Paroxysmal AF n=16	Persistent AF n=14	Permanent AF n=28	p value
Demographics				
Age (years)	69.6 ± 9.4	66.9 ± 12.2	74.0 ± 8.0	0.07
Female sex, n (%)	13 (76.5)	5 (38.5)	14 (50.0)	0.07
BMI (kg/m2)	29.3 (27.7-32.4)	32.3 (28.9-35.3)	29.4 (26.8 – 35.0)	0.41
Systolic BP (mmHg)	122.4 ± 4.7	111.7 ± 6.1	120.4 ± 3.6	0.36
Diastolic BP (mmHg)	75 (60-80)	74 (70-80)	77 (70-80)	0.45
Heart rate (bpm)	63 (60-66)	72 (62-88)	77 (66-84)	0.003†
Comorbidities and CVD risk factors				
Hypertension, n (%)	15 (88.2)	9 (69.2)	26 (92.3)	0.15
Hypercholesterolemia, n (%)	16 (94.1)	11 (84.2)	27 (96.4)	0.42
Diabetes mellitus, n (%)	6 (35.6)	1 (7.8)	11 (39.3)	0.07
Previous myocardial infarction, n (%)	2 (11.8)	2 (15.4)	0 (0.0)	0.12
Heart failure, n (%)	2 (11.8)	6 (46.2)	12 (42.9)	0.06
Previous cerebrovascular events, n (%)	2 (11.8)	1 (7.8)	6 (21.4)	0.44
Chronic kidney disease, n (%)	0 (0.0)	0 (0.0)	4 (14.3)	0.10
AF duration (months)	13 (2-24)	4 (2-36)	23 (11-51)	0.52
CHA2DS2-VASc score	3.7 ± 1.9	2.8 ± 2.0	3.9 ± 1.5	0.15
HAS-BLED score	1.9 ± 0.7	1.6 ± 1.1	2.4 ± 0.8	0.03‡
VKA	3 (17.7)	0 (0.0)	8 (28.6)	0.09
NOAC	14 (82.3)	13 (92.3)	20 (71.4)	0.09
ACEI	8 (47.1)	4 (30.1)	19 (67.8)	0.07
Statin	13 (76.5)	10 (76.9)	23 (82.4)	0.87
Beta-blocker	17 (88.2)	12 (92.3)	22 (78.6)	0.46
Laboratory parameters				
Creatine (μM)	77.4 ± 16.2	95.9 ± 16.7	91.9 ± 19.8	0.01*
C-reactive protein (mg/L)	1.2 (0.8-1.8)	2.3 (0.8-3.6)	2.1 (1.1-4.1)	0.22
NT-proBNP (pg/L)	202 (127-277)	667 (638-981)	1259 (794-1960)	0.07

*p <0.05 paroxysmal vs. persistent AF; †p <0.05; paroxysmal vs. permanent AF; ‡ p <0.05 persistent vs. permanent
Data are presented as mean ± SD, median (quartile range), and number (percentage) unless otherwise stated.
Abbreviations: BMI, body mass index; BP, blood pressure; CVD, cardiovascular; VKA, vitamin K antagonists (warfarin, acenocoumarol); NOAC, non-vitamin K antagonist oral anticoagulants; ACEI, angiotensin-converting enzyme inhibitors; NT-proBNP, N-terminal pro–B-type natriuretic peptide.

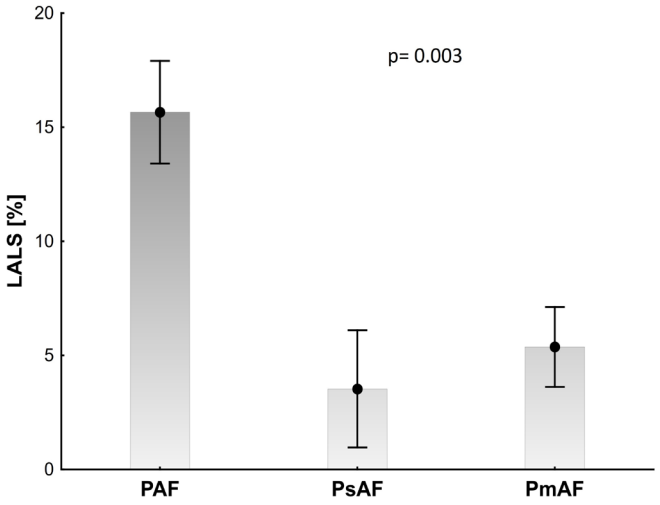

Figure 2: Left atrial longitudinal strain (LALS) in patients with paroxysmal (PAF), persistent (PsAF), and permanent (PmAF) atrial fibrillation are presented as mean values and standard error of mean, p < 0.05 for ANOVA.

test and Fisher's exact test. To assess linear dependence between variables, Pearson's correlation coefficient (for normal distribution) or Spearman's rank correlation coefficient (for non-normal distribution) were calculated. To identify independent predictors of LALS, all clinical and laboratory variables which associated with LALS in the univariate model ($P < 0.05$), but did not significantly correlate ($r \geq 0.5$) with another independent variable, were then included in the stepwise multiple linear regression analysis. P values less than 0.05 were considered statistically significant. Data were analyzed using STATISTICA version 13 (Statsoft Inc, Tulsa, OK).

Ethics approval and consent to participate

The study follows the principles of the Declaration of Helsinki. All study procedures involving human participants were performed in accordance with ethical standards of the institutional and national research committee. The study protocol was approved by the local ethics committee. Written informed consent was obtained from patients before enrollment.

Results

Patient characteristics

The study group was comprised of 58 patients with AF [Table 1], including 16 (27.6%) with PAF, 14 (24.1%) with PsAF, and 28 (48.3%) with PmAF. As shown in [Table 1], the prevalence of cardiovascular risk factors was high, across all AF groups. Most patients (n=49; 84.4%) were at high risk for stroke (CHA_2DS_2-VASc score ≥2). One patient (1.6%) had low stroke risk (score of 0).

Patients with PsAF had a higher HAS-BLED score when compared with PmAF patients. Patients with PmAF had higher mean heart rate, BSA-indexed LA volume, lower LVEF, EDT, and a trend toward higher E/septale e' when compared with PAF patients [Table 2].

Left atrial strain

Patients with PAF had higher LALS (15.7±12.0) when compared with PsAF and PmAF patients (4.3±7.9, 5.8±7.8, P=0.003) [Figure 2].

In the subgroup with PAF, LALS positively correlated with EDT (r=0.60, p=0.02) and E/lateral e' (r=0.73, p=0.02). In the PsAF group, LALS negatively correlated with creatinine (r=-0.58; p=0.02). In PmAF patients, LALS negatively correlated with CHA_2DS_2-VASc score (r=-0.47, p=0.01), HAS-BLED score (r=-0.55, p=0.002), E/lateral e' (r=-0.51, p=0.05), and positively correlated with lateral e' (r=0.59, p=0.01), LA width (r=0.40, p=0.04), and AF duration (r=0.89, p=0.02).

In the multiple linear regression model, independent predictors of LALS were as follows: diastolic blood pressure (β=0.95) in the PAF group (R^2=0.88); LAA (β=-0.56) and creatinine (β=-0.63) in the PsAF group (R^2=0.58); AF duration (β=0.89) in the PmAF group (R2=0.72) [Table 3].

In the entire AF group, LALS was predicted by LA AP/BSA (β=-0.39) and creatinine (β=-0.35 (R^2=0.27) [Figure 3].

Discussion

Our study shows that LALS depends on the type of AF, with the lowest values observed in PsAF and PmAF. Depending on AF type, LALS has various levels of association with kidney function, hypertension, and arrhythmia duration.

Decreased LALS values in patients with PsAF and PmAF may reflect progressive LA remodeling and dysfunction, not observed in the beginning of the disease, as is seen in PAF patients. Another finding of our study is an association of LA strain with impaired renal function. LA enlargement (including LAV and LA AP) is frequently observed in patients with chronic kidney disease linked to persistent pressure and volume overload [23]. Therefore, we believe that LALS may reflect chronic exposure to hemodynamic overload in patients with kidney disease. Atrial enlargement is an important marker of LA structural remodeling and a predictor of AF recurrence [24]. Previous prospective studies have shown a strong relationship between LA AP and the risk of new-onset AF [24]. In the Framingham study, a 5-mm increase in LA AP was associated with a 39% higher risk of AF [24-25]. In the Cardiovascular Health Study, subjects in sinus rhythm with LA AP >50 mm had approximately 4 times higher risk of AF [24,26].

LALS may help in the early detection of atrial dysfunction and remodeling and predict AF progression [27] which may lead to new therapies focusing on patients with "early" forms of AF. Atrial remodeling progresses with collagen deposition in the interstitium, with consequent alterations in conduction. Hirose et al. showed that in adults without a history of atrial arrhythmia, a reduction in LA pump function is associated with structural remodeling and initiation of AF development [27-28]. Impaired LA strain indicates reduced LA

Table 2: Echocardiographic characteristics of patients

	Whole group n=58	Paroxysmal AF n=16	Persistent AF n=14	Permanent AF n=28	p value
LVEF (%)	56 (50-60)	60 (60-65)	55 (45-62)	55 (50-60)	0.01 †
LAVI (ml/m²)	47.5 (35.7-53.8)	35.5 (34.1-36.7)	47.7 (43.1-53.4)	51.4 (44.1-55.4)	0.003 †
LA enlargement, n (%)	45 (76.2)	11 (78.6)	9 (81.8)	25 (92.6)	0.39
MAPSE (mm)	12 (9.7-16)	16 (11-10)	8 (10-13)	10 (12-14)	0.09
EDT (ms)	178 (148-232)	232 (176-246)	208 (148-229)	150 (144-180)	0.02 †
E (cm/s)	90.2 ± 23.2	77.4 ± 5.6	100.6 ± 6.5	94.4 ± 4.7	0.02 *
Septal e'(cm/s)	8.4 ± 3.0	7.7 ±0.8	8.5 ± 1.0	9.1 ± 0.7	0.45
Lateral e'(cm/s)	11.5 ± 3.8	10.4 ± 1.0	10.5 ± 1.1	12.9 ± 0.9	0.10
E/septal e'	11.9 (8.3-13.3)	8.1 (7.6-11.8)	13.2 (10.6-14.1)	12.0 (9.0-13.3)	0.07
E/lateral e'	9.3 (5.7-10.2)	8.0 (5.7-10.1)	10.2 (7.0-12.0)	8.9 (5.6-9.9)	0.09
E/mean e'	10.3 ± 3.6	9.7 ± 3.5	12.2 ± 4.6	9.7 ± 2.8	0.16
RV S' (cm/s)	12.1 ± 3.2	13.3 ± 1.0	12.1 ± 1.0	11.4 ±0.8	0.34
TAPSE (mm)	20 (17-24)	23 (20-30)	20 (17-25)	18 (17-22)	0.24

*p <0.05 paroxysmal vs. persistent AF; †p <0.05; paroxysmal vs. permanent AF; ‡ p <0.05 persistent vs. permanent
Data are presented as mean ± SD, median (quartile range), and number (percentage) unless otherwise stated.
Abbreviations: LAVI, left atrial volume indexed to Body Surface Area; LA enlargement, LAVI >34 ml/m2; LVEF, left ventricular ejection fraction; MAPSE, mitral annular plane systolic excursion; EDT, E-wave deceleration time; E, peak velocity of early filling; Septal e', peak early diastolic septal mitral annular velocity by pulsed tissue Doppler; Lateral e', peak early diastolic lateral mitral annular velocity; Mean e', mean mitral annular peak early diastolic velocity; RV S', peak systolic velocity of the tricuspid annulus; TAPSE, tricuspid annular plane systolic excursion.

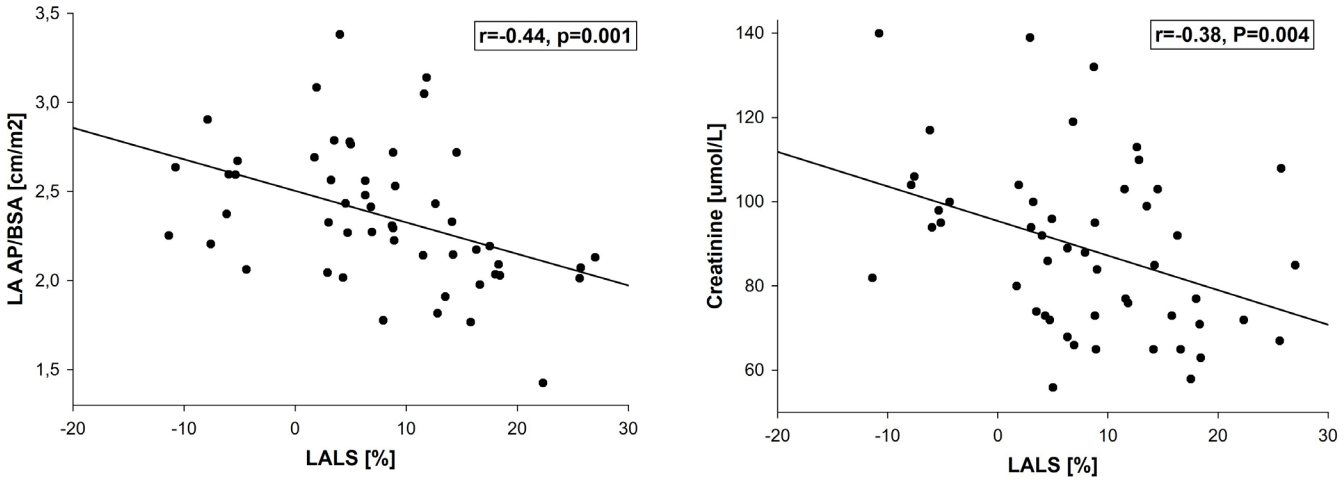

Figure 3: Correlation of left atrial longitudinal strain (LALS) with left atrial anteroposterior diameter - body surface area index (LA AP/BSA) (Panel A) and creatinine (Panel B).

Table 3: Multiple regression analysis of predictors of LA strain.

Variables	AF		Paroxysmal AF n=16		Persistent AF n=14		Permanent AF n=27	
	β (CI 95%)	P	β (CI 95%)	P	β (CI 95%)	P	β (CI 95%)	P
AF duration (months)							0.89 (0.24-1.52)	0.02
LA AP/BSA (cm/m²)	-0.39 (-0.14, - 0.63)	0.003						
LAA (cm²)					-0.56 (-0.16; -0.95)	0.01		
Creatinine (μM)	-0.35 (-0.10, - 0.60)	0.008			-0.63 (-0.24; -1.03)	0.005		
Diastolic BP (mmHg)			0.95 (0.67-1.23)	<0.001				

Abbreviations: LA AP, the anteroposterior diameter, parasternal long-axis window; BSA, Body Surface Area; LAA, left atrial area: average of measurements in the apical 4-chamber view and the apical 2-chamber view.

compliance and impaired reservoir function [4]. LA strain is associated with LA fibrosis, as measured by the degree of delayed-enhancement in cardiac MRI [22, 29].

We report that duration of arrhythmia is an independent predictor of LA strain in PmAF patients. The presented data indicates a relationship between AF duration, interstitial atrial remodeling, and LA mechanical dysfunction [27]. Severely impaired LA strain may reflect more advanced LA remodeling [10, 30] and predict treatment results. In a study by Tops et al., 63% of participants presented with LA reverse remodeling after catheter ablation (CA) of AF with an accompanying improvement in LA strain [30]. LA strain at baseline was an independent predictor of LA reverse remodeling. Additionally, Parwani et al. demonstrated that LA strain measurement in patients with PsAF may be useful in the selection of patients who are unlikely to benefit from CA [31]. Patients with low LA strain (<10%) had significantly worse results in the long-term follow-up [31]. In AF patients undergoing electrical cardioversion (ECV), LA strain was an independent predictor of restoration and maintenance of sinus rhythm [4, 32].

Consistent with other studies, we observed a negative correlation between thromboembolic risk (assessed by CHA_2DS_2-VASc score) and LALS in PmAF patients. Cameli at al. demonstrated a correlation between reduced LALS, reduced LA emptying velocity, and/or thrombus in patients with PsAF before ECV/CA [33]. Zhu et al. suggested that decreased LA strain in the reservoir phase may become a useful tool for predicting LA appendage stasis in patients with AF [34].

The present study has several limitations. First, size of the investigated groups was limited. However, the number of subjects was sufficient to detect differences between groups based on results of the power calculation. Second, the lack of dedicated, well-established software for acquisition of LA strain meant that we needed to use software designed for LV assessment. Lastly, measurements in the PAF group were made while patients were in sinus rhythm. We cannot completely rule out the impact of sinus rhythm on our results. LALS measurement may facilitate appropriate management strategies in the AF subgroups through improved assessment of LA function, evaluation of LA changes in the course of arrhythmia, and

prediction of sinus rhythm return. Our findings should be considered as hypothesis-generating and further confirmation of results in larger prospective investigations is needed.

Acknowledgments

The study was supported by a research fund from the Jagiellonian University Medical College. The authors report no conflicts of interest.

Conclusion

LALS reflect different levels of LA dysfunction in patients with paroxysmal, persistent, and permanent AF. LA size, renal function, AF duration, and hypertension determine LALS. LA strain assessment in PAF, PsAF, and PmAF may be essential for future research and clinical applications.

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Complete AV Block Induced by Right Coronary Artery Spasm Following Radiofrequency Ablation for Atrial Fibrillation

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Abstract

Coronary artery spasm during catheter ablation for arrhythmias is a rare but previously reported complication. Timing of presentation, manifestations of vasospasm, and purported mechanisms vary somewhat in the prior literature. We present a case of chest pain, inferior lead ST elevation, and complete AV block with angiographically confirmed right coronary artery (RCA) vasospasm that occurred immediately after catheter ablation for atrial fibrillation.

Introduction

Catheter ablation for various arrhythmias may cause transient changes in autonomic tone. This may include acute changes in heart rate and/or blood pressure. We present a case of angiographically confirmed coronary vasospasm manifesting with inferior ST elevation, chest pain, and complete AV block developing immediately after radiofrequency (RF) ablation for atrial fibrillation. This phenomenon may represent a unique presentation of ablation related autonomic modulation.

Case Report

A 56-year-old male with a history of symptomatic persistent atrial fibrillation (AF) and likely tachycardia-induced cardiomyopathy status post implantable cardioverter defibrillator (ICD) was admitted for AF ablation. The patient had documented left ventricular (LV) dysfunction since 2013 with initial left ventricular ejection fraction (LVEF) of 20-25%. Over time, with medical therapy the LVEF improved to 45-49% prior to ablation in 2018. Cardiac dimensions prior to ablation included LVEDD of 5.5 cm with volume of 137mL, LVESD 3.6 cm with volume of 74mL and LA volume index of 34mL/m2. The patient had no prior clinical history of Prinzmetal angina. The ablation strategy employed included pulmonary vein isolation with LA roof line with further posterior wall isolation. Radiofrequency ablation was performed with power ranging from 20-30W. There were no hemodynamic derangements as well as no periods of ablation related bradycardia during the procedure. Furthermore, no ablation was performed within the right atrium or SVC.

Key Words

Coronary Artery Spasm, AV Block, Atrial Fibrillation Ablation

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In the recovery unit, the patient complained of retrosternal chest pain that radiated to the jaw with associated hypotension. ECG demonstrated ST elevations in the inferior leads and third degree AV block with junctional escape rhythm [Figure 1]. Complete resolution of ECG abnormalities and normalization of vital signs was evident after atropine injection and after initiation of dopamine infusion [Figure 2]. Normal wall motion and preserved LV function without evidence of pericardial effusion was confirmed by echocardiogram.

Urgent coronary angiography was performed which showed normal coronaries. There was no evidence of an acute obstructive lesion or thrombus. During the procedure, the patient once again developed chest pain and complete heart block with demonstration of severe vasospasm of the proximal RCA [Figure 3-4]. This resolved after multiple doses of intracoronary nitroglycerin and nicardipine. These findings were suggestive of vasospastic angina and patient was started on verapamil with no further episodes of heart block or ST changes. The patient has remained in sinus rhythm at 6 months post ablation without any clinical events related to coronary spasm.

Discussion

Apparent coronary ischemia during and following ablation has been attributed to several different mechanisms including air embolism [1], local catheter effects, and coronary vasospasm [2]. Coronary vasospasm has been noted both in those with traditional risk factors for vasospastic angina, i.e. tobacco use, in addition to those with no history of coronary vasospasm [3]. Given ablation and/or modification of left atrial ganglia during AF ablation, it has been proposed that a vagal mediated parasympathetic imbalance induced by ablation near ganglionated plexi surrounding the left atrium also may play a role in the vasospasm seen during ablation procedures [4], which may be exacerbated by anesthesia [5]. Aside from left atrial ablation lesions, prior reports describe similar responses (ST elevation, bradycardia, hypotension) during trans-septal puncture, possibly due to interatrial

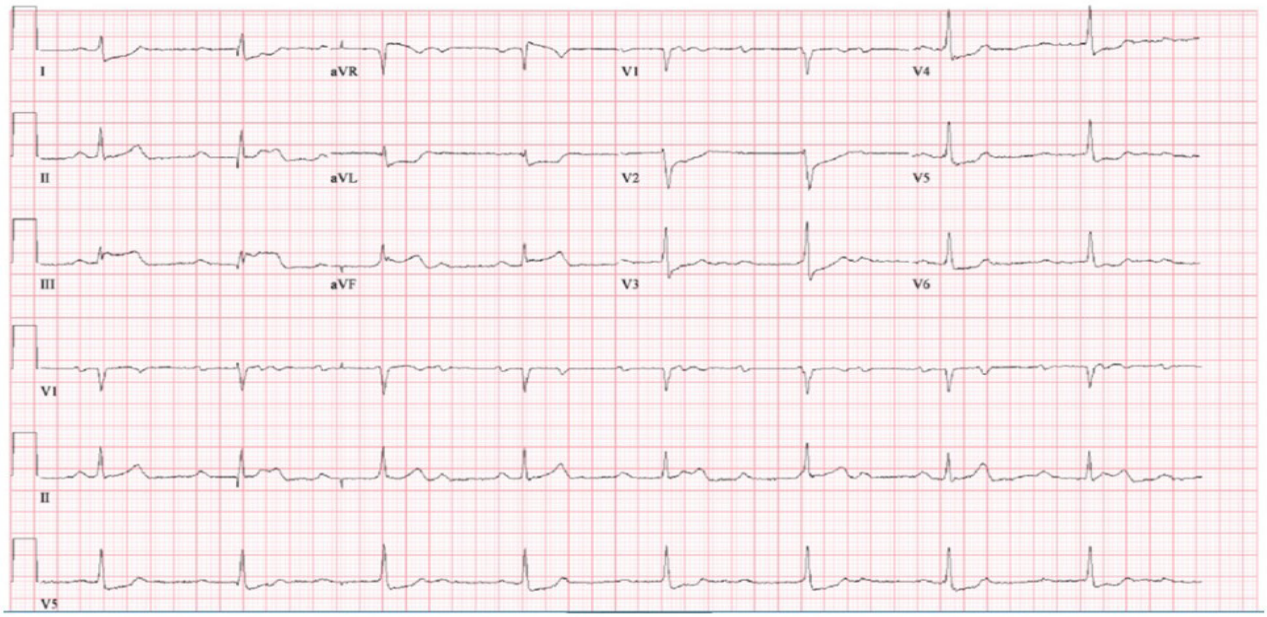

Figure 1: ST segment elevation in inferior leads and complete heart block with junctional escape rhythm

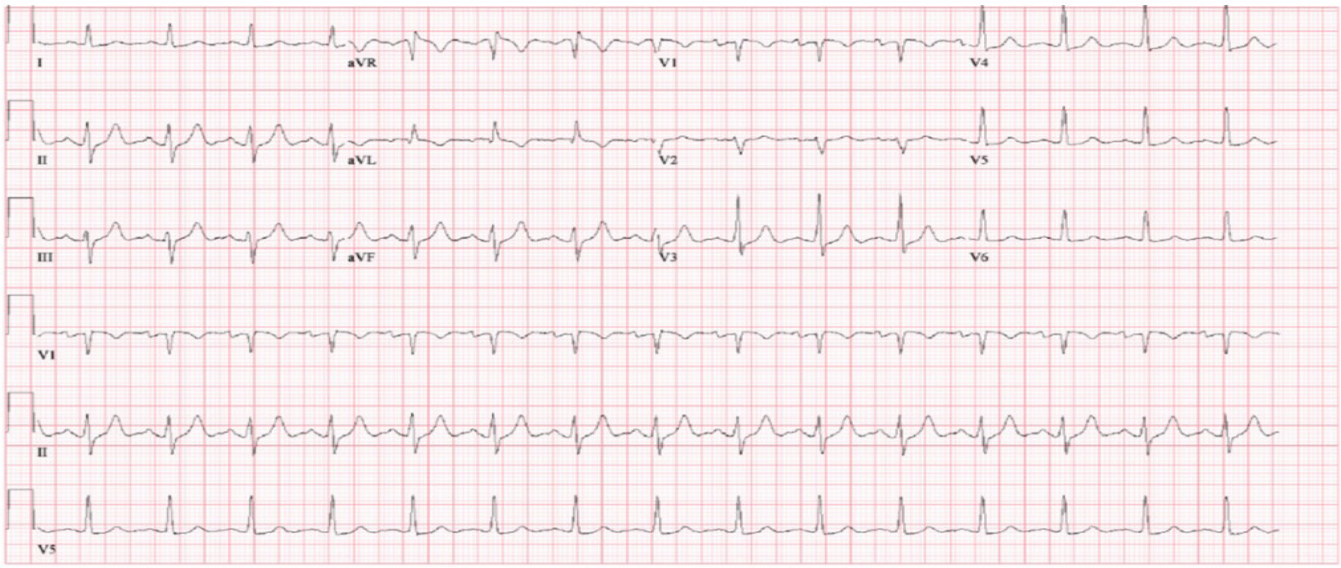

Figure 2: Resolution of ECG abnormalities after atropine injection and dopamine infusion

vagal network stimulation [6,7].

As to why this occurs, Kawakmi, et al. found that AF patients seem to have higher rates of drug provoked coronary spasm, implying baseline autonomic differences in AF patients. Spasm in our case was limited to the RCA, which has been suggested to be more susceptible to vagally mediated vasospasm than the left coronary system [8]. Signs and symptoms in prior reported cases have varied from transient with normal angiography [9] to cardiac arrest requiring cardiopulmonary resuscitation [10]. Complete heart block, as seen in our circumstances, has also been reported [5,6]. Additionally, the timing of onset appears to vary. Most cases in the literature have noted symptoms during the actual procedure, but symptoms in the post-operative period as in our case have been reported as well [9,11]. Most cases show good response with nitrates as was also seen in the presented case [12]. Of the cases evaluated in our literature search, no death or persistent morbidity were noted, although symptoms of frank syncope/aborted sudden death or new onset AV block may warrant evaluation for coronary spasm.

Aside from coronary spasm occurring after ablation at a distant site, multiple prior reports have described direct coronary spasm/

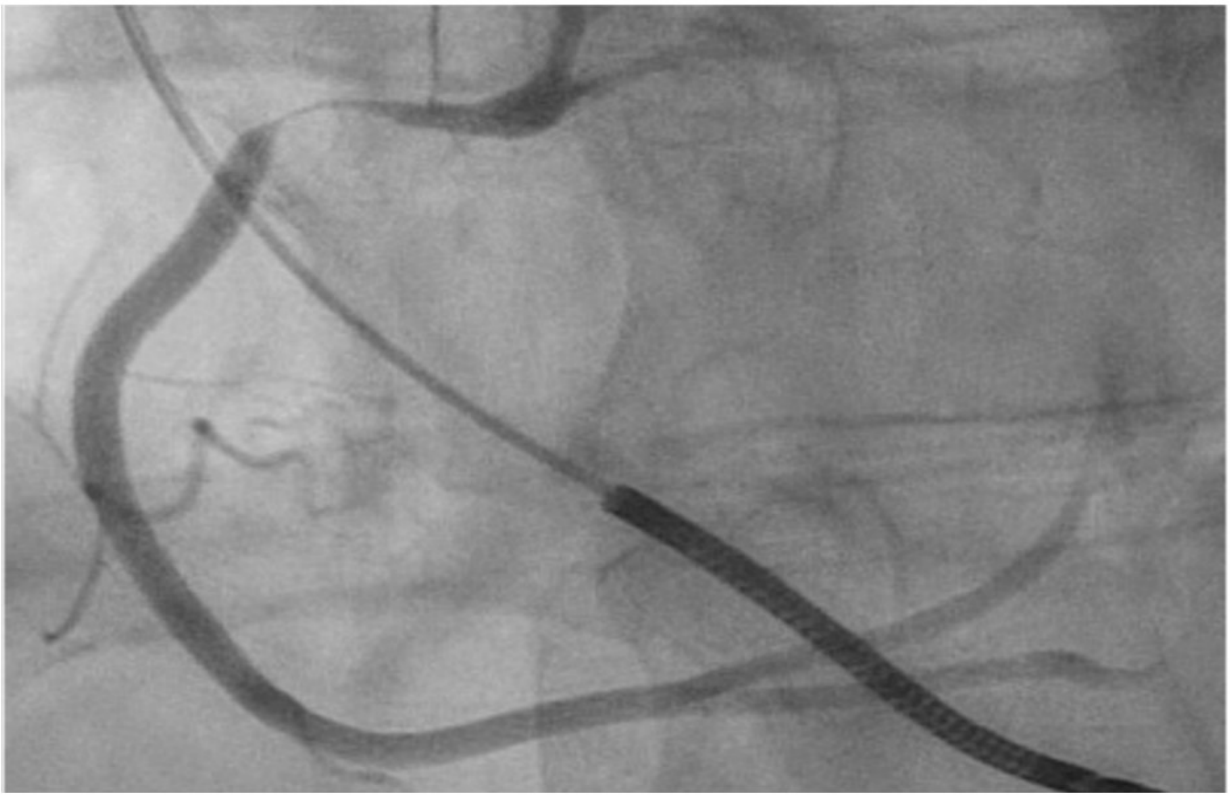

Figure 3: Severe spasm of proximal RCA

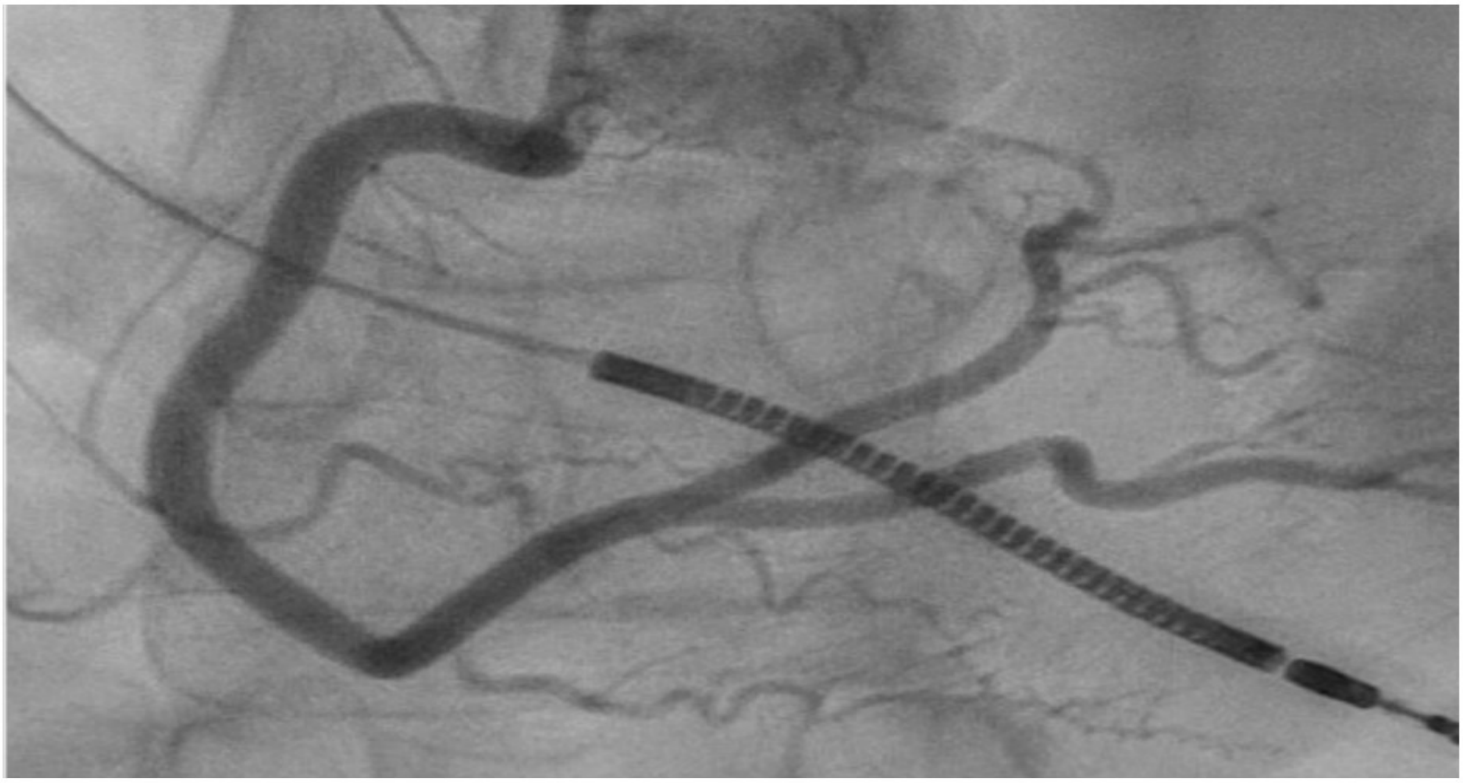

Figure 4: LAO image of proximal RCA after intracoronary nitroglycerin and nicardipine

injury from direct local catheter ablation. This includes RCA injury during cavotricuspid isthmus ablation for typical RA flutter and posterior descending artery injury during posteroseptal accessory pathway ablation and circumflex artery injury during LAA isolation. Given the sites of ablation and site of coronary spasm in the patient presented, a local ablation effect did not seem to apply.

Conclusion

Here, we present a case of inferior ST elevation and complete heart block presenting immediately following AF ablation due to right coronary artery spasm. This is a rare and potentially under-recognized complication of AF ablation and should be considered in patients post ablation with new onset AV block, ST elevation ECG pattern and/or unexplained syncope.

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Transient Left Atrial Appendage Inversion During Transcatheter Closure Device Placement

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Abstract

A 72-year-old female patient underwent left atrial appendage closure. During recapture of the occlusion device, transient inversion of the appendageal wall occurred. We describe the mechanism with real-time imaging and share our experience of handling this situation. To the best of our knowledge, this is the first case report of this unique recapture complication.

Introduction

Left atrial appendage (LAA) closure is a feasible alternative to patients with non-valvular atrial fibrillation at increased risk of ischemic stroke. Although the procedure is generally considered safe, complications still can occur. We report the first case of transient LAA inversion during transcatheter LAA closure device placement.

Case Presentation

A 72-year-old female with past medical history including persistent atrial fibrillation and essential hypertension was referred for LAA closure. She never underwent any cardiac surgery. She had been on anticoagulation with warfarin for increased risk of cerebrovascular accidents (CHA_2DS_2-VASc score of 3); However, she had previous massive gastrointestinal bleeding from underlying ulcerative colitis and esophagoduodenoscopy revealed a non-bleeding gastric ulcer. Ultimately, she was deemed a candidate for LAA closure. A standard procedure protocol was followed. Transesophageal echocardiogram (TEE) was used throughout the procedure. Multiplane images and measurements of the LAA were obtained [Figure 1A]. There was no evidence of thrombi or spontaneous echo contrast ("smoke") inside the LAA. Following the preliminary images, right femoral venous access was obtained and transseptal puncture was performed. A 14-F delivery sheath (Watchman Double Curve) was then advanced into the left atrium. Through the double curve sheath, a pigtail catheter was then used to engage the LAA and allow for safe advancement of the sheath. After the Watchman closure device was deployed, positioning and compression were verified using TEE and fluoroscopy ([Figure 1B]; Videos 1-3, available online). The position of the device was deemed too proximal to the intended landing zone and compression of the device was less than 10%.

During an attempt at full recapture of the device through the sheath, inversion of the LAA was noticed on TEE and the device failed to retreat into the sheath [Figure 2A]. The distal aspect of the inverted LAA attached to the anchors of the device and appeared as a finger-like heteroechogenic projection pointing towards the endovascular space of the left atrium ([Figure 2B]; Video 4, available online). There was no significant change in the patient's hemodynamic status or evidence of pericardial effusion on TEE.

Entrapment of the device and inversion of the appendage resolved after a few series of partial deployment and recapture along with minimal gentle clockwise and counterclockwise rotation ([Figure 3A], Video 5, available online). The retrieved device showed no apparent signs of damage or malfunction. A new Watchman device of the same size was then deployed and released after proper position, anchor, compression and seal were confirmed ([Figure 3B-3E]; Videos 6-8, available online). Postoperatively, anticoagulation with warfarin was resumed. A repeat TEE 6 weeks later showed the Watchman device in place with adequate seal and no peri-device leak. Warfarin was then stopped and aspirin 81 mg daily was started. After 1 year follow up, the patient was doing well and had no symptoms of cerebrovascular accident (CVA).

Discussion

LAA closure has been shown as an effective alternative to anticoagulation to help reduce stroke risk in patients with atrial fibrillation.[1, 2] The procedure is generally considered safe and carries low rates of complications including pericardial effusion, air embolism, thrombus formation during device implantation, and device embolization.[3] Left atrial appendage inversion during this procedure has never been reported. Partial or full recapture might be needed to attain appropriate positioning of the device. It is done by advancing the sheath over the deployed device with constant traction.

Key Words

Left atrial appendage inversion, Transcatheter closure, Atrial fibrillation

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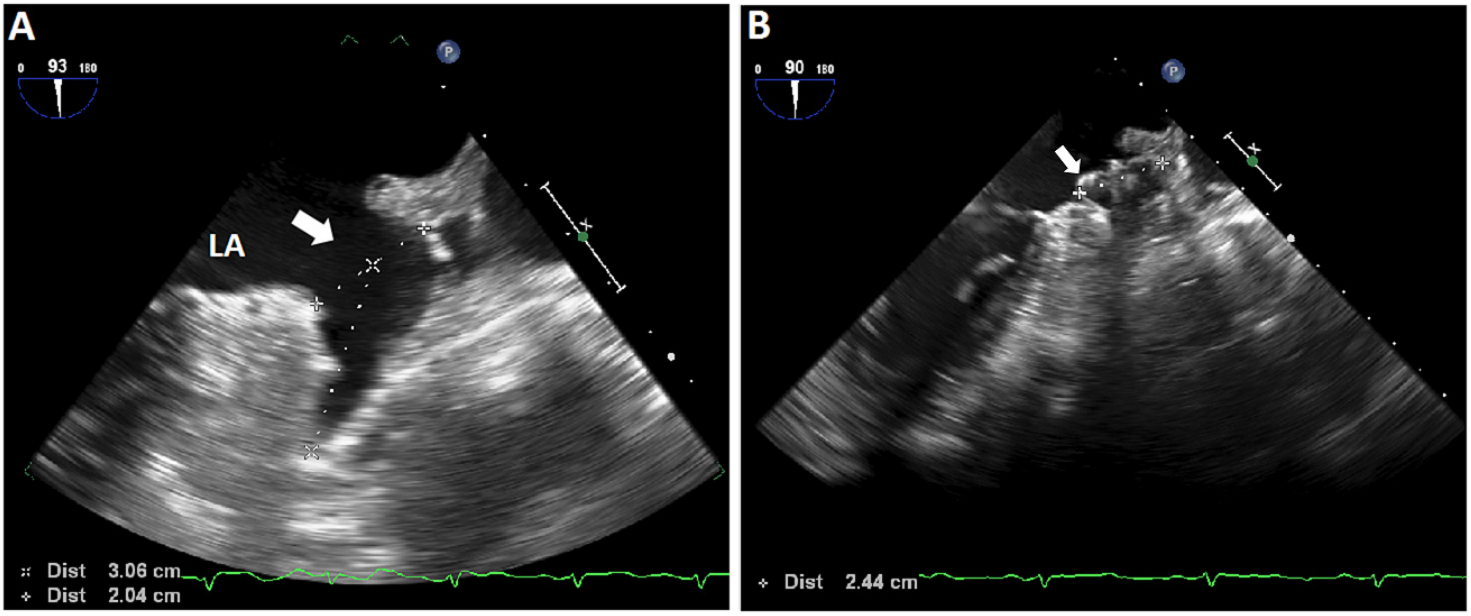

Figure 1: LAA closure using Watchman device. A: Intraprocedural TEE imaging and measurement of the LAA at baseline. There is no evidence of sludge, thrombus or spontaneous contrast. B: The deployed Watchman device (arrow) measuring 2.44 cm in diameter (9.6% compression).

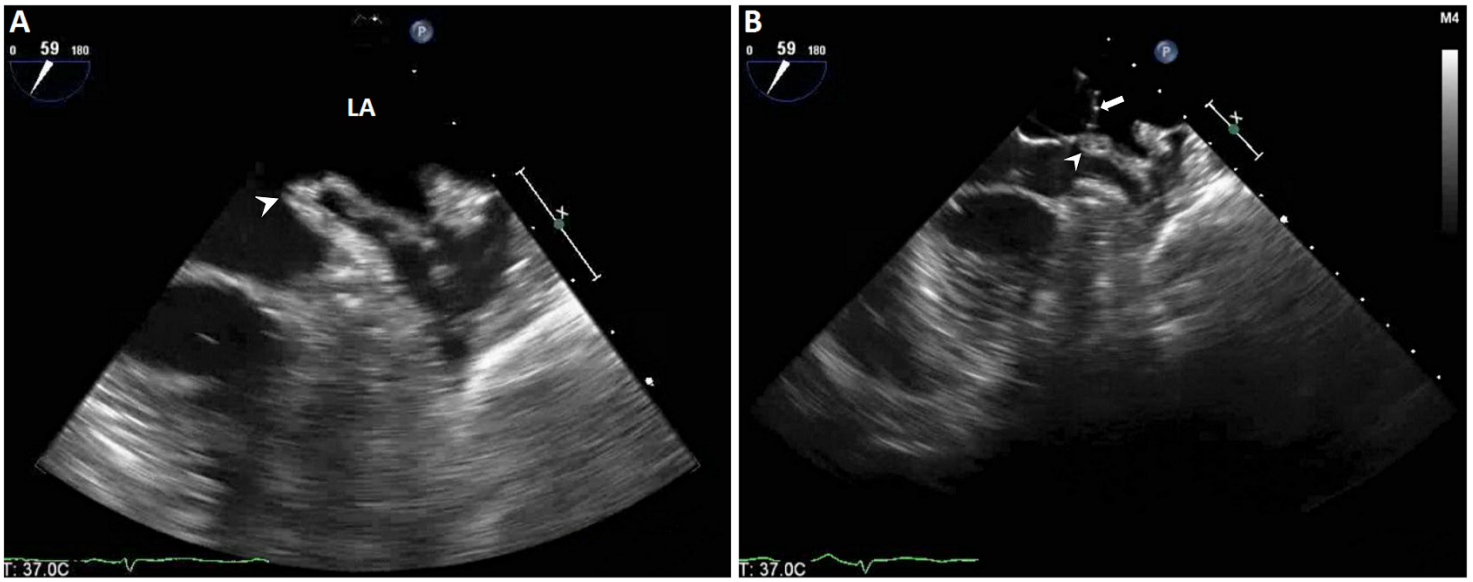

Figure 2: Intraprocedural TEE imaging during recapture of the deployed Watchman device. A: A finger-like projection (arrow head) captured extending into the LA and represents LAA inversion. B: The Watchman device pedicles (arrow) fixated to the inverted LAA wall (arrow head). LA = left atrium.

During this process, the LAA luminal surface can potentially remain attached to the anchors and lead to inversion. Inversion of the LAA is generally rare. It has been reported in the majority of the cases following cardiac surgeries, mainly after corrective procedures of congenital cardiac anomalies.[4-9] Rarely, LAA inversion is found without preceding history of cardiac surgery.[10-15] Inverted LAA is often discovered incidentally on postoperative echocardiograms where it appears as left atrial elongated, pyramidal structure and frequently leads to further imaging investigation or surgical exploration.

The unexpected presence often leads to the suspicion of thrombus formation, vegetation growth, tumors, or even foreign bodies. Understanding of the LAA anatomy and comparison with prior echocardiograms can greatly help identify this condition. In our case, the continuous TEE monitoring during recapture highlights a potential hidden complication of recapture, namely atrial appendage inversion secondary to the Watchman pedicle entrapment of endocardial tissue and possible appendage tear with continued sheath advancement.

Operators need to be aware of potential complications during recapturing appendage occlusion devices. Such complications can include appendage tear and acute obstruction of the mitral annular

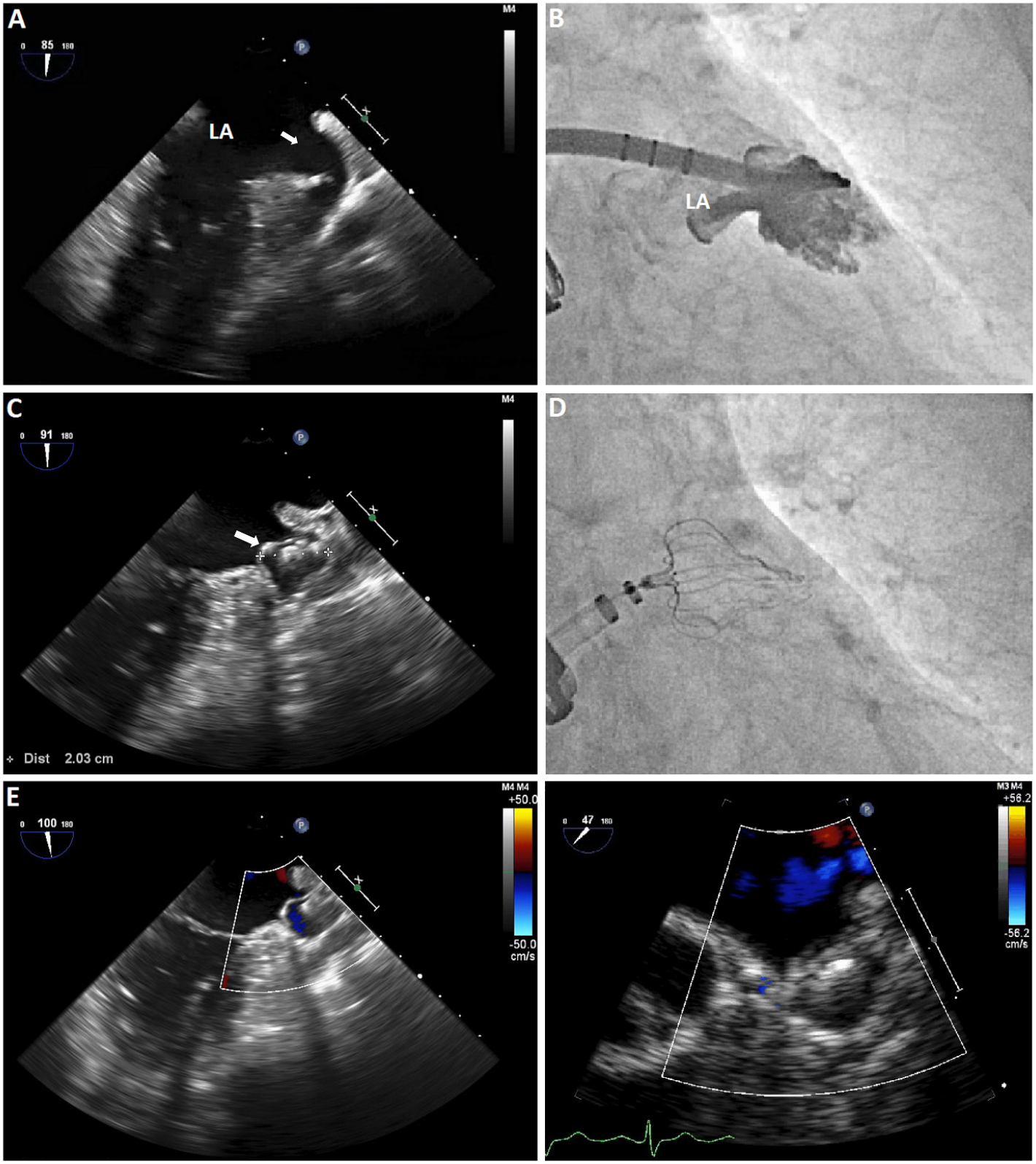

Figure 3: Closure of the LAA with new Watchman device. A: TEE image of the LAA (arrow) after full device recapture and resolution of the inversion. B: Fluoroscopic appendogram revealing no contrast leakage ruling out perforation of the LAA wall. C: New Watchman device deployed and adequately seated in the LAA with a diameter of 20.3 mm (24.8% compression). D: Fluoroscopic image of the new Watchman device with adequate position and compression. E: Doppler TEE revealed adequate seal with no flow around or across the closure device. F: Six-week follow up TEE shows maintenance of adequate seal and no residual peri-device shunt.

inflow tract with hemodynamic compromise. We emphasize on the importance of careful balance between sheath advancement and traction on the device with continuous monitoring on TEE to detect possible inversion as soon as it develops.

Acknowledgments

None.

Funding Sources

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conclusion

Inverted LAA may result during LAA closure device position adjustment. The appearance of an intraatrial projection on TEE is very suggestive. Attention is needed to prevent further complications from the inverted LAA.

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The Choice of Antithrombotic Therapy in a Patient with New-Onset Atrial Fibrillation and High Coronary Thrombotic Risk.

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Abstract

Current guidelines are mandatory in the choice of anticoagulant and/or antiplatelet therapy in patients with atrial fibrillation undergoing percutaneous transluminal coronary angioplasty and in patients with coronary artery disease and previous percutaneous transluminal coronary angioplasty that develop atrial fibrillation. However, in the real world there are crossroads with multiple choices, especially taking into account patient's peculiar characteristics and risk factors, which sometimes are not well represented in the guidelines.

The reported clinical case focuses on the choice of anticoagulation therapy in a patient with chronic and severe coronary artery disease and new diagnosis of atrial fibrillation who,considering his specifically high coronary thrombotic risk, probably should continue antiplatelet therapy.

Case Report

A 51 years old man with a severe coronary artery disease was admitted to emergency department (ED) with a history of 3-days of palpitation and dyspnoea and a new onset of chest pain.

The patient was smoker and was affected by symptomatic heart failure with mid-range ejection fraction (45%) and NYHA class II-III, type 2 diabetes, dyslipidaemia and hypertension.He had normal renal and hepatic function and had no history of clinically relevant bleeding.

One year earlier, in a different hospital, the patient underwent coronary artery bypass graft with left internal mammary artery (LIMA) graft for intermediate coronary artery (ICA),great saphenous vein (GSV) for left descending coronary artery (LDCA) and GSV for posterior descending coronary artery (PDCA) [Figure 1A]. During hospitalization,due to recurrent angina, the patient underwent coronary angiography and percutaneous transluminal coronary intervention (PCI) with stent placement in left main coronary artery (LMCA) [Figure 1B]. At discharge, an echocardiography showed heart failure with midrange ejection fraction of 40-45% and akinesia of septum and apex.

Six months after discharge, due to recurrent low threshold angina (Canadian Cardiovascular Society Angina Grade = III-IV), an additional coronary angiography was performed and showed:LMCA completely occluded by in-stent restenosis; LDCA and circumflex coronary artery were not viewable from anterograde flow; the right coronary artery (RCA) was severely atheromatous with diffuse plaques and critical stenosis in the middle and distal pre-crux tract; GVS for RCA was patent and functional as well as GVS for septal LDCA, although the downstream vessel appeared thin and widely atheromatous swith sub-critical stenosis; diagonal LDCA filled up with flow coming from collateral vessels of septal LDCA; the LIMA for ICA was hypoplastic with markedly reduced flow and the downstream vessel was thin and diffusely atheromatous [Figure 1C]. No additional PCI was performed; on the other hand, medical therapy was optimized.

Thus, the patient was on dual antiplatelet therapy (DAPT) with ticagrelor 90 mg bid and aspirin; bisoprolol 2,5 mg/day, ranolazine 500 mg bid, zofenopril 7,5 mg/day, furosemide 25 mg/day, pantoprazole 20 mg/day, atorvastatin 40 mg/day and metformin 500 mg tid. At the admission to ED, the electrocardiogram (ECG) showed atrial fibrillation with mean heart rate of 120 bpm [Figure 2] and diffuses but non specific alterations of ST segment and T wave. Since the symptoms had been starting 3 days earlier, the first therapeutic strategy was heart rate control in order to target amean heart rate < 110 bpm.

In order to set up a strategy for the prevention of cardioembolic stroke in atrial fibrillation, CHA_2DS_2-VASc was calculated and resulted 4 (1 congestive heart failure, hypertension, diabetes and vascular disease each) with an estimated annual stroke risk of 5,9%. The HASBLED score was 1.

Key Words

Atrial Fibrillation, Oral Anticoagulant, Antiplatelet Therapy, Coronary Artery Disease, Percutaneous Transluminal Coronary Angioplasty, Guidelines.

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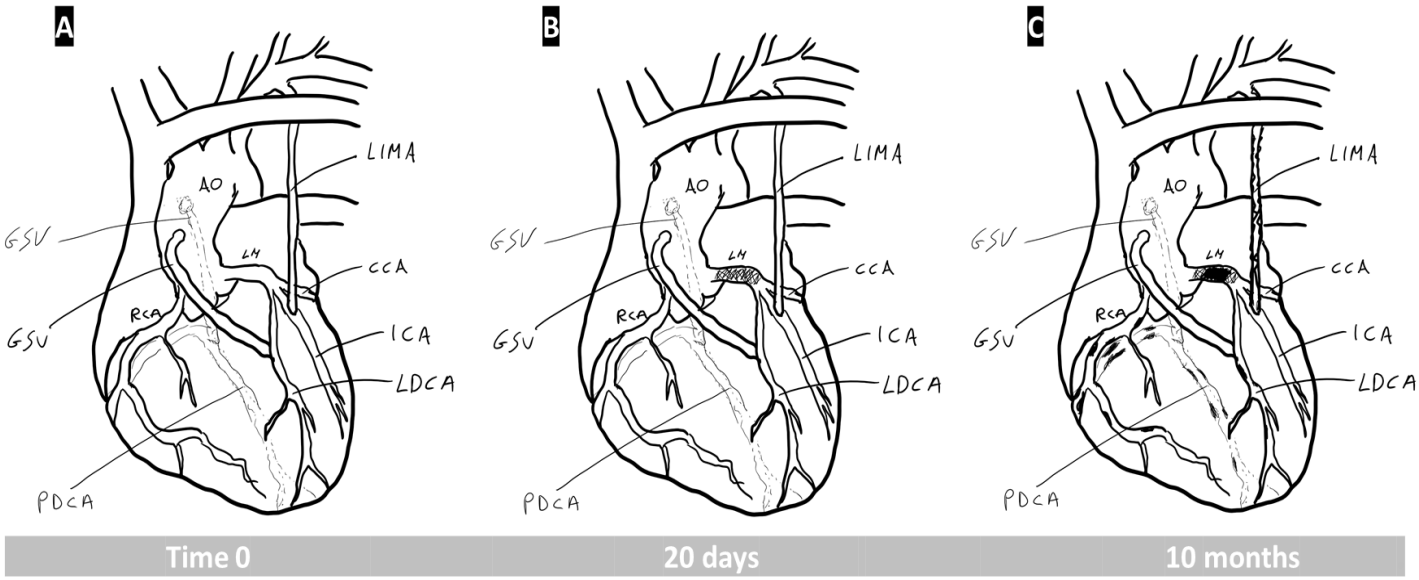

Figure 1: **Schematic representation of coronary anatomy and intervention during the time (time 0 refers to time of surgery). A: undergone coronary artery bypass graft with left internal mammary artery (LIMA) graft for intermediate coronary artery (ICA), great saphenous vein (GSV) for left descending coronary artery (LDCA) and GSV for posterior descending coronary artery (PDCA); B: stenting of left main coronary artery (LMCA) C: LMCA completely occluded by instent restenosis; LDCA and circumflex coronary artery were not viewable from anterograde flow; the right coronary artery (RCA) was severely atheromatous in the middle and distal pre-crux tract; GVS for RCA was patent and functional as well as GVS for septal LDCA, although the downstream vessel appeared thin and widely atheromatous with sub-critical stenosis; diagonal LDCA filled up with flow coming from collateral vessels of septal LDCA; the LIMA for ICA was hypoplastic with markedly reduced flow and the downstream vessel was thin and diffusely atheromatous**

Discussion

According to CHA_2DS_2-VASc score, the anticoagulant therapy was mandatory. However, considering the progressive worsening of CAD, the choice whether to maintain or not DAPT represented a therapeutic challenge.

The opportunity of long term DAPT was determinate from DAPT score (www.daptstudy.org) and PRECISE-DAPT 5-item bleeding risk score (age, creatinine clearance, Hemoglobin, white blood cell count, and prior spontaneous bleeding) is used for the prediction of out-of-hospital bleeding hazard as a complementary tool to the DAPT score (Capodanno D, 2018) (Costa F & Inves, 2017).DAPT score indicates the opportunity of long term DAPT (30 months) in case of a score ≥ 2 (Marco Valgimigli, 2018). In the present case, the DAPT score was 3 (smoking, diabetes, prior PCI), suggesting the need of long term DAPT. Nevertheless, the DAPT score does not take into account additional potential risk factors for ischemic coronary events suchinstent re-stenosis or site of stenting (left main) or the rapid progression of CAD, all conditions found in the present case.

In the current guidelines on DAPT, for patients with an indication for oral anticoagulation (OA) undergoing PCI there are only class IIaB or IIaA recommendations. While these recommendations

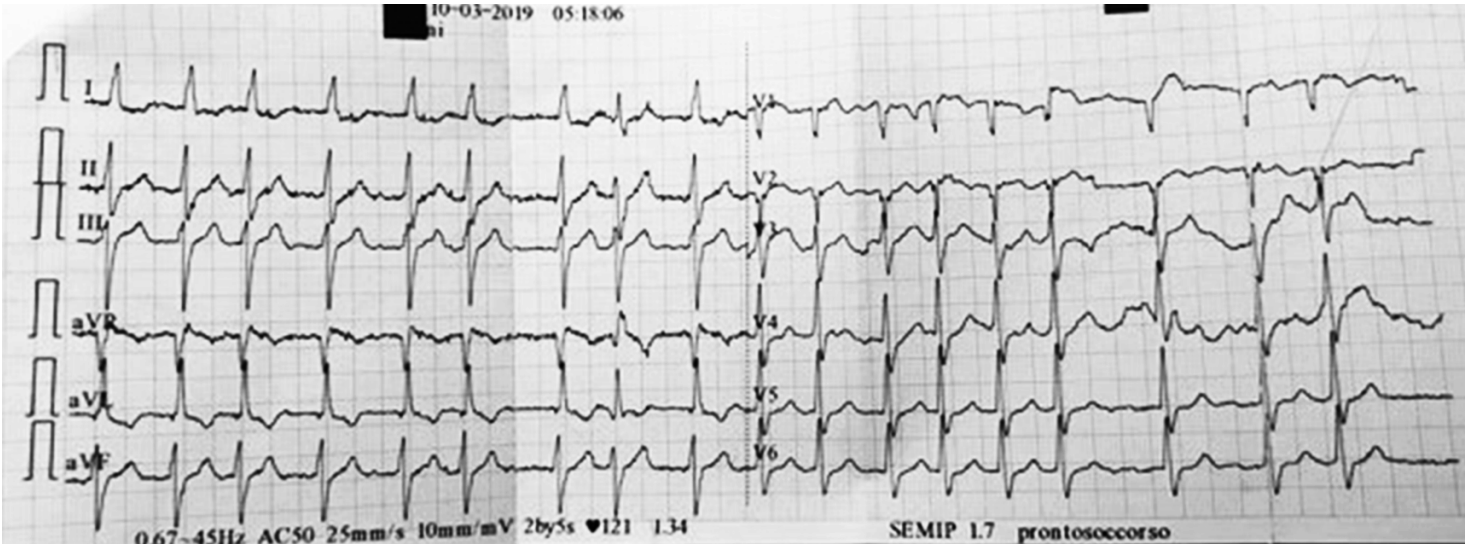

Figure 2: **The ECG at admission to emergency department showed atrial fibrillation with an average ventricular rate of 120 bpm and with diffuses but non specific alterations of ST segment and T wave.**

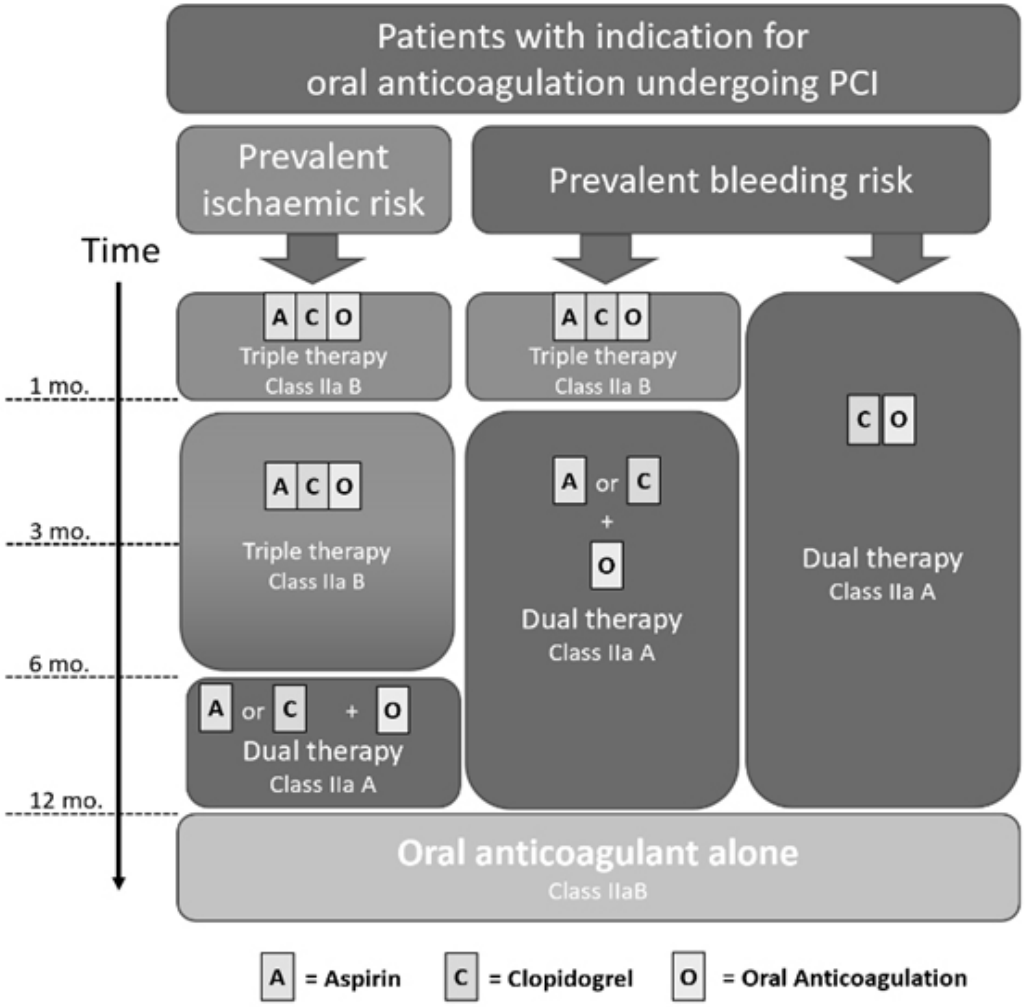

Figure 3: **Adapted from Esc Guidelines 2017. Algorithm for dual antiplatelet therapy (DAPT) in patients with an indication for oral anticoagulation undergoing percutaneous coronary intervention (PCI). Triple therapy denotes treatment with DAPT plus oral anticoagulant (OAC). Dual therapy denotes treatment witha single antiplatelet agent (aspirin or clopidogrel) plus OAC. ABC = age, biomarkers, clinical history; ACS = acute coronary syndrome; mo. = month(s); PCI = percutaneous coronary intervention.**

take into account the prevalence of ischemic risk and bleeding risk in the first 12 months from PCI [Figure 3], they do not consider the "coronary history" and the severity of CAD. However, the same guidelines recommend to use only anticoagulant therapy after 12 month from PCI.

In order to choose a double-therapy regimen, clopidogrel is indicated as preferred antiplatelet in accordance with the recent clinical trial regarding patients with atrial fibrillation treated with OA undergoing percutaneous coronary intervention(Gibson CM, 2016), (Renato D. Lopes, 2019)(Christopher P. Cannon, 2017); moreover, in the WOEST trial the use of clopidogrel without aspirin was associated with a significant reduction in bleeding complications and no increase in the rate of thrombotic events (Willem J M Dewilde, 2013).

In literature there are different opinions regarding dual and triple antithrombotic therapy, especially when it comes to long-term therapies. In a recently published position paper, Angiolillo et al. suggest that in patients undergoing PCI a double-therapy (DT: OA and antiplatelet) regimen by the time of hospital discharge should be considered for most patients, whereas triple therapy (TT) beyond hospital discharge should be considered only for selected patients at high ischemic/ thrombotic and low bleeding risks and for a limited period of time(Angiolillo DJ, 2018).

The duration of DT and TT in selected patients is controversy. Although Angiolillo et al. affirm that most patients need a DT by the time of hospital discharge, current guidelines indicates TT up to 1-6 months in according to bleeding/ischemic risk and recommended DT up to 12 months from PCI. Moreover, in some patients with high ischemic risk, the DAPTscore indicates the use of DAPT up to 30 months and it is considerable prolonged DAPT if CAD is not resolved or still ongoing. The progression of coronary heart disease as a new event, regardless of the execution of an angioplasty or a stent placement, should be taken into consideration and DT or TT has reason to be maintained over time, above all in relation to age and low risk of bleeding. Certainly, in these selected cases it may be necessary

to provide other therapeutic strategies as left atrial appendage closure or to evaluate the hypothesis of cardiac transplantation in order to severe coronary artery disease and heart failure.

Conclusion

In our clinical case, considering the severity and rapid progression of CAD and the low bleeding risk, we decidedtoadd OA to the DAPT regimen and to prolong the use of DAPT over 12 months (30 months long DAPT).Since continuing ticagrelor is not recommended as a part of the triple antithrombotic therapy, a switch to clopidogrel was decided. As for OA therapy, five possible scenarios were available: one of the four new oral anticoagulant (Apixaban, Edoxaban, Dabigratan, Rivaroxaban) at the lowest approved dose effective for stroke prevention (IIaC) or the use of rivaroxaban 15 mg o.d. instead of rivaroxaban 20 mg o.d. (IIbB). In the present case, rivaroxaban 15 mg o.d. was chosen and added to clopidogrel and aspirin for a total of 30 months, according to PIONEER AF-PCI (Gibson CM, 2016) demonstrating that 15 mg was as effective as 20 mg. After 30 months from the last "coronary event" the antithrombotic therapy will be re-evaluatedand other therapeutic hypotheses (left atrial appendage closure or the hypothesis of cardiac transplantation) will be take into account. At three months follow up, neither cerebral and cardiovascular ischemic events, nor major or clinically relevant non-major bleeding were observed; long term follow up is going on.

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Acute Procedural Complications of Cryoballoon Ablation: A Comprehensive Review

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Abstract

Catheter ablation is increasingly performed for treatment of atrial fibrillation (AF). Balloon based procedures have been developed aiming at safer, easier and more effective treatment as compared to point to point ablation. In the present review article, we aimed to discuss acute procedural complications of cryoballoon ablation.

Introduction

Atrial fibrillation (AF) is the most common sustained arrhythmia in Europe and U.S [1,2]. Despite promising improvements in the management of patients with AF, this arrhythmia remains one of the leading causes of stroke, heart failure, sudden death, and cardiovascular morbidity [3]. Once the demonstration of that the pulmonary veins (PVs) and also non-PV triggers initiates AF, catheter ablation has developed as gold standard method in selected population of patients for AF treatment [4]. CABANA trial tested whether primary catheter ablation for the elimination of AF was superior to state-of-the-art drug therapy and demonstrated that ablation is a safe and effective therapy for AF and, in some cases, is superior to drug therapy [5]. Pulmonary vein isolation (PVI) is now widely accepted as the cornerstone of AF ablation procedures. Radiofrequency based ablation techniques try to achieve this goal by "point by point" ablation; however, in the last years, the use of novel alternative ablation strategies such as cryoballoon (CB) or laserballoon is growing rapidly [6–8]. As expected, CB ablation is related to a significantly had a shorter procedure time and a non-significantly shorter fluoroscopy time compared with radiofrequency catheter ablation because the single or just a couple bonus applications are adequate for durable and complete lesions [6,7, 9]. Cryoballoon ablation technique as a single shot deviece also provides acceptable success rates in complex AF substrates such as; persistent AF, elderly patients, patients with PV abnormalities and even in patients with heart failure [10-14]. With its relatively short learning curve, use of CB has been increased. And the possible concern about the efficacy and safety of the procedure in relatively low-volume centers may be raising. Good news is that, experience does not influence long-term outcome and peri-procedural complications after cryoballoon ablation of paroxysmal AF patients [15]. In the present article, we try to comprehensively review acute procedural complications associated with CB ablation.

Key Words

Atrial fibrillation, Atrio-oesophageal fistula, Bronchial injury, Catheter ablation, Cryoablation, Cryoballoon, Phrenic nerve injury.

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Definition and classification

By definition, peri-procedural complications and complications occurring within the first 24 hours denote as acute complications. Ablation-related complications can be classified into following 4 groups according to their severity: (1) life-threatening complications; (2) severe complications; (3) moderate or minor complications; and (4) complications with unknown significance [3]. Simply, potentially fatal complications such as esophageal injury, cardiac tamponade, and periprocedural stroke are classified as life-threatening complications. Although the definition of serious complication is unclear, when life-threatening complications are removed, it seems to state the same as the definition of major complication used in previous studies. According to this classification, PV stenosis, persistent phrenic nerve palsy (PNP), vascular complications requiring transfusion or surgical intervention, and other rare complications such as mitral valve damage, cardiac conduction system damage requiring pacemaker implantation, and myocardial infarction are called as severe complications. However, there are some limitations related to this classification method. A moderate or minor complication such as femoral hematoma may convert a major complication during the course of the illnes, when it requires transfusion or surgical intervention. Contrary, most patients with significant PV stenosis and persistent PNP remain asymptomatic or have few symptoms [16,17].

In the rest of the article, acute procedural complications of CB ablation will discuss according to place of occurrence.

Complications related to vascular access site

Peripheral vascular complications are the most common complications of AF ablation regardles of used energy type [18]. The complications consist of bleeding, groin or retroperitoneal hematomas, pseudoaneurysms, arteriovenous fistulas, arterial thromboembolism, and arterial air embolism which are cumulatively reported in about 1-2% of cases [19,20]. Theoratically, the risk of access site bleeding should be more during ablation of AF than other cardiac arrhythmias due to peri-procedural anticoagulation requirement. Fortunately, the study results did not confirm this assumption and periprocedural uninterrupted oral anticoagulation therapy was found to be associated with more effective for preventing thromboembolism without any increase in incidence of bleeding complications [20,21]. Furthermore, under uninterrupted warfarine regimen with a therapeutic INR was associated with lower minor bleeding complications than bridging with heparin or LMWH [22]. During CB application, use of a special calibre delivery sheath (FlexCath Advance® Steerable Sheath, Medtronic Inc.) is needed. The sheath has a wide 12F inner and 15F outer diameters, respectively. This may be accepted as a potentially enhancing factor for the risk of vascular complications. However, larger size of the sheath does not seem to cause a serious problem in that case because the sheath is advanced via venous system. In the relevant literature, the similar vascular complication rates between CB and radiofrequency ablation confirms this reasoning [18,19].

The studies for radiofrequency ablation demonstrated that risk of vascular complications may be increased with female gender, older age, and less experienced operators [24,25]. Although similar factors were studied for CB, only female gender was found related to higher vascular complications [25-27]. Theoretically, a higher proportion of vascular access site complication in women might be associated with more, increased body mass index, more sensitive connective tissue and vascular wall or variable femoral veincourse in this population. In a Russian pilot survey, Mikhaylov et al [25] compared AF ablation results between high- and low-volume AF ablation centres. Surprisingly, a higher proportion of vascular access-site complications occured in high-volume AF ablation centres. As a potential explanation, they speculated that, in the lower-volume AF ablation centres, venous access was performed by well experienced vascular puncture operators whereas the higher-volume centres were mainly academic teaching centres, where preparations for ablation procedures were carried out by younger fellow physicians. Therefore, it should be kept in mind that operator experience is more important than volume of center to predict periferic vascular complications.

Arterial pseudoaneurysms are related to inadvertent punctures of the neighboring femoral artery during puncture of femoral vein. Mugnai et al [28] reported incidence of complications in those patients who underwent CBA for AF and the impact of novel oral anticoagulants on adverse events compared with vitamin K antagonists. The incidence of femoral pseudoaneurysms was 1.3%; 1 patient required surgical repair; 1 patient underwent percutaneous thrombin injection due to a false aneurysm; and the other 3 patients were successfully treated conservatively by compression only. Although there is no data related to CBA, ultrasound guidance during femoral puncture may be suggested to reduce this complications [29].

The great majority of bleeding and hematomas resolve spontaneously and are classified as minor complication. Any bleeding severe enough to require a blood transfusion or hematomas requiring surgical intervention is called as major bleeding and encountered in up to 1.5% of cases [30]. Arteriovenous fistula is a rare complication and should be treated surgically.

Despite various precautions to achieve complete hemostasis in a safe and effective manner, no standard approach or technique is available yet. Device-based invasive vascular closure techniques have significant cost with a risk of device failure and specific vascular complications [31]. Despite, modified figure-of-eight suture for femoral venous hemostasis has been found to be safe and time saving hemostasis method for CB procedures [32], manual compression is the most commonly used technique to achieve access site hemostasis after CB procedure. Protamine reversal of anticoagulation may be an option for veinous hemostasis during manual compression. Gurses et al.[33] studied safety and efficacy of protamine administration for reversal of heparin with manuel compression following CBA. Hospital stay was significantly shorter in patients who were administered protamine. Furthermore, all hematoma, pseudoaneurysm and arteriovenous fistula requiring surgical or interventional repair in the femoral access site were lower in patients who received protamine (1.1 %) than patients who did not (6.3%) ($p = 0.011$). In our clinic we routinely use manual compression without heparine reversal and major hematoma requiring intervention was detected in one case (2.1%)[34].

Complications related to transseptal puncture

AF ablation procedure requires transseptal puncture (TSP). In routine approach, Brockenbrough needles are used with a wide variety of sheaths to access the left atrium (LA). To understand complications related to TSP, it should be kept in mind that interatrial septum (IAS) is bordered by the ostia of the inferior vena cava, superior vena cava, coronary sinus, tricuspid septal leaflet, right atrial appendage and posterior wall folds. Therefore, only 20% of total septal area is suitable to be crossed without exiting the heart [35].

Cardiac perforation with or without tamponade is the most common acute procedural life threatening complication of TSP. The main cause is inadvertent penetration of the posterior segments. Less commonly, left atrial lateral wall, left atrial roof or left atrial appendage (LAA) may be damaged due to sudden jumping of needle across the IAS [36]. TSP guided only by fluoroscopy is complicated by tamponade in 0.1–3.2% of cases [37]. ICE or TEE provided direct visualization of the septum may offer a safer TSP, especially in atypical anatomy, a resistant/elastic septum and inexperienced operators [38-40]. As demonstrated in our recently published article, a simple deep inspiration maneuver during TSP may be a reliable and safe method after failed conventional attempts in some of these cases [41]. However, it should be kept in mind that the need for multiple punctures and intraprocedural systemic/ongoing oral anticoagulation may increase the risk or aggravate the consequences of complications. In the presence of hypotension, diaphoresis, sinus tachycardia or asystole, cardiac tamponade should be taken into

account, immediately. Although the diagnosis is easily confirmed by transthoracic echocardiography, fluoroscopic reduction in the excursion of cardiac silhouette on fluoroscopy is an early diagnostic sign of cardiac tamponade during the procedure and may be used to detect impending pericardial tamponade before hemodynamic collapse[42]. Once perforation or tamponade is detected, the effect of anticoagulants (heparin or oral anticoagulant) should be reversed by using proper reversal agent such as protamine, four-factor prothrombin complex concentrate rather than fresh frozen plasma, idarucizumab, andexanet alpha or recombinant factor VIIa in addition to fluid administration[43,44]. If tamponade does not resolve with these precautions, the patient should prepare for immediate pericardiocenthesis with autologous transfusion without wasting time. Urgent cardiac surgery should be attempted in case of continuos bleeding[45].

Due to large outer diameter of the FlexCath catheter the rate of iatrogenic atrial septal defect (ASD) may be high up to 38% at 6 months, with a mean size of 5.5 mm[46]. The incidence of iatrogenic ASD has been found significantly higher in CBA compared to double transseptal conventional radiofrequency ablation[47]. Despite hemodinamically significant iatrogenic ASD has been reported previously[48], in the majority of the cases this complication is not clinically relevant and mostly does not cause any adverse events not only in acute period but also during the follow-up.

Transient inferior ST-segment elevation accompanied by profound hypotension and bradycardia has been reported in 0.3% of cases[49]. The most plausible mechanism of this phenomenon is Bezold-Jarisch–like vasovagal responsedue to the mechanical effects of puncture on the vagal network located close to the puncture site. This vagal network usually innervates the right coronary artery and leaves it vulnerable to cholinergic vasospasm [50]. However coronary embolism should be kept in mind as an alternative diagnosis in all cases. If the cause is vagal hyperactivity, it usually resolves spontaneously. In rare situations, dopamine or fast saline drip can resolve the problem without sequelae or other complications [49].

Peripheral or central embolism including silent microemboli, transient ischemic attack and stroke is usually caused by thrombus formation in the space between the needle and the dilator, if proper anticoagulation is not administered prior to or immediately following TSP. Once the TSP system reaches the LA, ACT of at least 300-350 seconds with intravenous heparin should be achieved and maintained until all the catheters are removed from the LA. According to the latest expert consensus statement on catheter and surgical ablation of AF, uninterrupted oral anticoagulation regimen is recommended with VKAs or NOACs in addition to intraprocedural heparin infusion[4].

Air embolism to the systemic circulation is another important complication during TSP. Recurrent catheter exchanges and rapid removal of catheters or dilators, deep sedation and prolonged apnea periods with deep breaths during general anesthesia, and incomplete hemostasis valves are the most commonly reported causes of air embolism[51]. All these causes inadvertent negative pressure in catheter lumen or in the LA and air passage into the left hear chamber. To avoid this devastating complication, usage of a continuous flush through a closed system is mandatory. Also, the wire and dilators should be withdrawn from the catheter gradually. Also, the syringe should be held upright during hand injections. Once the complication is happening, the target should be to prevent further air entry, reduce the volume of the air embolus, and provide haemodynamic support. Administration of high-flow oxygen therapy is usually suggested to accelerate reabsorption of the air and minimize the size of the air bubble[52]. In a recently published article, Cay et al[53] presented a case of massive coronary air embolism and discussed its acute management. Excange of large diameter FlexCath with thinner transseptal sheath, aspiration of the air through coronary artery by an aspiration catheter solved the problem in their case. Then, full patency of the vessel and complete resolution of ST segment elevations was achieved after multiple rapid suctions through the catheter.

Aortic root injury is a rare complication of TSP due to penetration of the anterior segments. Proper usage of fluoroscopy, transesophageal or intracardiac echocardiography is mandatory to avoid inadvertent aortic root needle puncture. Also, contrast injection and pressure recording after the needle has been passed septum may facilitate to recognize aortic puncture before advancing the sheath. In case of aortic puncture with needle, withdrawing of the needle slowly is reported to be safe and effective strategy[54]. If the sheath entered the aorta, the sheath should be pulled back with a wire left in the aorta in the presence of surgical standby. Once ensuring hemodynamic stabilization, the wire may also be pulled back. Careful haemodynamic and echocardiographic observation is mandatory during all these steps. Gerbode defect is a rare congenital anomaly that permits shunting from the left ventricle to the right atrium[55]. Preprocedural evaluation of IAS with echocardiography is important in terms of uncovering existence of this defect because it may cause inadvertent aortic root puncture.

Complications during ablation

Pericardial effusion is a relatively common complication of CB ablation. In a recently published study, mild and moderate pericardial effusion was detected in 78% of patients undergoing CB ablation[56]. Although the incidence of cardiac tamponade has been reported to be higher with radiofrequency energy, the incidence of pericardial effusion were similar in both energy types[57,58]. Acute pericarditis is another pericardial complication of CB ablation and may occurr in up to 4% of patients[56]. The total number of cryoapplications and the total freeze duration were significantly higher in patients with pericarditis compared with those without. In patients demonstrating altering findings such as low blood pressure, tachycardia, and narrowed pulse pressure, a transthoracic echocardiography should be performed without wasting time. Becasue the approach in cardiac tamponade is described in detail in the above section; it is not mentioned again, here.

Although published complication rates of CB2 based-PVI are relatively low and several safety algorithms have been implemented in the protocols the most frequent complication is right-sided phrenic nerve injury (PNI). PNI develops due to the close proximity to the PNs with the PVs. Although the incidence of PNI has decreased over the years due to advanced balloon and improved techniques for early detection, PNI was noted in 3.2%-7% of patients [59,60]. High incidence

Table 1: Complications of CBA.

Complication	Mechanism	Incidence	Management	How to avoid
Vascular Access site: Inguinal bleeding, hematoma, pseudoaneurism, atriovenous fistula, arterial thromboembolism, arterial air embolism	Vascular damage, inadequate hemostasis, inadvertent puncture, inadequate anticoagulation	1-2% More common in women, elderly pts, less experienced operators, high volume centers	Conservative compression, thrombin injection, surgery for pseudoaneurism, Most hematomas resolve spontaneously Surgery for AV fistula	USG guidance during puncture, Protamine reversal, figure of eight suture for hemostasis
Cardiac perforation	During TSP inadvertent posterior segment penetration, LAA, LA lateral wall injury, Aortic root injury	0.1%-3.2%	Heparine reversal, fluids, pericardiocentesis, surgery, if the sheath advanced to aorta surgery is generally needed.	ICE/TEE guidance, Deep inspiration maneuver
Iatrogenic ASD	Thick transseptal sheath	38% at 6 months	Mostly clinical nonrelevant	
Transient ST elevation	Mostly Besold Jarich like reflex, Coronary embolism	0.3%	Coronary angiogram, Dopamine, fast saline drip	Proper anticoagulation, 300-500 ACT, uninterrupted anticoagulation
Air embolism	Recurrent catheter change, rapid catheter removal, deep sedation, deep breathing, incomplete hemostatic valves		Positioning, high pressure O2, hemodynamic support, air aspiration	Proper anticoagulation, 300-500 ACT, uninterrupted anticoagulation, removal of air bubbles from catheter
TIA, Stroke	Mostly due to air embolism	Silent cerebral lesions common, clinical TIA/ Stroke less than %1	Anticoagulation, consider neurology consultation	Proper anticoagulation, 300-500 ACT, uninterrupted anticoagulation, removal of air bubbles from catheter
PNI	Anatomical relationship between right sided veins and right PN Anatomical relationship between LAA and left PN	3.2-7%	Diagnosed by fluoroscopic evaluation 1-3 days 35% recovery 1-3 months 18% recovery 0.018% persistent and symptomatic	Operator hand control CMAP
Bronchial injury hemoptisis	Thermal trauma, Catheter injury	rare	Reverse anticoagulation, mostly recurs	Avoid lower freezing temperature
Gastroparesis, esophageal injury	Periesophageal plexus or esophageal thermal injury		Gastroparesis mostly during inferior sided vein application with large balloon in small LA	Use temperature probe
PV stenosis	Large PV ostia, low freezing temperature	rare	PV angioplasty, surgery	Avoid low freezing temperature
AV block		Very rare	Careful rhythm control	
Cx arterial vasosplasm	During LAA isolation	Very rare	ECG ST elevation	
Achieve catheter breakage	Mechanical	Very rare		

of PNI after CB ablation is related to close anatomical relationship between the PNs and PV anatomy. The right PN descends posteriorly in between the right PVs and the superior vena cava–right atrial junction. Sánchez-Quintana et al [61] studied by gross dissection the courses of the right and left PNs in 6 cadavers and demonstrated that the distance between the right PN and the anterior wall of the right superior PV may be as few as 2.1±0.4 mm whereas the distance with the right inferior PV is higher (7.8 mm±1.2). As an expected result of this close proximity, the risk of PNI is highest during ablation of the right superior PV[62] however, it is not clear why PNI appears to be more common with CB compared with radiofrequency ablation [63]. One suggested mechanism implicates anatomic distortion of the PV orifice/PN relationship, through increasing contact or shortening the relative distance between the ablation site and the PN, even without displacement of the balloon into the PV[64].

Although the left PN courses anteriorly across the LAA and is far from the left PVs, there are published cases of left PNI during CB ablation of the left superior PV[65,66]. The risk may be higher during isolation of the LAA by using CB[67]. Despite this general acceptance, the incidence and prognosis of left-sided PNI during CB ablation was recently evaluated by recording the amplitude of the compound motor action potentials during the CB ablation. Premature termination of the freezing was required to avoid PNP in 1.8% of patients [68].

Following pre-operative computed tomography findings have been associated with the development of PNI: (1) shorter distance between the right superior PV and right PN; (2) larger PV dimensions; (3) Larger external angle between the right superior PV and right anterolateral wall of the LA; and (4) smaller eccentricity index (ratio of maximum over minimum ostial diameter). In a recently published study, the prevalence of right common ostium and temperature drop velocity from basal to -20 °C were found as predictors of PNI in the multivariate analysis[69].

Additionally, type of CB has also an impact on possibility of PNI. Comparison of first and second generation of CB ablation showed significantly larger number of reversible and persistent PNI with the second-generation CB[70, 71].

The CB ablation protocol may influence the incidence of PNI. Rottner and coworkers studied to to assess the impact of different ablation protocols on the incidence and characteristics of procedural complications. Time-to effect protocol was found to be safe and effective. The observed difference in the occurrence of procedural complications between the ablation protocols is mainly driven by the higher incidence of PNI in bonus freeze and no-Bonus freeze arm.

However, distinctive risk factors for the occurrence of procedural complications could not identified, lower number and shorter length of the applied freeze-cycles in the 'time-to-effect' protocol could possibly explain the low incidence of PNI[72].

The diagnosis of PNI is usually made with evidence of diaphragmatic elevation at the chest X-ray or a paradox diaphragmatic movement in the fluoroscopy in a patient demonstrating complaints such as dyspnea, cough, or hiccups. To diagnose during CB ablation, anciently, the PN function was evaluated by direct visulation of diaphragmatic motion on fluoroscopy; however, it is the least optimal method as it exposes the patient and operator to additional radiation and may delay the diagnosis ([Figure 1], Movie 1-2). As a second method, the PN function may be evaluated by manual palpation of the patient's abdomen to monitor the excursion of the right hemidiaphragm during high amplitude pacing from the superior vena cava (Movie 3). Weakening of the diaphragmatic motion can indicate PNI. This method is easily applicable but the subjectivity associated with the measurement and respiratory variations in the diaphragmatic contraction strength can be mistaken as PNI. To provide earlier warning of PNI, novel techniques utilizing diaphragmatic compound motor action potential (CMAP) has been recently developped[73, 74]. During ablation of the right-sided PVs, CMAP recordings were obtained using two leads: a standard surface right arm ECG electrode positioned 5 cm above the xiphoid and a left arm ECG electrode positioned 16 cm along the right costal margin. The PN is paced continuously with high-output during CB application. A decrease in CMAP amplitude by 35% from baseline may predict and prevent PNI[73].

Link For Movie 1

Link For Movie 2

Link For Movie 3

Once the suspicion of PNI is determined by one of the methods described above, immediate termination of cryoenergy is the cornerstone of the prevention. If the PN function returns immediately, another CB application may attempt with condition more antral position of the balloon to be confirmed. Otherwise, ablation should be continued with radiofrequency energy. Prognosis of PNI after CBA has been investigated in a large YETI registry[74]. a total of 13693 patients received CB2 or CB3 based-PVI in 23 EP centers. A total of 596 (4.4%) of patients experienced PNI during treatment of the right superior (84%) right inferior (15%) right middle (0.3%) (and left superior (0.3%) pulmonary veins. After 1-3 months 18% of patients showed persistent PNI including 13% of patients complaining of dyspnea. After 6-12 months of follow-up including fluoroscopic evaluation PNI was persistent in 1.8% of patients while dyspnea was reported by 1.7% patients. Only 0.08% of the overall population of 13693 patients showed permanent and symptomatic PNI.

Bronchial injury is a less defined but potentially serious complication of CB ablation. While the most obvious finding is haemoptysis, cough or dyspnea may be the only complaint[75-77]. Persistent cough was reported as high as 17% in the STOP-AF Trial, and hemoptysis has been reported in 1% of cases in the cryoballoon STOP-AF Post Approval Study[75,76]. Unfortunately, the exact cause of this complication is uncertain. Although collateral thermal injury of the bronchial tree is the most widely accepted mechanism of haemoptysis, it might be related to pulmonary infarct, pulmonary haemorrhage or PV stenosis[77-79]. Also, direct damage to the tissue surrounding the PN or deeper inside the lung could be caused by catheterizing it with the guide wire or by distal inflation of the balloon. High-resolution computed tomography of the chest should be used to diagnose [Figure 2]. There is no well accepted treatment option for these cases. Although some groups suggest

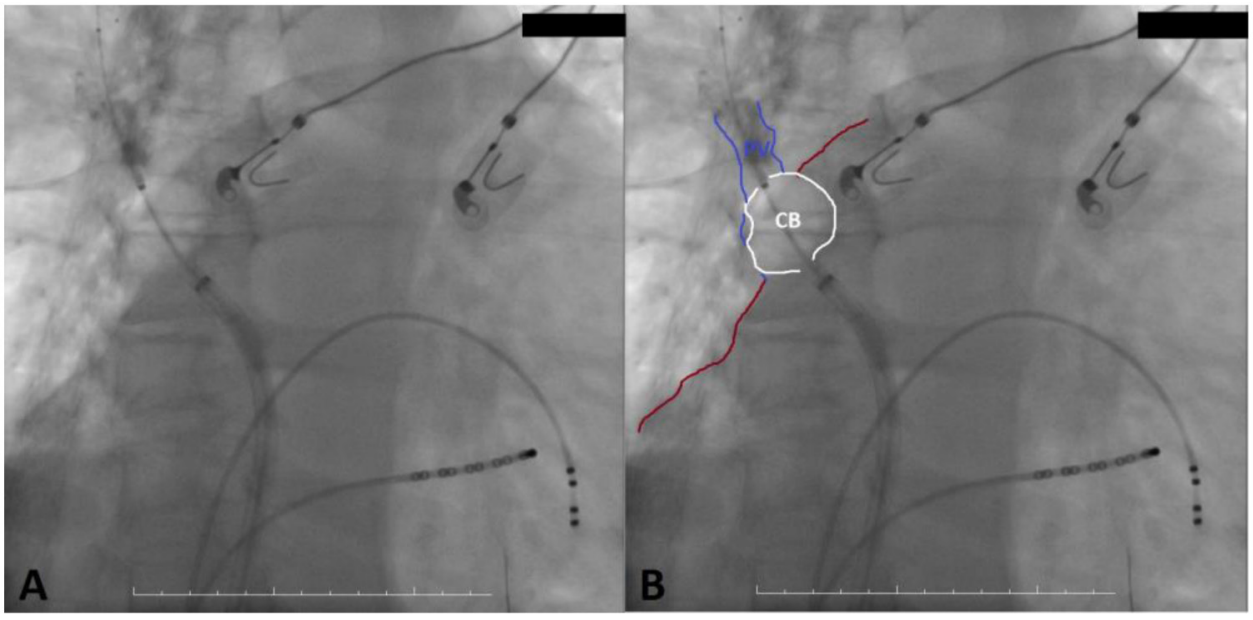

Figure 1: Deep settlement of cryoballoon catheter is seen on fluroscopy. To facilitate demonstration of catheter position and shape borders of cryoballoon, the right superior pulmonary vein, and the left atrium was drawn with White, blue, and red lines, respectively (B).

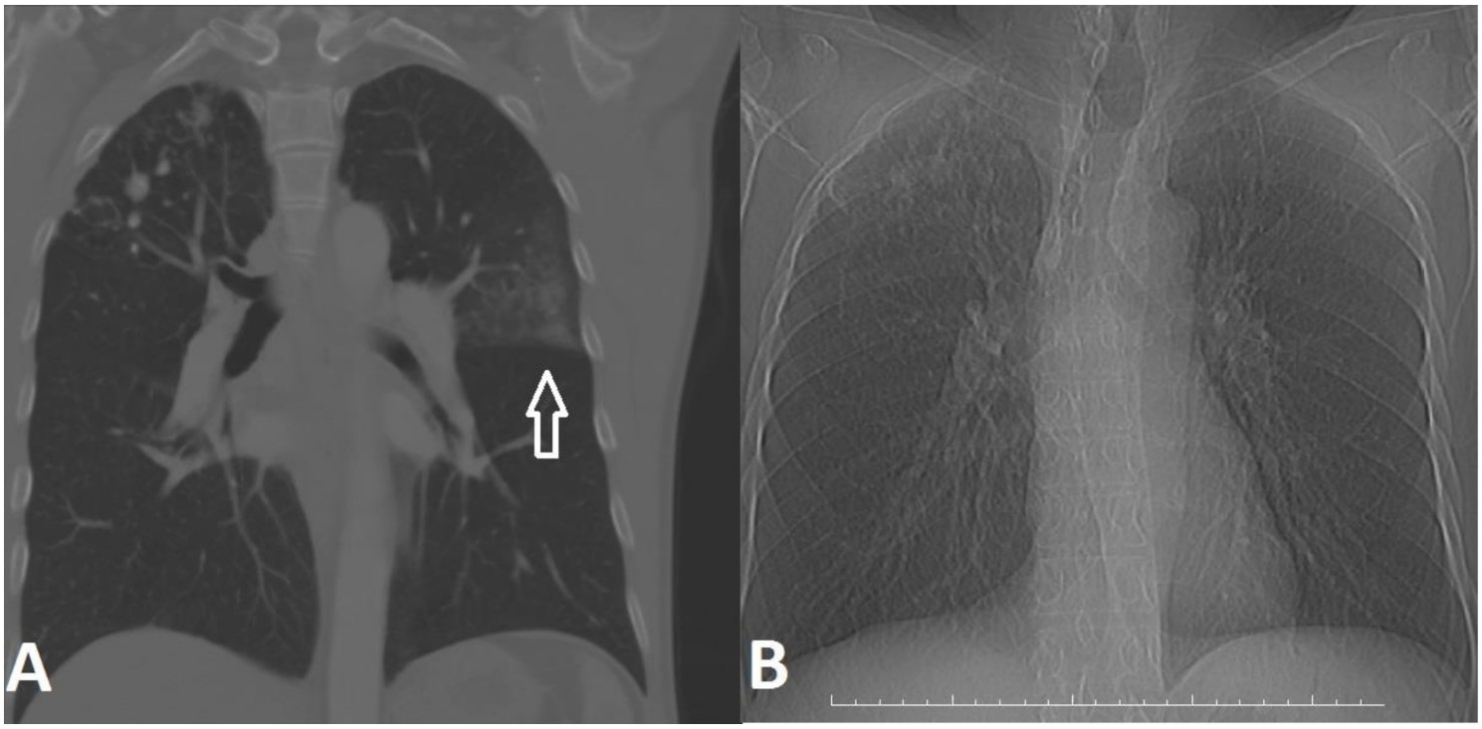

Figure 2: **A The computed tomography scan of the chest demonstrates the consolidation in the left lower lobe at the superior boundary suggestive of a pulmonary haemorrhage. B Complete resolution of pulmonary haemorrhage is seen in control computed tomography 1 month later.**

reversal of anticoagulation and urgent bronchoscopy, haemoptysis usually resolves spontaneously and does not reoccur after restarting anticoagulation theraphy[78-81].

Atrioesophageal fistula due to direct esophageal injury has been reported as anecdotal case reports after CB ablation[82,83]. Thus, knowledge about the clinical findings and the clinical course of the disease is derived from ablation studies using radiofrequency energy. It usually occurs within 1-4 weeks following ablation procedure with non-specific signs and symptoms such as fever, fatigue, malaise, chest discomfort, nausea, vomiting, dysphagia, odynophagia, hematemesis, melena, and dyspnea. Because the current article is dedicated to inform about acute complications of CB ablation, atrioesophageal fistula will not discuss in detail. But, in patients presenting with infection findings without a clear focus, retrosternal pain, and cerebrovascular findings, the diagnosis should be considered. The esophageal effects of CB have been studied by different groups by using endoscopy. Lower freezing temparature and lower average minimal luminal esophageal temperature was found related to higher esophageal effects and gastrointestinal complaints[84-89].

Although efficacy real-time luminal esophageal temperature monitoring by placing a temperature probe into the esophagus has not been investigated for CB ablation, the data from radiofrequency ablation suggests that it may be successful to detect a decrease in luminal esophageal temperature. There is no other well defined prevention strategy for this complication.

Gastroparesis is a relatively common but little known complications of CB ablation. The most possible mechanism of gastroparesis related with AF ablation is collateral periesophageal vagal nevre injury. Gastroparesis has been reported mostly occurring during CBA in inferior PVs with relatively larger balloon in small LA[90].

The diagnosis should be considered in the present of following symptoms: epigastric discomfort, abdominal pain, heartburn, bloating, nausea, or vomiting during the procedure. As it demonstrated in our report, all symptomatic patients may be evaluated by fluoroscopy for an air-filled stomach or air fluid level in the fundus of an enlarged fluid-filled stomach [Figure 3][90]. The patients showing these scopical findings should evaluated by gastric emptying scintigraphy (GES) to confirm the diagnosis. Although the FIRE AND ICE trial reported no instance of gastroparesis, the ratio of patients reporting symptoms that are shared with gastroparesis (abdominal pain, diabetic gastroparesis, epigastric discomfort, gastritis, impaired gastric emptying, nausea, and vomiting) was 3.2% for CB ablation and 2.1% radiofrequency ablation, respectively [91]. However, in our study gastroparesis was higher with CB ablation. Fortunately, gastroparesis had a good prognosis and resolving in all patients who received CB ablation [90].

Pulmonary vein stenosis (PVS) is a well defined and serious complication of point by point radiofrequency ablation. Evolving of ablation from osteal and segmental to wide area circumferential caused a decrease in the incidence of PVS from 20%-%30 to approximately 1%[92-95]. The incidence of PVS by CB ablation is approximately 3.1% after cryoablation with the first generation balloon[96]. The diagnosis should be considered in the patients demonstrating symptoms such

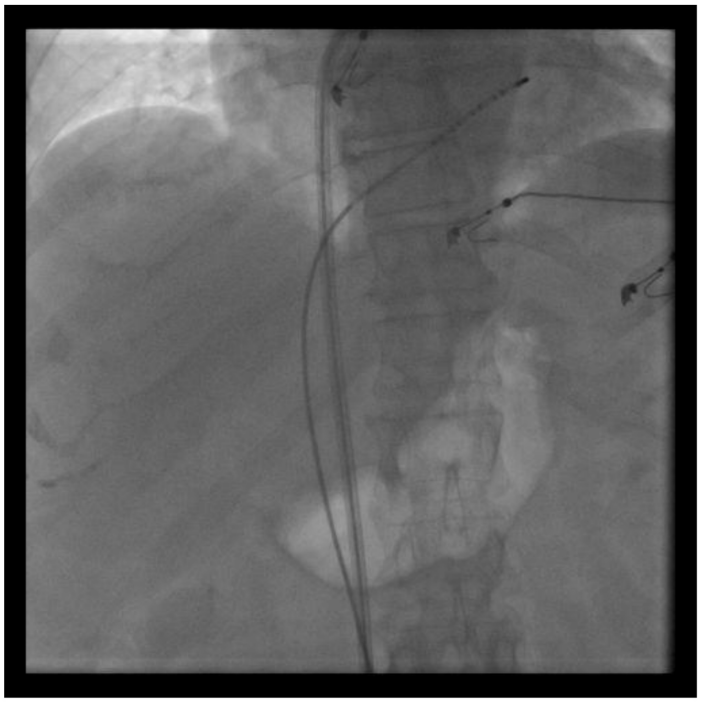

Figure 3: Fluoroscopy demonstrates the stomach which is completely full of air.

as cough, dyspnea, chest pain, and hemoptysis. The severity of PV stenosis is generally defined as mild (<50%), moderate (50–70%) or severe (>70%), according to the percentage reduction of the luminal diameter and it determines the severity of the clinical presentation[97].

In recently published studies, a larger PV ostium, lower minimum freezing temperature, and an increased number of applications per vein during CB ablation were found as independent predictors of PVS[98,99]. Although cardiac computed tomography and magnetic resonance imaging are well defined imaging modalities to diagnose, acute edema and dissection-like changes on intravascular ultrasonography might be used for early diagnosis during the procedure[100]. Although there is no an effective treatment strategy, percutaneous balloon angioplasty alone or in conjuction with stent implantation might be a potential alternative in the acute setting. However, high restenosis rish should be kept in mind in long-term follow-up[101].

Peripheral or central embolism is one of the most devastating complications of CB ablation. Theoratically, cryoenergy should be related to lower incidence of thrombus formation because it causes lower platelet and fibrin activation by preserving the endothelial layer during ablation[102,103] whereas recent studies reported similar levels of platelet activity and coagulation activation by cryoenergy and radiofrequency energy[102]. Besides symptomatic cerebral events such as transient ischemic attack or stroke, AF ablation also carries a risk of silent cerebral embolic lesions. By using pre and post-procedural cerebral magnetic resonance imaging, different groups demonstrated that new embolic lesions might be detected in up to 10% of cases after radiofrequency ablation[104,105]. A similar finding was recently demonstrated for CB ablation by using real-time transcranial doppler monitoring[106]. To reduce the incidence of asymptomatic cerebral embolism during cryoablation, the removal of air bubbles from CB in heparinized saline water with extracorporeal balloon inflation before utilization was suggested by Tokuda et al[107].

Despite high rate of silent cerebral embolic lesions, the incidence of TIA or stroke has been reported lower than 1%[108]. To decrease thromboembolic complications of ablation, uninterrupted anticoagulation strategy should be preferred compared with bridging strategies using heparin or enoxaparin regardles of used anticoagulant agent[109,110]. To reveal the presence of thrombus formation in the LAA, routine usage of transesophageal echocardiography is recommended by some authors. Although the incidence of LAA thrombus before AF ablation is low (0.6% to 2%) in patients using uniterrupted anticoagulation or bridging with low-molecular-weight heparin, it should be kept in mind that it is not 0%[111,112]. In a recently published study, dual-source cardiac-computed tomography was succesfully used to exclude thrombus formation. As a main advantage of this new modality, it may deliver additional anatomic details of PVs and LA anatomy with an acceptable radiation exposure[113]. The diagnosis of acute brain lesion can be detected by high-resolution diffusion-weighted magnetic resonance imaging [Figure 4]. Once the diagnosis is confirmed, treatment of the disease should be maintained under the supervision of a neurologist.

Transient ST-segment elevation during cryoballoon application due to coronary slow flow during CB application was firstly reported

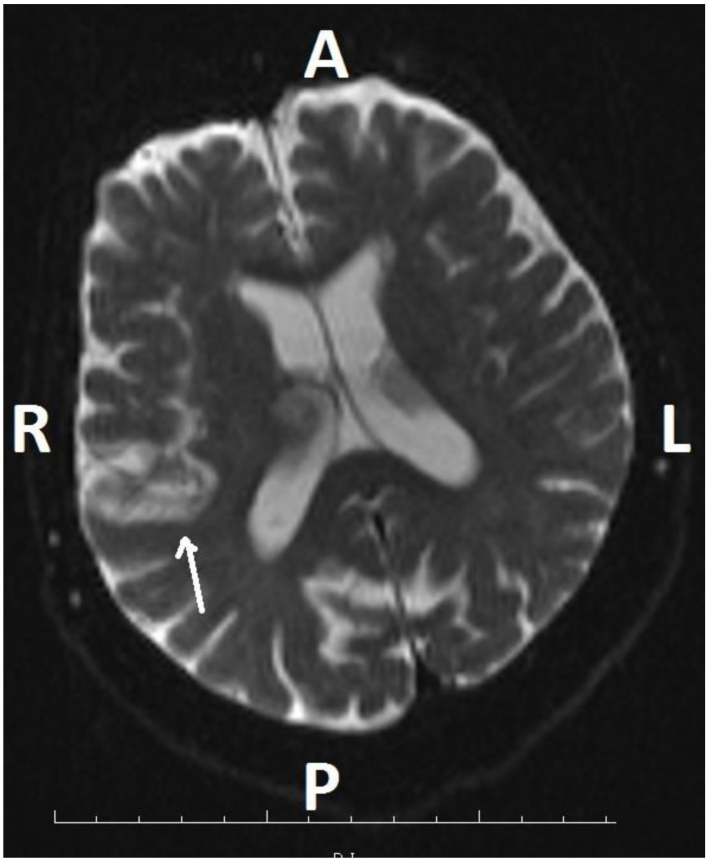

Figure 4: Acute cortical infarcts within the left parietal lobe is seen on diffusion weighted cranial magnetic resonance imaging.

by our group[114]. During the first freezing attempt in the left superior PV, at 188 seconds and -48°C, an ST-segment elevation was observed in the V1 and V6 leads, without any complaint. Coronary artery angiography was performed less than 5 minutes after balloon deflation and revealed coronary slow flow without any significant flow-limiting lesion, coronary vasospasm, thromboembolus, or air embolus. The ST-segment elevation started to decrease within 3 minutes and returned to baseline in 14 minutes, without any intervention.

Breakage of the achieve circular mapping catheter in a the right PV was recently reported by Makimoto et al[115]. As a main cause of this unique complication, authors accused the wedged position of the catheter in PV, although they had felt no grating or resistance during catheter advencement. The circular part of catheter was remained and followed-up in the right PV without any complaint.

Canpolat et al[116] recently published a case with vasospasm at the proximal segment of the circumflex artery after CB application in the LAA due to close relationship between the LAA and the the circumflex artery. After administration of intracoronary nitrate, vasospasm was rapidly relieved.

Atrioventricular block is a rare complication of CB ablation[117,118]. Atrioventricular node ischemia is hypothesized as the most probable mechanism because coronary angiography performed 30 min after atrioventricular block demonstrated a patent atrioventricular node artery originating from the right coronary artery. In the case of Fedida et al, a short distance between the RIPV ostium and aortic annulus at proximity of the AV node region showed by CT-scan reconstruction could explain mechanical AV bock during manipulation of the 28 mm cryoballoon catheter. This could be due to mechanical bump of the IAS and crux cordis, but also to left sided pathway of the AV-node. Data for comparison with CT-scan reconstruction are needed to confirm this hypothesis.

Conclusion

Cryoablation has become a commonly used tool for the management of AF due to require less experience than radiofrequency ablation without affecting effectivity. However, it can lead to some significant and even fatal acute complications. Although the ratio of these complications are rare, operators should know how to detect and manage the complications, quickly.

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The Association Between Atrial Fibrillation and Endurance Physical Activity: How Much is Too Much?

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Abstract

Atrial fibrillation (AF) is the most common arrhythmia in middle-aged athletes. Physical exercise performed in a regular basis has been shown to be beneficial for cardiovascular health. Moderate physical exercise, aside from producing a nice, peaceful and well-being sensation, has been associated with a reduced risk of AF. However, more strenuous endurance exercise, like the one experiencing marathon runners, seems to increase the risk of AF in healthy athletes without organic heart disease. On the other hand, low physical activity was found to be a risk factor for the appearance of AF. Nevertheless, the relationship of exercise to AF is complex, influenced by the intensity and the duration of the physical activity, and seems to have a U-shaped relationship with the greatest levels of physical activity possibly increasing AF incidence. There is cumulative data associating moderate physical activity to reduced AF incidence, hence physicians should recommend moderate exercise training to patients with AF. This may not only reduce AF risk, but would also contribute to an overall cardiovascular benefit. However, since there is also important data suggesting significant increased incidence of AF in elite athletes with long-term endurance physical activity, it may be a serious concern to go to the extreme. In most things in life it is much better and wiser to be well balanced, always in equilibrium.

Introduction

Atrial fibrillation (AF) is the most common arrhythmia in clinical practice affecting an estimated 1% of the U.S. population and over 30 million individuals worldwide [1-4]. AF is usually associated with hypertension, diabetes, aging, obesity, heart failure, ischemic heart disease, and other organic heart diseases. AF is also related to high comorbidities and mortality and severe prognostic implications. Moderate physical exercise, aside from producing a nice, peaceful and well-being sensation, has been associated with a reduced risk of AF [5-7]. However, more strenuous endurance exercise, like the one experiencing elite athletes and marathon runners, seems to increase the risk of AF in healthy athletes without organic heart disease [7-10]. Indeed, it was demonstrated that 5% of moderately trained endurance athletes had asymptomatic AF recorded with implanted cardiac monitor device during a 12-month surveillance period [4]. Since most of the episodes of AF appear at night or after a meal, well-trained athletes usually do not blame exercise or training as the cause of their palpitations [9].

About 20 years ago Karjalainen J, et al. published the first study linking AF with high intensity physical activity [10], and it is estimated that the risk of AF in elite athletes is more than 5 times that in the general population [7]. On the other hand, low physical activity was also found to be a risk factor for the appearance of AF. It seems that both extremes in physical activity intensity tend to promote episodes of AF. There are several changes produced within the heart by endurance exercise. Structural, functional, and electrophysiological alterations occur, namely, atrial enlargement and ventricular hypertrophy practically without systolic function modifications [11]. Ventricular compliance was found to be improved which may provide an improvement in ventricular filling [12]. Another established cardiovascular adaptation is enhanced parasympathetic activity with sinus bradycardia [13]. There is also evidence for an alteration in the intrinsic electrophysiological properties of the heart [14]. Increased occurrence of premature atrial contractions has been reported in elite athletes [15], which may represent a potential trigger for AF development [16]. Premature atrial contractions may act as triggers which may induce sustained AF episodes dependent on the presence of atrial vulnerability [17].

We performed a search in PubMed, SCOPUS and Medline using the MeSH headings or text words atrial fibrillation and exercise, or physical activity or athletes or sports. Conclusions regarding quality and strength of evidence were based on the grading of recommendations, assessment, development, and evaluation system. Since no randomized trials neither interventional studies were available, observational studies were considered acceptable. Long-term prospective cohort studies, case-control or cross-sectional

Key Words
Atrial fibrillation, Endurance physical activity, Sports; Elite athletes, Physical exercise.

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studies were also included in this review. Therefore, we aim to analyze the cardiovascular response to different intensity of endurance exercise and the atrial electrophysiological changes, as well as, the potential pathophysiological mechanisms underlying an increased risk of AF in endurance physical activity.

Possible mechanisms involved in AF development in athletes

There are several possible mechanisms which may be acting together as etio-pathogenic factors influencing the development of AF in endurance athletes [Figure 1]. It is well known that AF depends on triggers, substrates, modulators, and these factors may be present in association with endurance physical activity. An increased in vagal tone and cholinergic stimulation which occurs in endurance athletes with any vigorous exercise session has been proposed as a plausible mechanism for the genesis of AF in these mentioned subjects. It has been shown in pioneering experimental studies that increased vagal tone shortens the atrial refractory period, and increases dispersion of refractoriness creating appropriate conditions for reentrant circuits to occur [18]. Therefore, the increased vagal tone induced by endurance sport practice may facilitate AF appearance.

In addition, structural changes of the heart mediated by hypertrophy, extensive stiffening of the myocardium with the resultant diastolic dysfunction may cause remodeling and enlargement of the left atrium, pulmonary vein ectopy as triggers and modulators of atrial fibrillation associated with strenuous endurance exercise. Atrial premature contractions, particularly pulmonary vein ectopy, have been shown to be the trigger in most episodes of paroxysmal AF [16]. Atrial premature contractions may be increased as a consequence of physical activity [19]. Therefore, increased ectopy associated to an appropriate atrial substrate may be one of the mechanisms explaining the increased risk for AF associated with sport practice. However, Baldesberger et al. [19] did not find an increased incidence of atrial ectopy in their study in former professional cyclists.

Hemodynamic changes and inflammation

Athletes may experience a chronic increase in atrial pressure due to endurance training. Elevated atrial pressure by itself can lead to atrial dilatation, shortening of atrial refractory periods, and increased incidence of AF. Moreover, atrial inflammation and fibrosis due to repeated exposure to the acute increase in inflammation after prolonged vigorous exertion, was proposed as another underlying possible cause [10]. Indeed, excessive endurance exercise and overtraining can lead to chronic systemic inflammation with inflammatory infiltration as structural atrial changes, and there is a direct relationship between AF and C-reactive protein [20].

There are some hemodynamic changes that occur during exercise. Circulatory flow is 8-fold increased during intense exercise training [21]. The diastolic phase decreases to approximate that of the systolic phase. Hence, the atrioventricular valves are closed for approximately one-half of the cardiac cycle time. This potential for obstruction is attenuated by increases in atrial pressure and contractility during exercise [22]. There is a dilatation of all 4 cardiac chambers due to the intermittent hemodynamic stretch of the myocardium caused by both pressure and volume load during endurance exercise. The right atria and right ventricle may be of greatest clinical relevance given that an excess of cardiac arrhythmia has been demonstrated to originate from these chambers [23].

There are some other aspects related to serum biomarkers in elite athletes. In this context, Stumpf C, et al. [24] studied a total of 25 professional major league soccer players with a mean age 24±4 years and compared them to 20 sedentary controls with a mean age 26±3 years. All subjects underwent physical examination, electrocardiography, echocardiography, exercise testing on a bicycle ergometer, and laboratory analysis of interleukin (IL)-6, tumor necrosis factor (TNF)-a, IL-8, and IL-10. The athletes were divided into two groups according to presence or absence of an early repolarization (ER) pattern. Athletes with an ER pattern showed significantly lower heart rate and an increased E/e´ ratio compared to athletes without an ER pattern. The pro-inflammatory cytokines IL-6, IL-8, TNF-a as well as the anti-inflammatory cytokine IL-10 were significantly elevated in all soccer players. However, athletes with an ER pattern had significantly higher IL-6 plasma levels than athletes without ER pattern. Furthermore, athletes with "high" level IL-6 had significantly larger LA volumes than players with "low" level IL-6. Therefore, the authors concluded that those athletes with an ER pattern had significantly higher atrial filling pressures, higher LA volume, and higher IL-6 plasma levels.

Although all these factors may contribute to atrial remodeling over time and thus increase the risk of AF in long-term endurance sports, the actual AF development should be corroborated in long-term follow-up. In addition, whether the levels of circulating cytokines have an impact on atrial conduction and arrhythmias over time should also be examined in a larger study with a longer follow-up.

MicroRNA in atrial remodeling

In recent years, microRNAs have been shown to play an important role in in the mechanism of AF development and its pathophysiology by regulating remodeling processes [25]. MicroRNAs are short, single-stranded, and non-coding RNA fragments that bind to the 3' UTR of their target genes leading to inhibition of mRNA translation. Therefore, micro RNAs are post-transcriptional regulators of gene expression. MicroRNAs have been shown to play an important role in atrial remodeling, and especially MiR-1 and MiR-26a are implicated in electrical remodeling by regulating ion channels or calcium homeostasis [26]. On the other hand, MiR-29b, miR-30a and miR-133a are predominantly involved in structural remodeling causing enhanced atrial fibrosis [27]. Another study has shown that endurance sport and aerobic exercise impact on the level of circulating microRNAs [28]. This latter study investigated how the plasma profile of microRNAs and conventional cardiac injury markers like troponin differed, suggesting a potential role for microRNAs as biomarkers for exercise-induced cardiac adaptation. In order to determine the potential value of microRNAs as biomarkers for acute atrial remodeling in athletes, Clauss S, et al. [29] performed the miRathon study, in which they analyzed the plasma profile of 5 microRNAs associated with atrial remodeling in marathon runners. MicroRNAs are important mediators of pro-arrhythmogenic remodeling and have potential value as biomarkers in cardiovascular diseases. In this context, they studied 30 marathon runners who were divided into

two age-matched groups depending on the training status: elite (ER, more than 55 km/week, n=15) and non-elite runners (NER, less than 40 km/week, n=15). All runners participated in a 10 week training program before the marathon, and MicroRNA plasma levels were measured at 4 time points: at baseline, after the 10 week training period, immediately after the marathon, and 24h later [29].

In addition, clinical data were obtained including serum chemistry and echocardiography at the four each time point [29]. The authors found that MicroRNA plasma levels were similar in both groups over time with more pronounced changes in elite runners. After the marathon MiR-30a plasma levels increased significantly in both groups. MiR-1 and miR-133a plasma levels also increased but showed significant changes in elite runners only. 24h after the marathon plasma levels returned to baseline. MiR-26a decreased significantly after the marathon in elite runners only and miR-29b showed a non-significant decrease over time in both groups. MicroRNA plasma levels showed a significant correlation with LA diameter in elite runners. However, microRNA plasma levels did not correlate with echocardiographic parameters in non-elite runners [29]. With these results, the authors concluded that microRNAs were differentially expressed in the plasma of marathon runners with more pronounced changes in elite runners. MicroRNA plasma levels correlate with left atrial diameter in elite runners suggesting that circulating microRNAs could potentially serve as biomarkers of atrial remodeling in athletes. The expression levels of these microRNAs observed in Clauss S, et al. are confirmed by other studies that demonstrated a role of these microRNAs in cardiac remodeling [26].

These mentioned results obtained from several studies further support circulating serum microRNAs as potential biomarkers for cardiac remodeling. However, these results should be considered only as hypothesis-generating data and do not prove a direct causal link between circulating serum microRNA levels and the genesis of AF in elite athletes. Long term follow-up clinical studies in endurance physical activity are necessary to provide definitive evidence of this association.

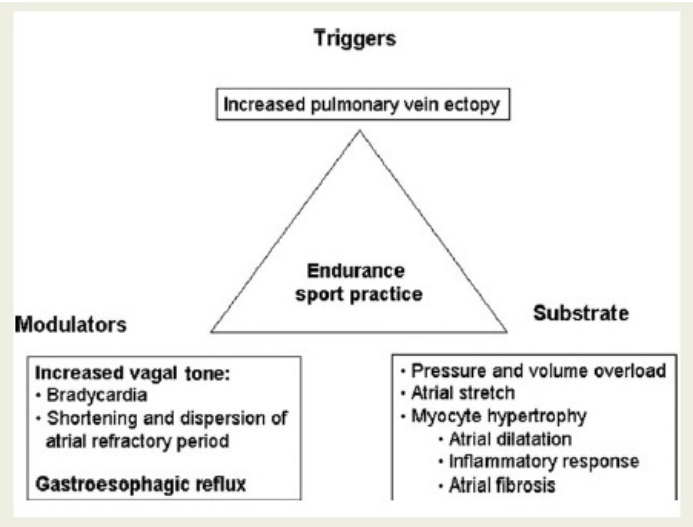

Figure 1: Classical triangle of Coumel suggesting possible etio-pathogenic factors influencing the development of atrial fibrillation in athletes. Reprinted with permission from Mont L, Elosua R, Brugada J. Endurance sport practice as a risk factor for atrial fibrillation and atrial flutter.

Increased vagal tone

There are some interesting animal experiments that shed light into the mechanisms underlying AF development related to chronic endurance training. Guasch E, et al [30] subjected rats to daily 1-hour treadmill training for 8 or 16 weeks. This mimicked chronic endurance-exercise in athletes. Based on maximum oxygen-uptake, the authors suggested that the 16-weeks treadmill-training regimen in rats corresponds roughly to about 10 years of exercise training in humans. They demonstrated that the rats subjected to chronic exercise were more susceptible to pacing induced AF associated with an enhanced vagal tone, atrial dilatation and increased fibrosis.

These results were similar to findings in humans with long-term endurance training [31]. However, the cessation of exercise reversed AF inducibility in the animal experiments, suggesting a cause-effect relationship between endurance exercise and AF development [30]. It was very interesting to note that although this deconditioning protocol decrease AF inducibility, it did not attenuate atrial dilatation and fibrosis, suggesting that molecular pathways other than structural remodeling also contribute to the AF development in athletes. In this context, Guasch E et al. observed that an enhanced baroreflex and sensitivity to cholinergic stimulation of the G protein-gated K+ channel play central roles in this experimental exercise model [30]. Furthermore, molecular studies suggested that altered mRNA expression levels of several regulators of G-protein signaling proteins may contribute to the increase sensitivity to vagal tone. This study suggested that enhanced vagal activity plays an important role, through increased baro-reflex responsiveness and increased sensitivity to cholinergic stimulation at the level of the atrial cardiomyocytes.

Clinical studies associating AF to physical exercise

AF has been linked to extensive and long-term exercise, as prolonged endurance exercise has shown to increase the incidence and risk of AF. In contrast, light to moderate physical activity is beneficial since it is associated with a decreased risk of AF, and current research indicates a J-shaped association between AF and the broad range of physical activity and exercise [32-49].

Light to moderate physical activity and AF

There seems to be no doubt about the fact that light to moderate physical activity is not associated to higher incidence of AF. Indeed, the Cardiovascular Health Study [32] investigated the association between habitual physical activity and AF among 5,446 adults. The subjects were 65 years of age or older and were followed-up for over a 12-year period. The results showed that, unlike high intensity exercise, light to moderate physical activity is associated with a lower incidence of AF. In addition, a meta-analysis [33] including 95,526 subjects confirmed that regular physical activity is not associated with a higher risk of AF compared with sedentary lifestyle. This result provided additional relevance to the already known beneficial effects of regular exercise on cardiovascular risks.

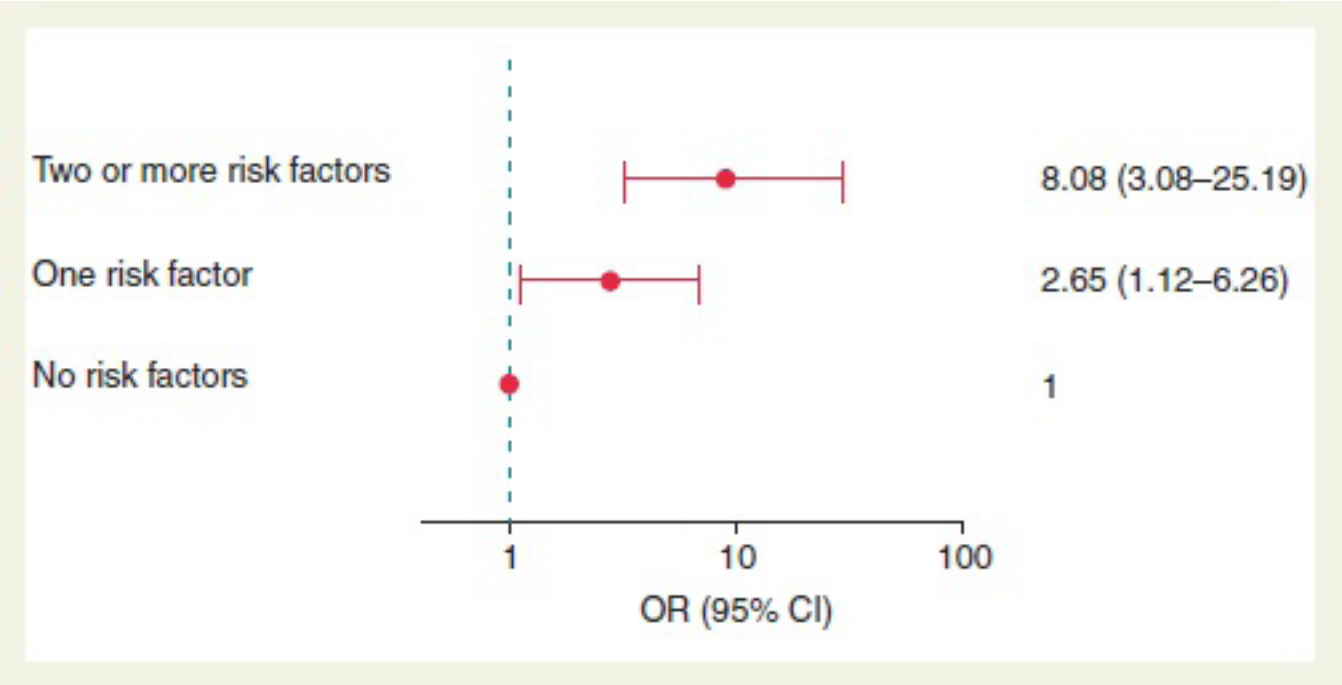

Figure 2: **Risk of atrial fibrillation in patients according to the presence of risk factors and the impact of physical activity. Reprinted with permission from Calvo N, Ramos P, Montserrat S, et al. Emerging risk factors and the dose-response relationship between physical activity and lone atrial fibrillation: a prospective case-control study.**

AF is the most common arrhythmia in middle-aged athletes. Moderate physical exercise performed in a regular basis has been shown to be beneficial for cardiovascular health [41]. Moderate levels of physical activity reduce AF risk as demonstrated in the following study. Physical activity was assessed in 36,513 women at baseline in the Swedish Mammograph Cohort study [42]. Of the total number of women, 2,915 developed AF. The incidence of AF over a median follow-up of 12 years was 15% lower in women exercising over 4 h weekly versus those exercising less than 1 h weekly.

Physical activity was also assessed at baseline in 81,317 women in the Women's Health Initiative Observational Study [43]. In this study 9,792 developed AF. The incidence of AF over an average follow-up of 11.5 years decreased with progressively more physical activity and was 10% lower in women exercising >9 MET task hours per week versus those with no reported weekly exercise. This effect was independent of the body mass index. In this study even the most physically active women, those exercising >15 MET task hours weekly in strenuous physical activity, had a 9% lower rate of AF [43].

In the Women's Health Study, out of 34,759 women, 968 developed AF after a median of 14.4 years [44]. Women exercising 7.5 MET hours weekly had a 14% lower risk of AF, but this was not significant after adjusting for body mass index. On the other hand, AF incidence was 28% lower in the Cardiovascular Health Study with moderate-intensity physical activity [45]. However, those exercising at the highest intensity had a risk of AF not significantly different from the no-exercise group.

Very recently, in the middle of last year, Albrecht M, et al. [34] investigated the association of total and types of physical activity, including walking, cycling, domestic work, gardening and sports, with atrial fibrillation in the Rotterdam Study. The authors studied a prospective population-based cohort which included 7018 participants aged 55 years and older with information on physical activity between the years 1997-2001. They utilized Cox proportional hazards models to examine the association of physical activity with atrial fibrillation risk. Physical activity was categorized in tertiles and the low group was used as reference. They observed during 16.8 years of follow-up that 800 episodes of AF occurred (11.4% of the study population). However, the authors found no association between total physical activity and AF risk in any model. After adjustment for confounders, the hazard ratio and 95% confidence interval for the high physical activity category compared to the low physical activity category was 0.71 (0.80–1.14) for total physical activity [34]. Therefore, they concluded that physical activity is not associated with higher or lower AF risk in older adults. Neither total physical activity nor any of the included physical activity types was associated with AF risk. However, this is not the case with endurance physical exercise in elite athletes.

Endurance physical exercise and AF

The clinical outcome is different with endurance physical exercise in elite athletes. At the beginning of last year, Elliot AD, et al. [35] recruited 99 recreational endurance athletes who were grouped according to lifetime training hours. The athletes underwent evaluation of atrial size, autonomic modulation, and atrial premature contractions. They were grouped by self-reported lifetime training hours: low (<3000 h), medium (3000–6000 h), and high (>6000 h). Left atrial (LA) volume, left ventricular (LV) dimensions, and LV systolic and diastolic function were assessed by echocardiography. A

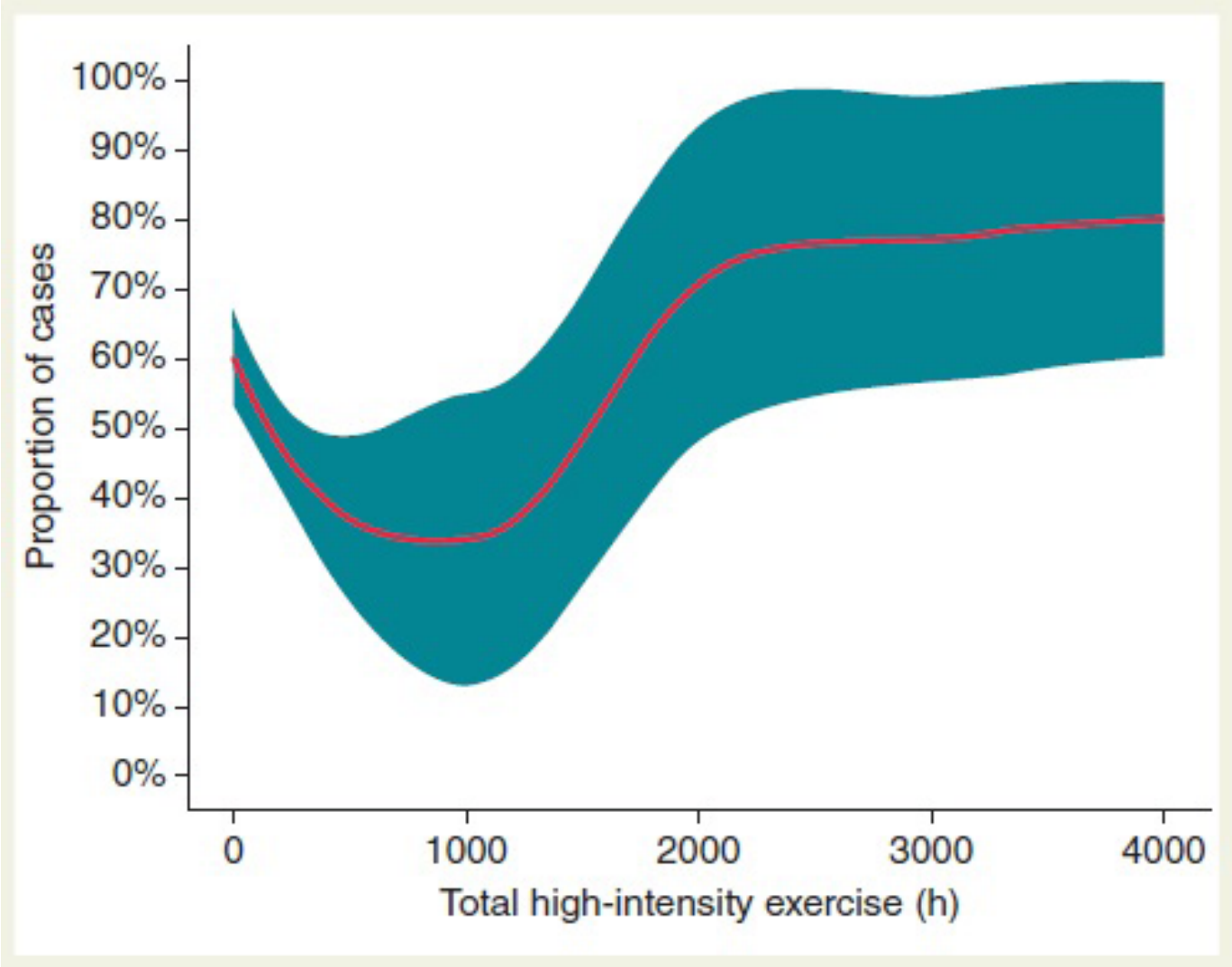

Figure 3: **Percentage (95% CI) of participants with lone AF (cases) according to accumulated high-intensity physical exercise (local likelihood regression). Of note, proportion is dependent on cases/control matching in a specific study sample. When considered as a continuous variable, the relationship of lifetime-accumulated high-intensity training to AF risk followed a U-shaped dose–response curve. Reprinted with permission from Calvo N, Ramos P, Montserrat S, et al. Emerging risk factors and the dose-response relationship between physical activity and lone atrial fibrillation: a prospective case-control study.**

48-hour ambulatory electrocardiographic monitoring was utilized to determine heart rate, heart rate variability, premature atrial contractions, and premature ventricular contractions. The authors found that LA volume was significantly greater in the High (+5.1 mL/m2, 95% CI: 1.3–8.9) and Medium (+4.2 mL/m2, 95% CI: 0.2–8.1) Groups, compared with the Low Group. LA dilatation was observed in 19.4%, 12.9%, and 0% of the High, Medium, and Low Groups, respectively (P =0.05). They did not observe any differences regarding LV dimensions or function, heart rate variability indices, or premature atrial and ventricular contraction [35]. Therefore, they concluded that increased lifetime training is associated with LA dilatation in the absence of increased vagal parameters or atrial premature contractions in recreational endurance athletes, which may promote incidence of AF in this cohort.

Pathak et al. [40] demonstrated that people with greater exercise capacity with increasing exercise training reduce AF recurrence. These authors evaluated 1,415 consecutive clinic patients with AF. The patients with a body mass index equal to or greater than 27 kg/m2 had a program designed to produce weight loss and increase exercise activity. The patients were divided into low, adequate, and high cardiorespiratory fitness groups on the basis of their baseline exercise performance with an average follow-up of 4 years. Freedom of AF episodes was 12% in the low group, 35% in the adequate group, and 66% in the highest fitness group demonstrating that baseline fitness predicts future AF [40].

This study [40] demonstrated that higher fitness predicts less frequent episodes of AF. However, this is not a randomized controlled clinical trial, but a prospective, observational study, and those individuals adopting an active lifestyle may have made other changes that affected AF risk. Nevertheless, the relationship of exercise to AF is complex, influenced by the intensity and the duration of the physical activity, and seems to have a U-shaped relationship with the

greatest levels of physical activity possibly increasing AF incidence. Indeed, the relationship between AF and exercise intensity suggests a curvilinear response with diminishing benefit or even risk with the most intense exercise.

In a similar manner, AF risk increased with the frequency of vigorous exercise in the Physicians' Health Study [46]. Out of 16,921 male participants, 1,661 men developed AF over 12 years of follow-up. Men exercising vigorously 7 days per week had a 20% higher risk. In this regard, a systematic review [47] and a meta-analysis [7] suggested that athletes who engaged in long-term, endurance exercise training have an increased AF incidence. Moreover, among 52,755 cross-country or Nordic skiers who participated in the 90-km races from 1989 to 1998, 919 developed AF before December 2005 [48]. Those athletes who participated in more than 5 races were 30% more likely to develop AF than those who participated in only 1 race.

Another interesting study demonstrated high AF prevalence among long-term, competitive swimmers. Schreiner AD et al. [49] designed a cross-sectional study utilizing survey data to compare the prevalence of AF in swimmers to a general internal medicine population. A multi-national group of swimmers over the age of 60 were surveyed, and a chart review was performed on a random sample of age-matched internal medicine patients. The primary outcome was the diagnosis of AF. Univariate analysis was used for means of proportions of the responses, and a multivariate logistic regression analysis was performed with diagnosis of AF as the dependent variable. Forty-nine swimmers completed surveys and 100 age-matched internal medicine patients underwent chart review. The group of swimmers had 13 cases of AF (26.5 %) compared to 7 (7 %) in the comparison group (p = 0.001). A diagnosis of hypertension or diabetes mellitus was present in 23 (46.9 %) and only 1 (2 %) of the swimmers, respectively, as compared to 72 (72%, p=0.003) and 32 (32%, p<0.001) in the comparison group. Swimming was associated with an odds ratio of 8.739 (95% CI 2.290 to 33.344, p=0.015) [49]. The authors concluded that long-term, competitive swimmers have an increased prevalence of AF compared to internal medicine patients, despite the higher burden of diabetes mellitus and hypertension in the internal medicine group. This suggests that competitive swimming should be included in the list of aerobic activities associated with AF.

Influence of aging and endurance exercise

Myrstad M, et al. [36] investigated the influence of aging and long-term endurance sport practice as a risk factor for AF in elderly men. They compared in a cross sectional study a total of 509 men aged 65–90 years who participated in a long-distance cross-country ski race with a control group of 1768 men aged 65–87 years from the general population. Long-term endurance sport practice was the main exposure. Self-reported AF and covariates were assessed by questionnaires [36]. The authors estimated the risk differences for AF by using a linear regression model. After multivariable adjustment, a history of endurance sport practice gave an added risk for AF of 6.0 percent points (95% confidence interval 0.8–11.1).

Of interest was the finding that light and moderate leisure-time physical activity during the last 12 months reduced the risk with 3.7 and 4.3 percent points, respectively, but the risk differences were not statistically significant. They concluded that this study suggested that elderly men with a history of long-term endurance sport practice have an increased risk of AF compared with elderly men in the general population [36]. This study has the added strength that has a low prevalence of traditional risk factors for AF. Very few of the long-term endurance skiers were smokers, had coronary heart disease or diabetes. The prevalence of hypertension among the athletes was much lower than in the general population.

Risk factors influencing AF development with exercise

Besides the high-intensity exercise, there are other emerging risk factors that influence the AF development. The more risk factors a patient has, the greater the chances of developing AF [Figure 2]. Calvo N, et al. [37] analyzed several risk factors in a group of 115 patients with lone AF who were compared to 57 age and sex-matched healthy controls in a 2:1 prospective case–control study. The authors obtained and analyze clinical and anthropometric data, transthoracic echocardiography, lifetime physical activity questionnaire, 24-h ambulatory blood pressure monitoring, Berlin questionnaire score, and, in patients at high risk for obstructive sleep apnea syndrome, a polysomnography. Based on conditional logistic regression analysis they found an association of the following four risk factors to a higher AF risk, namely, height [odds ratio (OR) 1.06 (1.01–1.11)], waist circumference (OR 1.06 [1.02–1.11]), obstructive sleep apnea syndrome (OR 5.04 [1.44–17.45]), and 2000 or more hours of cumulative high-intensity endurance training [37]. Of interest, their data indicated a U-shaped association between the extent of high-intensity training and AF risk. The risk of AF increased with an accumulated lifetime endurance sport activity of more than 2000 h compared with sedentary individuals (OR 3.88 [1.55–9.73]). Nevertheless, a history of less than 2000 h of high-intensity training protected against AF when compared with sedentary individuals (OR 0.38 [0.12–0.98]). Therefore, the authors concluded that a history of more than 2000 h of vigorous endurance training, tall stature, abdominal obesity, and obstructive sleep apnea syndrome are frequently encountered risk factors in patients with lone AF. Fewer than 2000 total hours of high-intensity endurance training associates with reduced lone AF risk [37].

This study described for the first time a U-shaped association between the duration of high-intensity training and the risk of developing lone AF [Figure 3]. Although Calvo N, et al. [37] demonstrated that 2000-h threshold of endurance training better discriminated individuals at risk for exercise-induced AF, the upper limit of safety endurance training has been elusive. In this regard, Elosua R, et al. [38] demonstrated that an accumulated sport practice of more than 1500 h was associated with an increased risk of AF. Data from Drca N, et al. [39] suggested that more than 5 h/week of vigorous intensity exercise at 30 years of age increased AF incidence after 60 years of age. Nevertheless, the dose–response curve of intensity training/AF risk is likely to be continuous showing a high inter-individual variability.

Strain rate and speckle-tracking echocardiography in exercise

In recent years, atrial strain and strain rate analysis by 2-dimensional speckle-tracking echocardiography has emerged as a novel method

to evaluate atrial functions. The assessment of atrial function by strain rate and speckle-tracking echocardiography has been used as a predictor of AF recurrence in various clinical situations and in the evaluation of atrial function in male elite athletes [50].

Sanz-de la Garza M, et al [51] designed a study to better understand and characterize the acute atrial response to endurance exercise and the influence of the amount of exercise achieved. They performed 2D ultrasound speckle-tracking strain Echocardiography in 55 healthy adults at baseline and after a 3-stage trail race: a short race (14 km), n=17; a medium race (35 km), n=21; and a long race (56 km), n=17. The authors found that after the race the reservoir function of the right atrium decreased in the medium race group (Δ% SRs: -12.5) and further in the long race group (Δ% SRs: -15.4), with no changes in the short race group. The contractile function of the right atrium decreased in the long race group (Δ% SRa: -9.3), showed no changes in the medium race group (Δ% SRa: +0.7), and increased in the short race group (Δ% SRa: +14.8).

A similar trend was documented in the reservoir and contractile function of the left atrium but with less pronounced changes [51]. The decrease in the reservoir function of the right atrium after the race correlated with the decrease in the global longitudinal strain (GLS) of the right ventricle (Δ% RVGLS vs. RASt and RASRs: +0.44; $p<0.05$ and +0.41, respectively; $p<0.05$) [51]. Therefore, the authors concluded that during a trail-running race, an acute exercise-dose dependent impairment in atrial function was observed, mostly in the right atrium, which was related to systolic dysfunction of the right ventricle. The impact on atrial function of long-term endurance training might lead to atrial remodeling, favoring arrhythmia development.

These data from Sanz-de la Garza et al [51] provided some important new insights about post-race cardiac function. They observed a post-race reduction in RV but not LV function. The novel finding was the changes in atrial function which, relative to baseline, augmented after 14 km of running but then progressively reduced over 35 km and 56 km. Dysfunction of the right atrium occurred earlier and was more profound than for the left atrium. It is of interest that the athletes completing the longest race had greater atrial dysfunction despite better pre-race conditioning. It seems that training cannot adequately offer cardiac protection from the significant hemodynamic stress of elite endurance racing.

Data found in previous studies mentioned above indicate a higher incidence of AF among athletes and former competitive athletes compared with the general population. However, this occurs predominately in middle-aged athletes engaged in endurance sport activities over a long time period, which supports the concept that years of endurance training may be necessary before the development of AF [51-53]. The lack of vast prospective studies where the amount of exercise is accurately measured with many years of long-term follow-up does not allow at present time the inception of lifetime hour threshold of sport practice for AF development. Future research should focus on the physiopathology of AF, on the increasing role of inflammation and novel serum biomarkers associated with strenuous physical activity. It is essential to develop effective treatment approaches and to determine to what extent could be useful to utilize anti-inflammatory drug agents.

Declaration of Interest and Funding

None. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conclusion

In conclusion, there is cumulative data associating moderate physical activity to reduced AF incidence, hence physicians should recommend moderate exercise training to patients with AF. This may not only reduce AF risk, but would also contribute to an overall cardiovascular benefit. On the other hand, more strenuous elite endurance exercise increases the risk of AF in healthy athletes without organic heart disease. Indeed, there is a relationship between accumulated hours of practice and AF risk indicating a U-shaped association between the extent of high-intensity training and AF risk. It seems that training cannot adequately protect the heart from the significant hemodynamic cardiac stress of elite endurance exercising. Therefore, since there is a significantly increased incidence of AF in elite athletes with long-term endurance physical activity, it may be of serious concern to go to the extreme. As in most things in life it is much better and wiser to be well balanced, always in equilibrium.

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