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World Atrial Fibrillation Day – Is it time to recognize the beast?

Dhanunjaya Lakkireddy MD, FACC, FHRS

Introduction

This entire journal is dedicated to the science related to Atrial Fibrillation (AF) and yet we cannot publish enough about this most heterogeneous disease process that is a lot more complex than our current understanding. There are many interesting and well known facts about AF. It is common knowledge that it is the most common arrhythmia that affects several millions of people across the globe and remains the number one cause of stroke. Thanks to advances in therapies that there is increasing awareness both in the professionals and lay public. With billions of health care dollars that get spent in treating the disease and the related complications, AF is slowly moving up on the notoriety scale with most of the world's health care delivery systems.

The important question that remains partially answered is – how do we recognize this beast of a disease that has such a profound social and personal impact? The current status of AF is what CAD used to be in the early 60s. Understanding the pathophysiology, early recognition, appropriate tools of diagnosis, intervention and prevention took more than 5 decades of intense work from all fronts on CAD to finally lose its place to cancer as the number one killer of the human race. AF is slowly creeping up in its prevalence and has evolved to be a familiar subject of health related discussions at all levels. The number of scientific publications that targeted AF alone has increased by 1500% in the last decade. There are more than 100 medical device and pharmaceutical companies that have AF diagnosis and or treatment related products in their portfolio. More than 15% of hospitals in the United States now have Centers of Excellence in Atrial Fibrillation Management or have the infrastructure to offer AF related therapies. All these growing facilities and access to therapy still seems to be not sufficient enough to make a significant dent in the overall clinical morbidity and mortality imparted by AF. Some of the most easily recognizable problems to effective diagnosis and therapy for AF remain obvious but still worthwhile to discuss. Awareness and understanding of the disease is still relatively low both in patients and health care professionals. This issue seems more profound in the developing and underdeveloped nations. Significant inequality of patient access to appropriate and timely care remains another major bottle neck. This inequity seems to be determined by the regional, racial and socioeconomic differences in access. Lapses in communication for a more effective care continuum once the patient is recognized to have AF and standardization of therapy that is evidence based and guideline driven stands out prominently why AF therapy is complicated. Limited effectiveness of the currently available treatment strategies limits our ability to tackle AF full force.

Patient advocacy and awareness campaigns are very important to promote the grass root level engagement in our fight against AF worldwide. This strategy has been proven to be very effective in successfully eradicating several communicable diseases and prevent/treat several many chronic diseases. Several organizations have started working on the patient education front and one such body that has been doing commendable work is Global AF Alliance (GAFA) Foundation. This article highlights some of the important ground work this organization has been doing in the last few years. GAFA is a not –for-profit organization founded for the purpose of bringing together patients, physicians and industry world-wide for the common goal of improving the knowledge, awareness, and support for the management of AF. GAFA aspires to overcome both the cultural, linguistic, and geographical barriers among physicians who treat AF and the communication barriers that can exist between patients and their physicians by creating a common resource that is available to all. GAFA aims to use this alliance as a proactive tool in involving patients in their health care decisions regarding treatment of AF. It is important to provide people who have been affected by AF with adequate knowledge through the most current news and developments in research, information on prevention, management, and their treatment of AF, along with outlets for support and ways raise awareness in their community and on a more global front.

September has been recognized as the AF month. Taking this further GAFA has officially obtained a proclamation by the governments of states of Kansas and Arkansas to celebrate the second Saturday of September as the World Atrial Fibrillation Awareness Day. The goal is to have the federal government pass a resolution to recognize the same on a national level. GAFA worked together with numerous cities internationally to plan events that continue to bring attention to the prevalence of AF in society and its potential impact on patient and family quality of life. These events included educational talks and fundraising activities to benefit investigator initiated research for the treatment and management of AF. There has been a significant focus not only on diagnostic treatment and tools, but also on alternate forms of AF management such as yoga and lifestyle changes. The Arkansas chapter of GAFA led by Dr. Raj Chaka and team have done exceptionally well in organizing big run

and educational event in the last few years.

On a more global level GAFA is striving to decrease the knowledge gap between nations with well-established AF treatment centers and countries with few learning opportunities about AF management through networking that will allow interested physicians to partner with electrophysiologists. The Global Atrial Fibrillation Alliance pledges to create an active, informed, and united community in our endeavor to provide the best healthcare possible for AF.

As a part of the World AF Awareness Day, GAFA recognizes individuals and organizations who have done exemplary work in the field of AF with the GAFA ambassador awards. This year the GAFA physician ambassador award was given to a house hold name in the AF world and editor-in-chief of JAFIB Dr. Andrea Natalee. Dr. Natalee serves as the Executive Medical Director of the Texas Cardiac Arrhythmia Institute at St. David's Medical Center, Austin, Texas. He has distinguished appointment in multiple other institutions. He is a true global physician whose foot print spreads from Italy to USA to China. Born and raised in Italy he moved to the United States 1991 and continued his electrophysiology research and clinical work. Built on the solid foundation of his early scientific interests he continued to challenge the field of electrophysiology with his innovative techniques and provocative ideas. He infused significant energy into a static field and redefine the direction of its progress.

Dr. Andrea Natale,
recipient of the GAFA Physician Ambassador of the Year
Award for 2015

Dr. Natale has more than 800 peer reviewed abstracts and manuscripts that were published and presented in various international journals and meetings. Despite a very busy clinical schedule he manages a large research operation. He is the most prolific researcher that the field has ever seen. He has received many awards in recognition of his work, including the most recent American College of Cardiology's Simon Deck Award for outstanding scholarship in 2014. He popularized the role of intracardiac echo in EP procedures. The roving lasso approach use intracardiac echo during Pulmonary vein antral ablation can be otherwise called the Natale approach. He is one of the first to recognize the arrhythmic role of left atrial appendage and the value of effective isolation of the same for raising the success bar for persistent AF undergoing ablation therapy. He has been an invited speaker at more than a 1000 national and international meetings and directs five major international meetings every year. Dr. Natale has the credit of being an amazing mentor to several electrophysiologists around the world. His trainees cover many countries in the world. I had the personal pleasure of being one of his trainees during my EP fellowship years at the Cleveland Clinic. He remains an amazing source of inspiration for an entire generation of people for work ethic, dedication to medicine, scientific advancement, compassionate care and the power of human determination.

Mr. Shannon Dixon,
recipient of the GAFA Patient Ambassador of the Year
Award for 2015

The GAFA patient ambassador award for 2015 went to Mr. Shannon Dixon (Figure-2). Sixty three year old Shannon Dickson's early adult life included a successful career as owner of a design-build mechanical engineering firm focused on large-scale alternative energy projects for cooling and water heating of hotels, high-rise condominiums and hospitals in the state of Hawaii. By 1988, his company was absorbed by Hawaiian Electric, the state's largest utility, and morphed into their alternate energy division. In 1992, at age 40, a family history of Atrial Fibrillation caught up to Shannon, beginning his almost quarter century experience of dealing with progressively evolving AFIB, which ended in a highly successful two-step persistent AFIB ablation process performed by Dr Andrea Natale, including LAA isolation in the second procedure.

At the beginning of 2014, Shannon was asked to take over ownership and editorial duties of the website: www.afibbers.org and companion bi-monthly newsletter, The AFIB Report. This website represents the oldest AFIB-centric patient education and advocacy resource on the web. Shannon's long and eventful personal AFIB history, spanning many evolutionary changes in AFIB treatment and understanding, combined with his avid patient advocacy work online, and by phone, with fellow AFIB patients from around the world over the past 12 years, brings Shannon to Kansas City this week to help celebrate World AFIB Day 2015.

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A Grand Tribute To A Pioneer In Electrophysiology

Andrea Natale MD, Editor-in-Chief

Dear Colleagues

We welcome you to the September issue of the Journal of Atrial Fibrillation. Hope you enjoyed the summer and getting ready for the flavors and colors of fall. The 7th annual edition of the Kansas City Heart Rhythm Symposium (KCHRS 2015) just got wrapped up in Kansas City. My special congratulations to our associate editor Dr. Dhanunjaya Lakkireddy and group for putting together another fabulous arrhythmia meeting that brought experts from far and wide to participate in this 2 day event. Over the years, the KU team has successfully transformed this meeting to a very popular regional education resource that draws attendees from all over the country. Kansas City in August is beautiful as always and quite a few electrophysiologists from around the world had the opportunity to enjoy the Midwestern hospitality. KCHRS 2015 brought state-of-the-art in electrophysiology while comprehensively covering the basics and providing an opportunity to enjoy the Barbecue and Royals.

Dr. Jeremy Ruskin
Founder and Director ,
The Cardiac Arrhythmia Service, Massacsetts.

Another important part of this meeting is their KU Pioneer in Cardiovascular Electrophysiology Award. This year Dr. Jeremy Ruskin, from Massachussets General Hospital has been recognized with this honor. Dr. Jeremy Ruskin is Founder and Director of the Cardiac Arrhythmia Service at Massachusetts General Hospital and Professor of Medicine at Harvard Medical School. Dr. Ruskin received his undergraduate degree summa cum laude from Tufts University in 1967 and his medical degree cum laude from Harvard Medical School in 1971. He completed a residency in Internal Medicine at Beth Israel Hospital in Boston from 1971-1973 after which received his training in clinical cardiac electrophysiology at the USPHS Hospital in Staten Island, New York under the mentorship of Dr. Anthony Damato from 1973-1975. He then completed a clinic and research fellowship in Cardiovascular Disease at the Massachusetts General Hospital from 1975-1978.

Soon after, Dr. Ruskin founded the MGH Cardiac Arrhythmia Service and Clinical Electrophysiology Laboratory, the first subspecialty service dedicated to the care of patients with cardiac arrhythmias in New England and one of the first in the United States. Since its inception, the MGH Cardiac Arrhythmia Service has been a leader in cutting edge clinical care, the training of future leaders in clinical cardiac electrophysiology, and research on the mechanisms of and innovative therapies for the treatment of cardiac arrhythmias. As founder and director of the MGH Fellowship training program in clinical cardiac electrophysiology in 1978, Dr. Ruskin has been responsible for the training and mentorship for more than 110 clinical and research fellows in the subspecialty of cardiac arrhythmias over the past 37 years, many of whom are in leadership positions at academic centers throughout the world. Dr. Ruskin serves as a member of the FDA Cardiovascular and Renal Drugs Advisory Committee for 5 years and as a consultant to the National Center for Health Services Research and Healthy Care Technology Assessment. For the past twenty five years, he has worked extensively on the scientific and regulatory aspects of medical device and drug development as wells as cardiovascular drug safety. In 1995, Dr. Ruskin founded the Annual International Atrial Fibrillation Symposium which he has directed since its inception and is the largest and longest running free-standing academic meeting on atrial fibrillation worldwide, now entering its twenty first year.

Dr. Ruskin's major research interests include the mechanisms and management of atrial fibrillation, new antiarrhythmic drugs and innovative technologies for catheter ablation of atrial fibrillation, the

mechanisms and prevention of ventricular arrhythmias and sudden cardiac death, risk stratification for sudden death, the proarrhythmic effects of cardiac and non-cardiac drugs and cardiac safety issues in new drug and device development. He is an author of more than 400 original scientific publications, chapters, reviews, guidelines and monographs. Dr. Ruskin also maintains an active regional, national and international referral practice in the field of cardiac arrhythmias and electrophysiology and is recognized annually in Best Doctors in America and Best Doctors in Boston. Dr. Ruskin is the recipient of the 1997 Michel Mirowski Award for Excellence in Clinical Cardiology and Electrophysiology and the 2002 Heart Rhythm Society Pioneer in Pacing and Electrophysiology Award. A special coverage of the meeting and all the talks will be accessible online in the Journal.

In this issue of the Journal we have exceptional original manuscripts, featured reviews and case reports covering a wide range of topics related to atrial arrhythmias.

We wish you a great thanksgiving and a happy holiday season

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Preferential Conduction Properties Along The Left Lateral Ridge And The Arrhythmogenicity Of The Left Pulmonary Veins In Patients With Atrial Fibrillation

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Abstract

Purpose: In this study, we examined the hypothesis that the preferential conduction property along left lateral ridge (LLR) might affect the arrhythmogenicity of left pulmonary veins (LPVs).

Methods: The study population included 40 consecutive AF patients. Radiofrequency energy (RF) was sequentially delivered along the LLR from a lower to upper manner during postero-lateral CS pacing during an isoproterenol infusion.

Results: The conduction time during pacing from the CS was significantly prolonged during radiofrequency (RF) deliveries (before vs. after, upper; 91±26ms vs. 127±38ms, p<0.001, lower; 86±21ms vs. 103±22ms, p<0.001). Remarkable prolongation of more than 30ms was observed in 19 of 40 patients (48%) (both LPVs, 6; only the upper LPVs, 12; and only the lower LPV, 1). Sites with a remarkable prolongation were observed at the carina between the LPVs,[4] anterior site of the upper LPV carina,[10] anterior wall of the lower LPV,[3] and bottom of the lower LPVs [2] Thirty-three arrhythmogenic foci (AMF) from the LPVs were observed in 23/40 patients (56%). The conduction time during pacing from the LPVs during the RF delivery was significantly longer in the patients with AMF from the upper LPV than in those patients without (107±36ms vs. 146±40ms, p<0.01).

Conclusion: The LLR includes the preferential conduction properties between the CS and LPVs, and the observation of the serial changes during the RF delivery could provide us information about the LPVs arrhythmogenicity.

Introduction

The Left lateral ridge (LLR) between left atrial appendage and left pulmonary veins (LPVs) showed a fiber orientation perpendicular to LPVs ostium, and it includes the ligament and vein of Marshall with the ganglia and fibers of the autonomic nervous system. The ligament and vein of Marshall containing the Marshall bundle (MB) with richly innervates the sympathetic and parasympathetic nerves can serve as a source of triggers and the substrate of reentry of atrial fibrillation (AF).[1,2]

Histological studies indicated that the proximal portion of the MB directly connects to the muscular sleeve of the CS, and the distal portion connects to the left atrial wall along the LLR and LPVs with wide variations.[3,4] Because the dominant electrical connections and the conduction of the MB could serve as substrates for reentry as well arrhythmogenicity, the change of activation pattern along the LLR during radiofrequency application (RF) may be associated with the arrhythmogenicity of the LPVs. Actually, our previous study confirmed that the sites of AF initiation can be identified by using the angiographic vein of Marshall with balloon-occluded venography of CS during isoproterenol infusion.[5] In this study, we examined the relationship between the conduction properties along LLR and the arrhythmogenicity of the LPVs.

Methods

The study population consisted of 40 out of 47 consecutive patients with drug-refractory AF episodes who underwent radiofrequency catheter ablation (CA). Seven patients were excluded because sinus rhythm could not be maintained during the RF ablation. Exclusion criteria for the patient characteristics were as follows, 1) a left atrial diameter (LAD) of more than 50mm, 2) significant valvular disease requiring surgery, 3) an ejection fraction of less than 40%, 4) hypertrophic obstructive cardiomyopathy, and 5) long lasting AF of more than 5 years. The patients' mean age was 63 years, 29

Key Words:
Marshall Bundle, Coronary Sinus, Atrial Fibrillation, Catheter Ablation.

Disclosures:
None.

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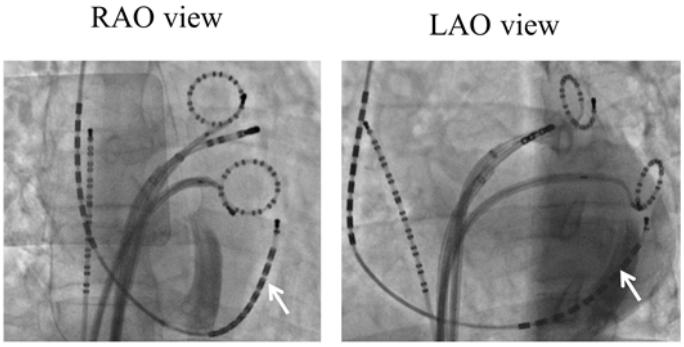

Figure 1: **Catheter locations**
Twenty-pole adjustable circular catheters (OPTIMA, St. Jude Medical, Minneapolis, Minnesota, USA) were simultaneously positioned at the upper and lower LPVs. A 20-pole catheter was positioned in the CS, and the SVC and crista terminalis were covered with a 20 pole catheter. The roving catheter was initially positioned around the LPVs. The white arrow indicates the location of the pacing site during RF.

(73%) were male, and 8 (20%) had persistent AF. Persistent AF was defined as that lasting longer than 7 days, not self-terminating and usually requiring medical intervention. Structural heart disease consisted of 10 patients (25%). The mean period of suffering from an AF episode was 55 months. The mean left atrial diameter was 39.6±5.6 mm, and left ventricular ejection fraction was 60.1±13.0%. All antiarrhythmic drugs were generally discontinued for at least 3 days before the CA. All patients provided written informed consent for the electrophysiological study and CA.

Electrophysiological Study And Catheter Ablation

A single 3000 IU bolus of heparin was administered and then an activated clotting time of >300 seconds was maintained after the transseptal puncture. A 20-pole diagnostic catheter was positioned in the CS for pacing and recording. A 20-pole catheter was placed in the right atrium to cover the area along the crista terminalis or superior vena cava (SVC). The LA and PVs were accessed by a transseptal approach. We introduced 3 steerable catheters, including two spiral curve catheters, into the left atrium through a single transseptal puncture site. The upper and lower LPVs were simultaneously mapped with two adjustable 20-pole catheters (OPTIMA, Irvine, USA) (Figure 1).

Coronary angiography was performed to evaluate the junction of the CS and great cardiac vein to identify in the orifice of Marshall vein and ligament. The features of the CS were determined by a subsequent filling and staining with contrast and/or by noting the location of the multipolar electrodes of the catheter within the CS. The 3D constructed geometry of the entire left atrium including the LPVs and LLR was created by using a NavX system (St. Jude Medical, St. Paul, Minnesota, USA). At first RF energy during CS pacing was delivered along the LLR as a part of the LPV ablation (Figure 2), and each ablation site and the conduction pattern during the RF delivery were monitored and recorded by fluoroscopy and a 3D electroanatomical system. The surface ECG and intracardiac electrograms filtered between 30 to 500 Hz were recorded simultaneously with a polygraph (Cardiolab; GE, USA or EP workmate; SJM, USA).

Radiofrequency (RF) energy was delivered for 30 to 60 seconds at each site using a dumbbell shaped 8 mm tip (Japan Life Line, Fantasista, Tokyo, Japan) or 3.5-mm irrigation tip catheter (St. Jude Medical, Minneapolis, Minnesota, USA). The RF energy was delivered with a power of 35 W with 8-mm-tip catheters, and 30 W with 3.5-mm-tip catheters.

The Detection Of Arrhythmogenic FOCI

An isoproterenol (ISP) infusion (0.5-2μg/min) was administered to determine the arrhythmogenicity of the LPVs during the left PV ablation. If AF persisted or spontaneously occurred under the ISP infusion, we attempted to cardiovert the AF up to 3 times. The DC energy was delivered with an external biphasic wave form of up to 270 J.

Arrhythmogenic foci (AMF) were detected using our previously reported methods. In summary, we simultaneously used five multipolar catheters to record the electrograms from the LPVs to search for any AMF. A 20-pole catheter (2 mm inter-electrode spacing) covered the area from the SVC to the crista terminalis, and the coronary sinus in addition to the ostium of the left PVs.[6] AMF were defined as direct AF triggers or spontaneous reproducible atrial premature beats with coupling intervals of < 350ms or frequent repetitive firings. The earliest activated sites were determined according to the sequence and time difference recoded by multipolar catheters. The early activated double potentials of the AMF from the PVs and SVC were reversed, and we considered that those AMF originated from each site. If the AMF were suspected to have originated from a non-PV area uncovered by the catheters, we attempted to search the location with a roving catheter around the early centrifugal activated sites.

Statistical Analysis

The continuous variables are expressed as the mean±SD. The variables were compared by a t-paired test or chi-square test. The data without a normal distribution were compared by a Mann–Whitney U test, which was used for the non-parametric analysis. A $P<0.05$ was considered statistically significant. All analyses were performed using SPSS 10.0 statistical software (SPSS Inc., Chicago, IL, USA).

Results

The change in the conduction properties during ablation along the left lateral ridge

The earliest activated site of the upper LPV during CS pacing was

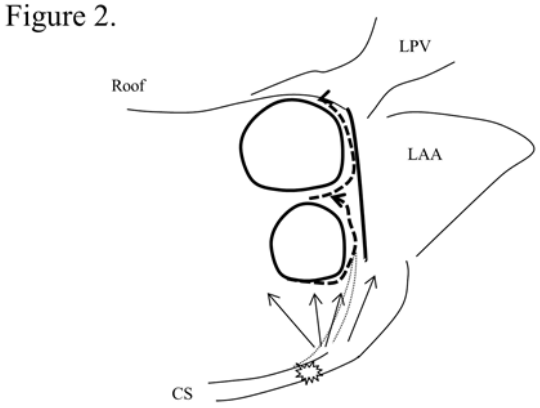

Figure 2: **The schema of the RF delivery along the LLR during CS pacing. The pacing site during the RF application was delivered from the postero-lateral CS, possibly from the take-off site of the MB. The RF application along the LLR was sequentially delivered in a lower to upper manner (from the bottom of the inferior LPV, anterior wall of the inferior LPV, and LPV carina, to the anterior wall of the superior LPV) during CS pacing.**

observed at the carina lesion in 32 of 40 patients (80%), anterior wall in 4 of 40 (10%), and posterior wall in 4 of 40 (10%). The earliest activated site was at the upper LPV in 34 of 40 (85%), bottom of the lower LPV in 4 of 40 (10%), and posterior site in 2 of 40 (5%).

After the RF delivery along the LLR, the PV potentials of the upper LPV completely disappeared in one patient and that of the lower LPV in 2 patients. The conduction time between the LPVs and CS stimulus site was significantly prolonged during the RF delivery (before vs. after, upper; 91±26 ms vs. 127±38 ms, p<0.001, lower; 86±21ms vs. 103±22ms, p<0.001). A remarkable prolongation of more than 30 ms was observed in 19 of 40 patients (48%) (both LPVs; 6, only the upper LPVs; 12, and only the lower LPV; 1). The sites of the remarkable prolongation during the RF delivery were observed at the carina between the LPVs,[4] anterior site of the upper LPV carina,[10] anterior wall of the lower LPV,[3] and bottom of the lower LPVs[2] (Figure 3).

The Features Of The Arrhythmogenic Foci And Their Relationship To The Conduction Properties

Thirty-three AMF from LPVs (upper; 22, lower; 11) were observed in 23/40 patients 56%. Fifteen of the detected AMF directly shifted to AF, and 16 of them exhibited premature atrial contractions and/or transient frequent repetitive firings.

The patient characteristics in the patients with AMF and without AMF are shown in Table 1. There were no significant differences in the gender, age, AF period, hypertension, diabetes mellitus, history of heart failure, history of cerebral artery disease, left atrial parameters, and left ventricular ejection fraction, between the two groups.

The earliest activated site of the AMF from the upper LPV was found at the carina region in 12 of 22[55%], anterior wall in 3 of 22[14%], roof site in 3 of 22[14%], and posterior wall in 4 of 22. The earliest activated site of the AMF from the lower LPV was found at the carina region in 6 of 11 [55%] anterior wall in 2 of 1,18% bottom in 1 of 11[9%], and posterior wall in 2 of 11[18%].

The conduction time from the CS to the earliest activated upper PV after the RF delivery was significantly longer in the patients with AMF from the upper LPV than in those patients without (107±36 ms vs. 146±40 ms, p<0.01), and the conduction time from the CS pacing site to the earliest activation site of the upper LPV was significantly prolonged in the patients with AMF than in those without during the RF delivery (44±22ms vs. 17±11ms, p<0.01). The following AF after AMF was spontaneously terminated in 2 of 15 AF episodes [13%]during RF along LLR, and the prolonged conduction time after RF along LLR were 47 ms and 44 ms, respectively. The premature atrial contractions and/or transient frequent repetitive firings were no more observed after RF along LLR in 11 of 16[69%].

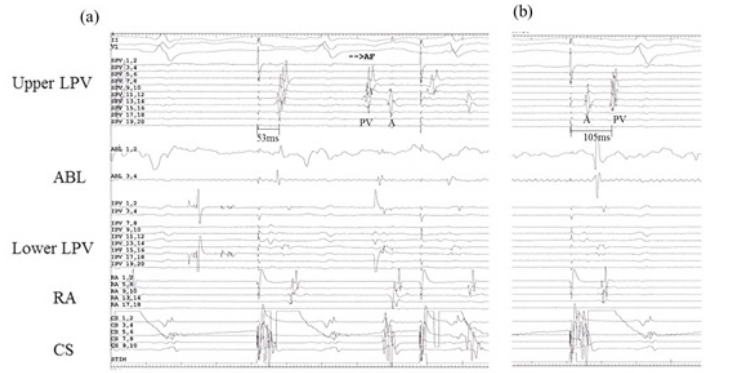

Figure 3: AF initiation and the prolongation of the upper LPV potentials during the RF delivery.
AF was initiated from the left upper PV during CS pacing. The early activated reversed double potentials represent arrhythmogenic foci from the upper LPV (a). AF was spontaneously terminated during the RF application on the anterior wall of carina, and the interval from the CS pacing site to the upper LPV suddenly prolonged at the earliest activation site (pre, 53ms vs., post, 105ms) (b).
PV; pulmonary vein potential, A; atrial potential

Discussion

In this study, the dominant conduction from the CS to the upper LPV was commonly observed in the carina region with its increased arrhythmogenicity. The conduction time between those was significantly prolonged during the RF deliveries along the LLR, and a remarkable jump prolongation of more than 30 ms in those was observed in approximately half of the patients. The extent of the prolongation was significantly higher in the patients with AMF, as compared to the patients without AMF. Thus, these findings could imply that the LLR containing the MB includes the preferential conduction properties between the CS and LPVs, and has an association with the increased arrhythmogenicity of the upper LPV. The observation of the change in the conduction properties during the RF delivery could provide us with useful information about the potential upper LPVs arrhythmogenicity.

Anatomical Myocardial Structure Of The Left Lateral Ridge

The LLR showed a fiber orientation perpendicular to the blood flow, and the LPVs and left atrial musculature are likely to be disconnected or was only connected via a narrow isthmus because of the bulging ridge structure.[7] There are abrupt changes in the fiber orientation in the middle portion of the LPVs.

The VOM, or LOM as the MB including the density of the ganglia and fibers of the autonomic nervous system, can be traced on the epicardial aspect of the LLR with a close proximity to the endocardial surface, and they course obliquely and superficially in the ridge at variable distances from the endocardial surface of the LLR within 3 mm from the endocardium. The other most dominant fiber of the LLR is Bachmann's bundle, which runs leftward to the neck of the left atrial appendage on the epicardial aspect of the LLR with a close relationship to the vein of Marshall or its ligament. Deeper than Bachmann's bundle is an another subepicardial fiber, which is the septopulmonary bundle that covers the orifices of the left PVs. Futhermore, the subendocardial septoatrial bundle forms a broad flat bundle towards the orifices of the left PVs.

Arrhythmogenicity Of The Marshall Bundle

The Vein of Marshall or its ligament containing the MB is a remnant of the left superior vena cava, and is accompanied with richly innervated sympathetic and parasympathetic nerves, and its arrhythmogenicity could be revealed during an ISP infusion.[6,8,9]

In this study, AMF were highly observed from both LPVs under an ISP infusion, and the earliest site of those from the LPVs was often determined to be around the carina region. These observations are likely to be consistent with the previous report.[10] In addition, the complex crossing of the muscular connections, bridges, neural inputs, and the adjoining muscle sleeves, possibly related to the MB conduction in the inter-PV carina, might promote electrical arrhythmogenicity including spontaneous ectopies of AF.[11] From those observations, intensified RF applications targeting the carina

Table 1:

	AMF (+) (N=23)	AMF (-) (n=17)	p value
Male (%)	67	65	0.624
Age (years)	68±10	68±10	0.985
AF periods (months)	5.5±5.4	6.4±8.4	0.596
Hypertension (%)	57	65	0.436
Diabetes Mellitus (%)	17	12	0.452
History of HF (%)	13	18	0.624
History of CI (%)	9	12	0.774
Left atrial diameter (mm)			
A-P	35.4±4.7	35.9±6.2	0.784
PV-MV	47.4±6.8	48.4±6.7	0.854
LVEF(%)	66.3±7.2	67.2±6.3	0.846

HF; heart failure, CI; cerebral infarction, A-P; anterior-posterior, S-L; septal- lateral, PV-MV; pulmonary veins-mitral valve

lesion and LLR should be required to delineate the arrhythmogenicity of the MB because of its epicardial location.

Conduction Properties Of The Marshall Bundle

The electrical connections and the conduction of the MB could serve as substrates for reentry as well as arrhythmogenicity. The MB runs along the LLR between the LAA and anterior wall of the LPVs. The proximal portion of the MB directly connects to the muscle sleeve of the CS, and the distal end of that connects to the left atrial wall and LPVs.[3, 4, 12] Our recent case report confirmed that the epicardial MB conduction could include a preferential conduction to the LPVs.[13]

In this study, the RF application along the LLR suddenly and remarkably prolonged the conduction time between the CS and LPVs in approximately half of the patients, and these observations might reflect the presence of a dominant longitudinal conduction along the LLR. And then, the earliest activated site of the upper LPVs during CS pacing was highly observed around the carina region, and also a remarkable prolongation jump during the RF delivery was highly observed around the carina and/or adjacent anterior area. A previous report suggested that the distal exit of the MB into the upper LPV is commonly located around the inter-PV junction, possibly bypassing the LPV junction to the left atrium.[7] These specific muscle orientations and the dominant MB conduction toward the carina region could promote the preferential conduction properties.

Recent studies demonstrated that the carina region should be the target site to achieve complete LPV-LA disconnection whether using circumferential or wide encirclement ablation strategies,[14, 15] and the additional ablation at the PV carina region may be sometimes required to achieve electrical isolation even after PVI.[16,17] In addition, the ablation of PV carina region may be associated with the improved outcome of AF ablation.[18,19] These reports consistently imply that the carina region can be a favorable target for an AF ablation strategy. In the meantime, we have to keep in mind that an excessive multiple RF energy toward carina may increase the risk of PV stenosis, and the careless catheter manipulation along LLR from LAA side may be prone to increase the risk of cardiac perforation, because the LAA has a very thin wall structure.

LPV Arrhythmogenicity And Prolonged Conduction

In this study, the prolongation of the conduction time between the CS and LPVs during the RF delivery was significantly more commonly observed in patients with upper LPV arrhythmogenic foci than in those without. The preferential properties of the MB connecting to the LPVs might involve cross-talk that promotes an increased LPV arrhythmogenicity.[3, 4, 12] Previous reports demonstrated that the presence of an LSVC and larger VOM were likely to be related to the increased chance of AF.[9,20] and thus a larger amount of preserved MB muscle as a remnant of the LSVC, which is related to the conduction properties of the LPVs, may be crucial for determining the increased arrhythmogenicity of the LPVs.

Limitations

CS pacing could not only capture the MB, but also atrial muscle. In addition, we could not directly record the MB potentials. When the rapid conduction endocardially traveled through atrium muscle, the interpretation of MB conduction could be limited. A previous study reported that the PV muscle covers a large extent of the PV perimeter, and there are specific breakthroughs from the left atrium.[21] If the continuous MB conduction is present, careful 3D mapping system should be required to assess the preferential conduction properties via the MB.

Conclusions

MB predominant conduction properties during the RF delivery could provide us with useful information about the potential upper LPV arrhythmogenicity. These findings imply the necessity for intensified RF applications in the carina region and entire LLR.

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Innappropriate Sinus Tachycardia After Superior Vena Cava Isolation In Addition To Pulmonary Veins Isolatin Of Paroxysmal Atrial Fibrillation Cryoballoon Ablation

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Abstract

We report a case of persistent inappropriate sinus tachycardia (IST) after pulmonary vein and superior vena cava (SVC) isolation with cryoballoon ablation for paroxysmal atrial fibrillation (PAF). After the cryoballoon ablation (CBA) procedure, the patient presented with sinus tachycardia of 105 beats/minute. The patient was successfully treated with metoprolol and ivabradine therapy

Introduction

Inappropriate sinus tachycardia after cryoballoon ablation for PAF has never been described. We defined a case of persistent inappropriate sinus tachycardia after pulmonary vein and superior vena cava isolation with cryoballoon ablation for PAF. This tachycardia was successfully treated with ivabradine plus metoprolol combinationResults.

Case Report

A 42-year-old man underwent pulmonary vein isolation with cryoballoon ablation for drug-resistant PAF. Pulmonary vein isolation was performed during atrial fibrillation. After successful pulmonary vein isolation with CBA procedure, a mapping catheter was positioned in the superior vena cava (SVC) to map the origin of the atrial fibrillation. We found superior vena cava triggers. During atrial fibrillation, intracardiac mapping indicated firing foci in the superior vena cava. Cryoballoon ablation successfully removed superior vena cava potentials, resulting conduction block between superior vena cava and right atrium. One month after the CBA procedure, sinus tachycardia was observed in the patient. Before ablation, his mean heart rate was 65 beats/minute and a 24 hour Holter recording revelaed a mean heart rate of 89 beats/minute (Maximum 112 beats/min – min 78 beats/min) after CBA (Figure 1). The resting heart rate was >100 b.p.m in the patients however average HR was 89-90 b.p.m on Holter recording. Additional causes of sinus tachycardia like pericardial effusion, fever and anemia were all excluded after the procedure. In our patient, increased heart rate was not evident shortly after the procedure but one month after the ablation procedure. In addition, transthoracic echocardiography or chest X-ray findings demonstrated no findings regarding pulmonary thromboembolism like increase in right ventricular dimensions, increase in tricuspid insufficiency or pulmonary artery pressure in our patient. Besides those, the decrease in mean heart rate just after ivabradine theraphy also confirms the diagnosis mainly based in the increased automaticity in sinus node. The ECG of the patient was not compatible with AT but a focal atrial tachycardia cannot be excluded just based on 12 lead ECG as in the case of focal atrial tachycardia originating from the superior part of crista terminalis. However, the initiation of the tachycardia was not abrupt and termination was not occurred suddenly in our patient indicating the rhythm originating from sinus node even the warming up and the cooling down of the atrial tachycardias are considered. Beyond those, the response of tachycardia after cryoablation to ivabradine is also compatible with sinus tachycardia apart from other rhythm disturbances. Because of the persistent complaint of palpitations, metoprolol succinate was introduced as 50 mg twice daily. This theraphy was continued for 2 weeks and because of the patient´s continuing complaints ivabradine was added to the therapy. During the metoproilol treatment a small decrease in heart rate was observed as 10 beats/min, but this was not enough for the patient and after that ivabradine treatment was added which caused a significant gradual decrease in heart rate as well as improvement in the patient`s symptoms with a mean heart rate of 65 b.p.m.

The procedural details of the pulmonary veins isolation with cryoballoon ablation have been described previously.[1] A 28 mm diameter balloon was used in the patient. During right pulmonary vein cryoballoon ablation application, the right phrenic nerve was continuously paced from the superior vena cava. If the strength of diaphragmatic contraction decreased, cryoballoon application was immediately stopped. In addition, we applied the same procedure

Disclosures:
None.

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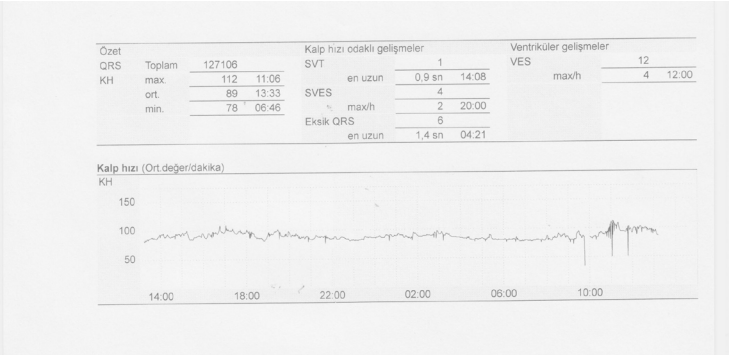

Figure 1: Superior vena cava potentials recorded during the procedure

during superior vena cava isolation. A circular mapping catheter was placed in superior vena cava, where large and high frequency signals were recorded (Figure 2). Isolation of electrical activity in superior vena cava was achieved with only one cryoballoon ablation procedure (Figure 3). After successful pulmonary vein and superior vena cava isolation, atrial fibrillation was terminated spontaneously. The termination of AF was after SVC ablation during the procedure and it was immediate after the end of the procedure. The rhythm

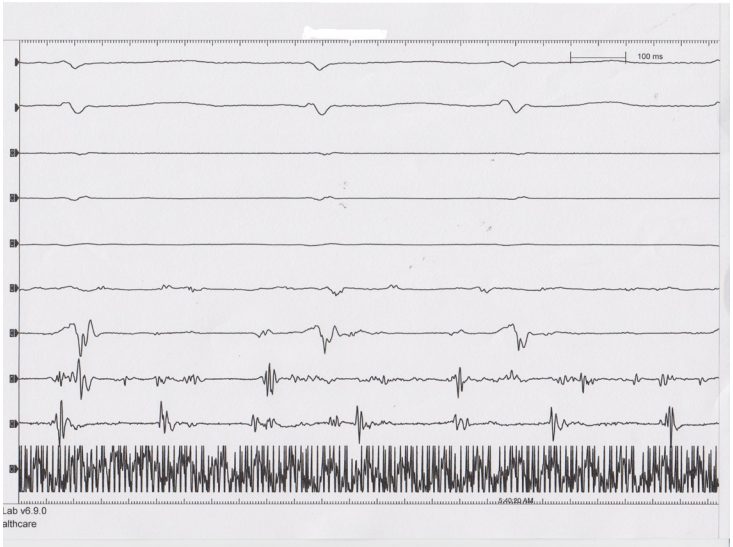

Figure 2: Cryoballoon application for superior vena cava

after the ablation was sinus rhythm and we did not observe any atrial fibrillation during the post procedural follow-up (Figure 4).

Discussion

Cryoballoon ablation of PAF can be safely performed without complications. Our case report has two clinically interesting points. First of all, to the best of our knowledge, this is the first case in the case in the literature describing the the occurrence of IST after cryoballoon ablation of PAF. Second important point is the firing SVC foci necessitating isolation during the cryoballoon ablation procedure for PAF. The patient was 42-year old male without any other risk factors according to the CHADSVASC scoring therefore anticoagulation as warfarin was just given for the 3 months after the cryoablation in this patient and warfarin was cessated after 3 months. Anticoagulation regimen was just given for the 3 months as warfarin after the procedure in this patient due to the zero CHADS2-VASC score.Inappropriate sinus tachycardia after pulmonary vein and superior vena cava ith cryoballoon ablation for PAF has not been reported before. Atrial fibrillation is also initiated by ectopic foci other than pulmonary veins.[2,3] The SVC is thought to be the most

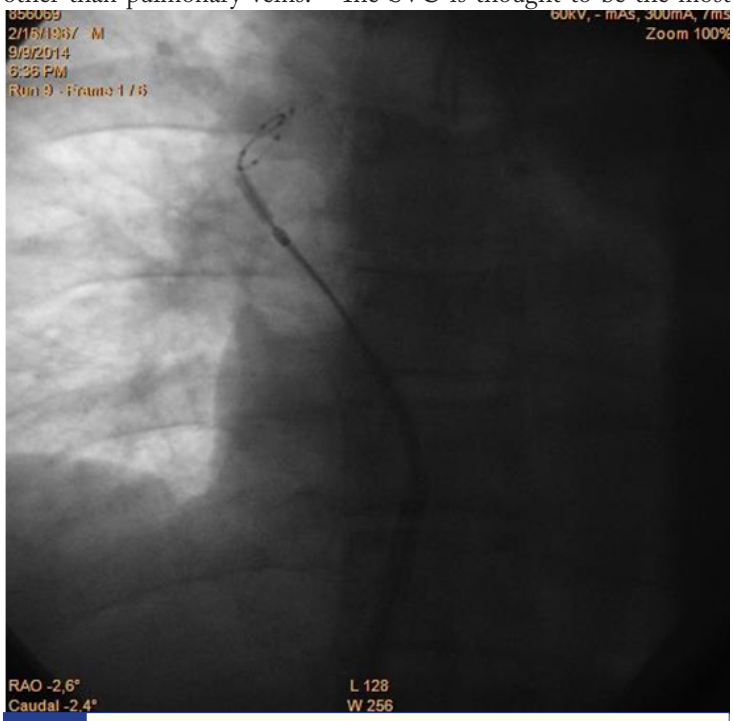

Figure 3: Holter monitoring After Cryoballon Ablation

common source of ectopic foci and has been reported to play a role in arrhythmia initiation and maintenance in 6%-12% of patients with PAF.[4] Corrado et al. reported in their randomized study that the patients who underwent SVC isolation as an adjunctive therapy to pulmonary vein isolation had significantly lower recurrence rate of atrial fibrillation than those who underwent only pulmonary vein isolation.[5] Inappropriate sinus tachycardia is likely due to cryoballoon ablation induced damage to autonomic ganglionic structures around the heart. Damage to the vagus innervation of sinus node could also be involved in the mechanisms of inappropriate sinus tachycardia

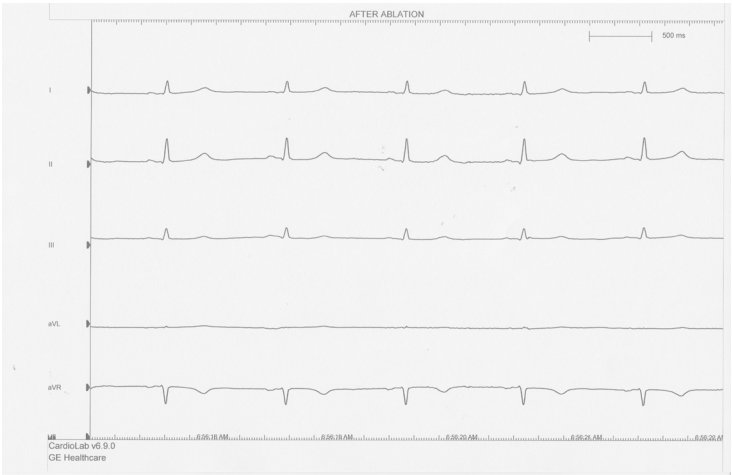

Figure 4: After Cryoballon Ablation ECG

after AF ablation.[6] Hyperactivity of the sympathetic nervous system that innervates the sinoatrial node has also been proposed to explain IST.[7] Inappropriate sinus tachycardia has also been reported as a complication of radiofrequency ablation of some supraventricular tachycardias.[8] Recently, De Sisti et al. reported the case of successful

use of ivabradine in a patient with inappropriate sinus tachycardia after cryoballoon ablation for atrioventricular nodal re-entrant tachycardia.[9] Similarly, in a previous study, we investigated the effect of cryoablation on external modifiers of AF-like ganglionated plexi which indicated that vagal reactions during cryoablation, as a surrogate marker of cardiac ANS modification, decreased AF recurrence in a subgroup of patients with paroxysmal and persistent AF.[10] In the light of those data, we think that local denervation during the cryoballoon ablation procedure causing modification of ganglionated plexi might cause the change in mean heart rate which was presented as IST in our patient.Beta blocking agents and calcium channel antagonists are commonly used in the treatment of IST. Ivabradine and metoprolol combination successfully controlled post-cryoballon ablation IST in our patient.

Conclusion

This is the first case of inappropriate sinus tachycardia after pulmonary vein and SVC isolation with cryoballoon ablation for PAF.

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Atrial Flutter In A Tetralogy Of Fallot Operated Patient: Importance Of A Rapid And Curative Treatment

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Abstract

A 51 male, affected by Tetralogy of Fallot, underwent a left Blalock-Taussig anastomosis at the age of two years and an aorto - right pulmonary artery tube graft when 8 years old. Complete surgical correction was performed at age 21 with closure of the ventricular septal defect and a large patch over the right outflow tract, shunts were discontinued. Then it was well up to 51 years old when he began to suffer shortness of breath with minimal exertion. with ECG evidence of supraventricular tachycardia. Suggestive signs of a typical atrial flutter led to early electrophysiological assesment and successful cavo-tricuspid isthmus ablation was successfully performed. Echocardiographic and magnetic resonance imaging and ergospirometry provided complete informations on anatomic and hemodynamic conditions but no other interventional procedure was necessary.

Introduction

Tetralogy of Fallot (ToF) is the result of anterior malalignment of the conal septum during embryological development. It is the most common cyanotic congenital heart defect, with an incidence rate of 32.6 per 100,000 live births.[1] Complete surgical repair has successfully been performed since 19542, but long-term outcome may be complicated by atrial and ventricular arrhythmias.[3–6] Patients over 50 years are rare and a very long term follow up has yet to be written. Conduction and rhythm abnormalities are associated with morbidity and increased mortality.[5] Atrial tachyarrhythmias (AT) such as atrial flutter or fibrillation are seen with increasing frequency beginning from the third decade of life.[6] We hereby describe a rare case of very long term follow up complicated by atrial flutter successfully treated with radiofrequency ablation.

Case Presentation

A 51-year-old male affected by an operated Tetralogy of Fallot was admitted to our Cardiological department for dyspnea on effort. When two year-old he underwent a Blalock-Taussig (BT) anastomosis as a palliation. He did relatively well until the age of 8 when he started having progressive symptoms with cyanotic spells for which reason, in right thoracotomy, a second shunt between ascending aorta and right pulmonary artery with a 7 mm tube graft was performed after which he did relatively well. At age 21 he manifested signs of increased cyanosis, marked limitation of activity and headache. He underwent cardiac catheterization whose findings were consistent with severe pulmonary stenosis, closed left BT shunt and poorly functioning aorto pulmonary shunt. Surgical correction was performed at the Texas Heart Institute, Houston, with closure of the ventricular septal defect and a large patch over the right outflow tract, which was found patent at surgery, the aorto pulmonary shunt was discontinued. No arrhythmias were present in the perioperative period.

The patient did relatively well until 51 years old when he developed progressively worsening dyspnea and was admitted in our Cardiological Department with the diagnosis supraventricular arrhythmia. The transthoracic echocardiogram showed a severely dilated right ventricle with the proximal outflow tract end-diastolic diameter 64 mm from the parasternal long axis view, the basal end-diastolic right ventricle diameter from the 4 chamber view was 63 mm, the left atrial are was 30 cmq and the right atrial area 34 cmq. The right ventricular free wall thickness was increased (6 mm) and the contractility moderately depressed with a fractional area change of 30% and a TAPSE (Tricuspid Annulus Systolic Excursion) of 16 mm. Tricuspid annulus S wave velocity was 10 cm/sec. The right ventricular outflow tract (RVOT) was not obstructed, the pulmonary valve insufficiency was moderate. A mild tricuspid insufficiency was present and the estimated ventricular systolic pressure was 38 mmhg. No residual ventricular patch shunt was present. The left ventricle ejection fraction was 54%. A transesophageal echocardiogram excluded auricular thrombosis.

12 lead ECG showed regular atrial arrhythmia at 105 bpm with a right bundle branch QRS morphology, regular atrial activation with inverted saw-tooth F-wave pattern in inferior ECG leads II, III, and aVF with low amplitude biphasic F waves in leads I and aVL, and upright F wave in precordial lead V1 and inverted F wave in lead V6 (Figure 1). These features suggested an isthmus dependent

Disclosures:
None.

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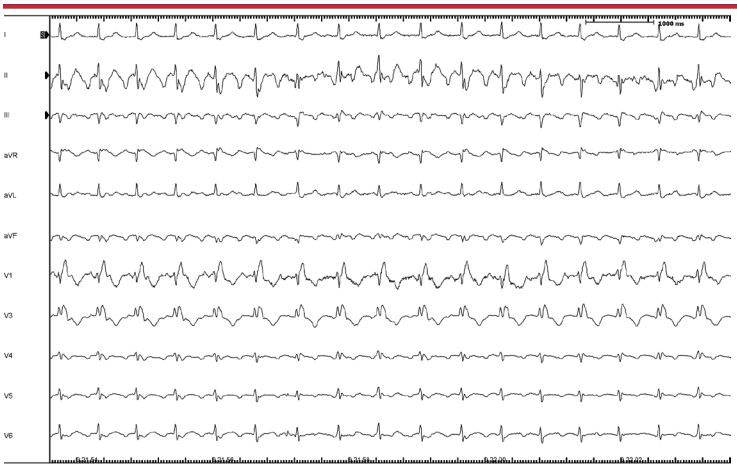

Figure 1: **Surface 12 lead electrocardiogram.**
Lateral, Augmented and Precordial leads shows atrial flutter with right bundle branch block morphology. F waves have saw-tooth pattern in inferior leads, flat aspect in I and aVL, and upright F pattern in V1 suggesting a typical atrial flutter.

atrial flutter, therefore an electrophysiological study was performed during ongoing arrhythmia. A decapolar deflectable mapping catheter was advanced into the coronary sinus showing proximal-to-distal activation with 2:1 atrial-ventricular conduction. Measured cycle was 286 msec. Ablator Catheter (Navistar DS 8 mm Biosense Webster, Diamond Bar, CA) was introduced in the right atrium and electro-anatomic map of the chamber was reconstructed using 3D computerized activation system (CARTO system Biosense Webster, Diamond Bar, CA). The activation and propagation maps showed counterclockwise activation pattern around the tricuspid valve with the typical aspect of early-meets-late at the cavo-tricuspid isthmus (Figure 3, Video 2). Pacing from the CTI demonstrated concealed entrainment thus confirming diagnosis of typical isthmus-dependent atrial flutter.

Application of radiofrequency (RF) (50 Watt, 65°) in the isthmus area (6 o'clock) determined arrhythmia interruption after 60 sec (Figure 4). Persistency of bidirectional conduction was verified. Detailed mapping of the ablation line was repeated identifying local conduction breakthroughs. Two selective applications of RF (320 sec each one) at these points led to complete and definite interruption of isthmus conduction (Figure 5). Results persisted after 20 minutes. The procedure terminated successful without acute complications. The ecg showed a sinus rhythm with atrio-ventricular first degree block, right ventricular hypertrophy and right bundle branch block with a QRS duration 180 ms.

Once in sinus rhythm, a cardiac magnetic resonance (CMR) and an ergospirometric evaluation was performed according to guidelines7-8. CMR showed an enlarged left ventricular volume: 83 ml/mq with mildly reduced ejection fraction: 50 %; dilated aortic root: 45 x 38 mm; right ventricular volume:133 ml/mq (z-value 3,3) with reduced ejection fraction: 37 %. The pulmonary infundibulum was dyskinetic due the presence of large patch but without significative delayed enhancement (Figure 2 Panel C). The pulmonary valve was present with moderate insufficiency and the regurgitant fraction was 31% (Video 1).

The ergospirometric study was interrupted after 13.2 minutes at the workload of 125 Watts due to dyspnea (Borg 4) but without arrhythmias. Peak O2 consumption was 73 % of the maximal predicted

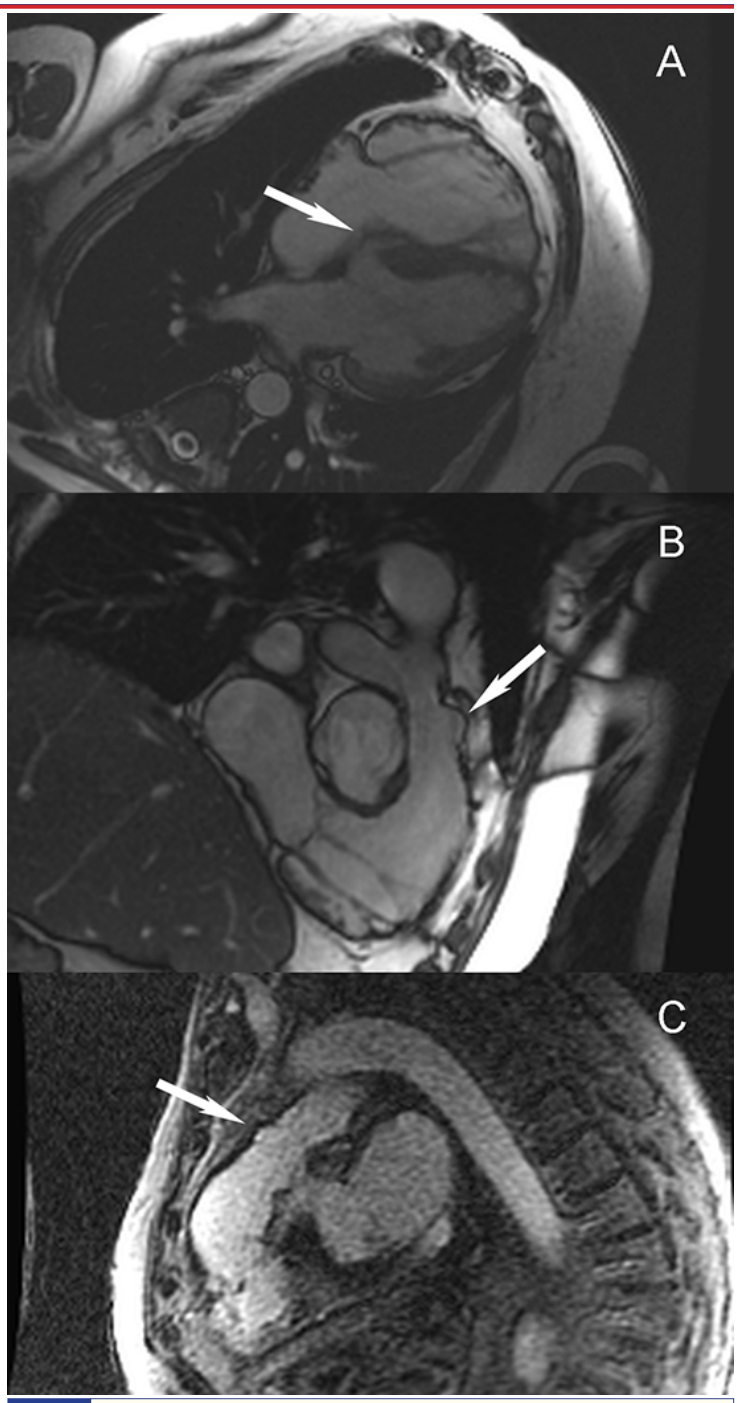

Figure 2: **Cardiac magnetic resonance.**
Panel A: steady state free precession still image, four chamber view shows the dilated right atrium and ventricle and the interventricular patch (arrow).
Panel B: steady state free precession still image, right ventricle 2 chamber view shows the inflow and outflow tract with the aneurismatic patch (arrow).
Panel C: T1 weighted post-gadolinium sequence shows absence of significative enhancement in the right ventricular outflow tract (arrow).

value: peak O2/Kg 22.9 mL/kg/min, VE/VCO2 slope.[25] VO2/work, slope pari a 11, Peak Respiratory Exchange Ratio (RER).[1,19] The anaerobic threshold was achieved at 44 % of the maximal predicted O2 consumption (59 % of the peak O2 consumption). No desaturation was present during the test.

After the ablation procedure the patient has been well without

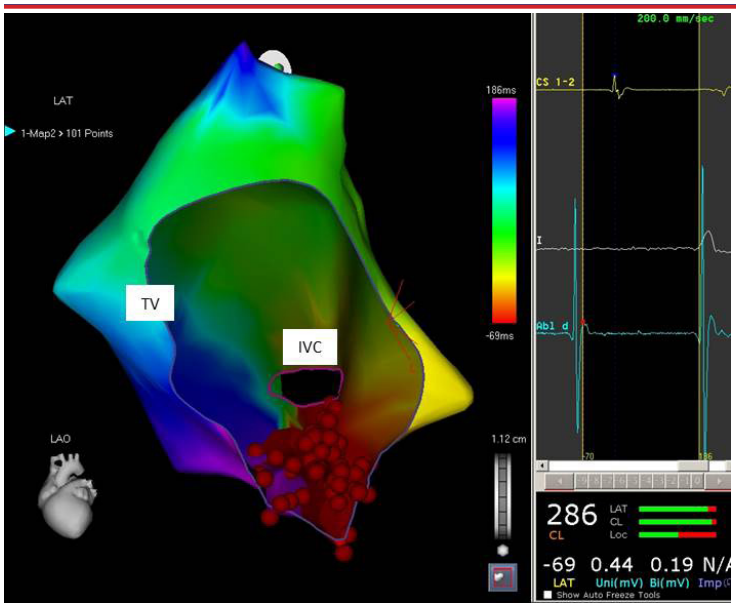

Figure 3: Left Anterior Oblique (LAO) view of three-dimensional electro-anatomic map (CARTO, Biosense Webster, Diamond Bar, CA). During ongoing arrhythmia with atrial cycle of 286 msec the map shows a typical counterclockwise activation pattern around the tricuspid annulus which is based on a color scheme indicating activation time from orange (early) to purple (late). The two colors are closed in the region of isthmus (early-meets-late) were red dots indicate ablation line. The right side of the figure shows intracardiac recording signals from coronary sinus catheter (CS 1,2) and ablator (Abld) and surface activation from I lead. Ablator, positioned in the isthmus region ablator displays two activation potentials respectively at the beginning and at the end of the cycle, atrial activation on the CS catheter is approximately mid-diastolic.

significant limitations to his physical activity and no arrhythmia recurrence.

Discussion

In ToF surgical relief of the RVOT obstruction involves infundibulotomy, resection of obstructive muscle bundles and the use of a patch to enlarge the pathway from the right ventricle to the pulmonary arteries. These procedures result in scar tissue and akinetic

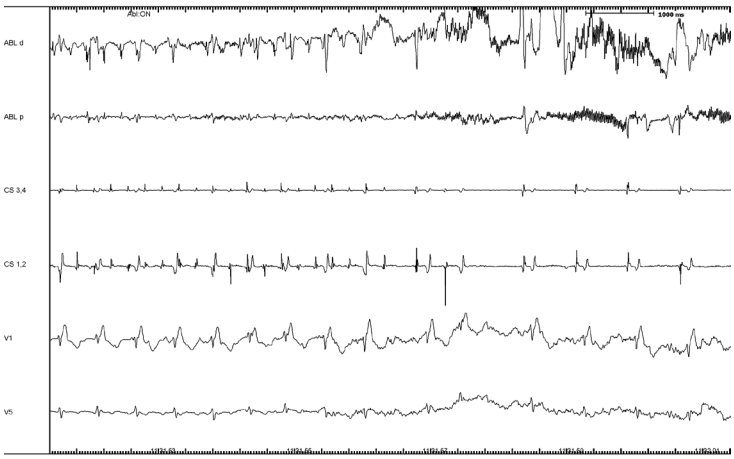

Figure 4: Arrhythmia interruption during radiofrequency application. Endocardial electrocardiogram from the ablator (ABLd , ABLp) and coronary sinus catheter (CS 3,4 CS 1,2). Surface activation from precordial leads (V1 and V6). 12th ventricular activation is in sinus rhythm. Real time cardioversion of atrial flutter happened 60 sec after initiation of radiofrequency applications.

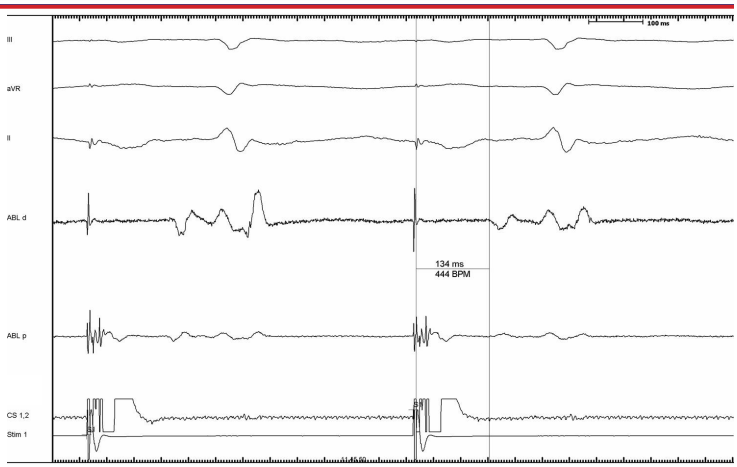

Figure 5: Confirmation of isthmus block after radiofrequency ablation. Surface electrocardiograms from III, aVR, II endocardial electrogram from the Ablator (ABLd, ABLp) and coronary sinus (CS 1,2). Activation on the ablator catheter lateral to the ablation line happens 134 msec after pacing stimulus from coronary sinus (S1), thus confirming a conduction block. SImilar results were obtained with pacing stimulus from the ablator with activation signals sampled on the coronary sinus, thus showing bilateral conduction block

RVOT free wall, which can become aneurysmatic, and pulmonary valve insufficiency. Other abnormalities that may be found in patients with repaired ToF are branch PA stenosis, residual atrial or ventricular septal defect, tricuspid regurgitation, right ventricular dilatation and dysfunction, aortic dilatation, aortic regurgitation, and left ventricular dysfunction. Corrective surgery requires ventricular and atrial incisions, therefore incisional reentrant tachycardias may develop, but the majority of AT are right atrial macro-reentrant tachycardias, most often involving the cavo-tricuspid isthmus9. Whatever the underlying electrophysiological mechanism, AT in TOF patients have a significative impact on clinical outcome and are associated with congestive heart failure, stroke, and death.[3–6] Even in a such distorted anatomy as in ToF , classic ECG signs of isthmus-dependent atrial flutter can lead to perform earlier electrophysiological evaluation to treat and rapidly solve the arrhythmia, due to its high therapeutical success (98%).

Conclusions

Development of atrial tachyarrhythmias in repaired ToF patients causes a severe worsening of the hemodynamic state and clinical outcome. This case report underlines the usefulness of an early invasive approach as effective and rapid curative treatment when the arrhythmia has typical signs of isthmus-dependent of atrial flutter which is an easy to ablate arrhythmia. After stabilization of hemodynamic compromise it highlights and the need of a complete evaluation of the post-operative anatomical and functional status.

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Review Of Obesity And Atrial Fibrillation: Exploring The Paradox

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Abstract

There is a well established association between obesity and atrial fibrillation (AF). Nevertheless, the effects of obesity in the outcomes of patients with AF has not been investigated since a few years before. In this regard, several studies have demonstrated a better clinical prognosis of AF in overweight and obese populations.

In the present manuscrit, we aimed to explore the main articles in which the "obesity paradox in AF" was found.

Obesity Burden

The prevalence of obesity has increased dramatically worldwide over the last decades and has now reached epidemic proportions. For instance, the global prevalence of obesity has nearly doubled between 1980 and 2008. According to the World Health Organization (WHO), 35% of adults worldwide aged more tan 20 years were overweight (34% men and 35% women) in 2008, including 10% men and 14% women being considered as obese. Prevalence is particularly high in America with a high proportion of overweight and obesity (62% and 26% respectively in both sexes and 3% for obesity).[1]

In the United States, the prevalence of obesity has increased by 8% between 1976 and 1980, by another 8% between 1988 and 1994 with similar increases between 1988-1994 and 1999-2000. In contrast, data from the last decade.[1999-2010] suggest that the prevalence of obesity may have plateaued in the USA.[2-4]

According to the latest National Health and Nutrition Examination Survey (NHANES), the age-adjusted obesity prevalence was 35.7% in the USA in 2010 with no sex differences. Extreme obesity has more than doubled since 1988-19944-5.

Such growing numbers are a source of concern since the negative consequences of obesity start as early as in childhood. Indeed, some experts predict a decrease life expectancy at birth in the USA during the first half of the 21st century[6].

Each year, 28 million individuals are dying from the consequences of overweight or obesity worldwide1. High body mass index (BMI) is associated with the development of cardiovascular (CV) risk factors such as hypertension, dyslipidemia, insulin resistance, and diabetes mellitus, leading to cardiovascular diseases (CVD) such as coronary heart disease and ischemic stroke.[7-9] The development of the comorborbidities is proporcionate to the BMI and obesity is considered as an independent risk factor for CVD.[10-11]

Several studies have documented that a high BMI is significantly associated, both in men and women, with manifestations of CVD such as angina, myocardial infarction, heart failure and sudden death.[12-13]

The higher incidence of CV events in obese patients seems to be related to endotelial dysfunction and subclinical inflammation in addition to the worsening of CV risk factors.[14] Overall, obesity is associated with an increased mortality rate15, but obesity grades must be considered in risk stratification. In a recent meta-analysis including 2.88 millions of individuals, all obesity grades combined were associated with an increased mortality rate, with an hazard ratio (HR) of 1.18 (95% confidence interval [CI], 1.12-1.25). However, when analyzed separately, obesity grade 1 was not associated with an increased mortality risk, with a HR of 0.97 (95% CI 0.90-1.09), compared to normal weight. In contrast, severe obesity (grades 2 and 3) was associated with and increased mortality risk (HR of 1.34-95% CI, 1.21-1.47).[16]

Atrial Fibrillation Epidemiology

Atrial fibrillation is the most common sustained cardiac arrthythmia, occurring in 1-2% of general population. Over 6 million European individuals suffer from this arrhythmia, and its prevalence is estimated to at least double in the next 50 years as the population ages.[17]

AF confers a 5-fold risk of stroke, and one in five of all strokes is attributed to this arrhythmia. Ischaemic strokes in association

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None.

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with AF are often fatal, and those patients who survive are left more disabled by their stroke and more likely to suffer a recurrence than patients with other causes of stroke. The risk of death from AF-related stroke is doubled and the cost of care is increased 1.5-fold. The prevalence of AF increases with age, from less tan 0.5% at 40-50 years, to 5-10% at 80 years. Men are more often affected tan women. It is well known that AF is associated with increased rates of death, stroke and other thrombo-embolic events, heart failure and hospitalizations, degraded quality of life, reduced exercise capacity and left ventricular dysfunction.[17]

AF is associated with a variety of medical conditions, which promote an additive effect on its perpetuation. Some of them described are ageing, hypertension, symptomatic heart failure, valvular heart diseases, coronary artery disease, thyroid dysfunction, diabetes mellitus, sleep apnea, chronic renal disease and obesity. Obesity is found in 25% of AF patients 15 in a large german AF registry.[17]

Above-mencioned data indicate that both, obesity and AF, are contemporary interlinked epidemics and will suppose a large public health burden in the future.

Prior studies have examined the relationship between obesity and AF.[18-21] Obese people have a 1.5 times higher risk of developing AF as compared with normal weighted individuals when BMI is considered as a categorical variable. Also, when BMI is investigated as a continuous variable, each unit increase in BMI has been associated with 4% increase in new-onset AF.[18-21] Although the precise mechanism for this association is not well understood, changes in atrial and ventricular structure diastolic function, autonomic function, and increased total blood volume might play a role.[22-26]

Furthermore, obesity is associated with left atrial enlargement, which is considered an "intermediate phenotype" for AF.[21] Obesity also is implicated as a risk factor for progression of paroxismal to permanent AF.[27] Although catheter ablation is successful in obese patients28, they often require more than twice the effective radiation dose as compared with normalweighted patients29. Also, obstructive sleep apnea (OSA), and its association with obesity, has been correlated with increased incidence, prevalence and recurrence of AF.[30-33]

Despite overwhelming data linking obesity and AF, the effect of obesity on outcomes in AF patients has not been investigated since a few years ago.

Obesity was traditionally associated with a higher prevalence of several medical diseases, worst outcomes and increased mortality rate. Surprisinly, recent studies in obese populations have shown positive results in terms of CV hospitalization, global and CV mortality. This has been termed as the "obesity paradox" in an attempt to reflect the paradoxical association between overweight, obesity and a more favorable prognosis, is poor understood but has been observed consistently in patients with established CV disease, including chronic coronary heart disease34, acute myocardial infarction,[35-36] acute and chronic heart failure35-39, peripherial arterial disease40, hypertension, chronic obstructive pulmonary disease41, and more recently in AF.[42-45]

Available Data

In a sub-analysis of the AFFIRM (Atrial Fibrillation Follow-up Investigation of Rhythm Management) study44, an inverse relationship between obesity and prognosis was described. A total of 2.492 patients were analyzed. BMI was evaluated as a categorical variable (normal 18.5 to <25 kg/m2, overweight 25 to <30 kg/m2 and obese ≥30 kg/m2) under the World Health Organization definition. Accordingly, the rate of all-cause death was higher in the normal BMI group (5.8 per 100 patient-years) than in the overweight and obese groups (3.9 and 3.7, respectively). In this study, CV death rate was also highest in the normal BMI group (3.1 per 100 patient-years), lowest in the overweight group (1.5 per 100 patient-years), and intermediate in the obese group (2.1 per 100 patient-years), being overweight associated with lower risk of CV death (HR 0.47, p=0.002). After adjustment for baseline factors, differences in risk of death from any cause were no longer significant.

At the same time, Apurva O. Badheka et al[43] performed a post hoc analysis of the AFFIRM study, where the same population of 2492 patients was analyzed. Patients with BMI ≥18.5 were slip into normal (18.5-25 kg/m2), overweight (25-30 kg/m2), and obese (≥30 kg/m2) categories as per BMI. Multivariate Cox proportional hazards regression was used in this cohort. Endpoints were all-cause mortality and CV mortality. They report 304 deaths (103 among normal weight, 108 among overweight, and 93 among obese) and 148 CV deaths (54 among normal weight, 41 among overweight and 53 among obese) over a mean period of 3 years of patient follow-up. On multivariate analysis, overweight (HR 0.64; 95% CI, 0.48-0.84; p=0.001) and obese (HR 0.80; 95% CI, 0.68-0.93; p=0.005) categories were associated with lower all-cause mortality as compared with normal weight. Overweight (HR 0.40; 95% CI, 0.26-0.60; p<0.01) also had lower CV mortality as compared with normal weight patients.

In a recent study performed by the AFBAR (Atrial Fibrillation Barbanza Area) research group,[42] obesity, defined as a BMI ≥30 kg/m2, was associated with better prognosis in a community-based cohort of patients with AF. A total of 746 patients who were prospectively included were studied. They were categorized into 3 BMI groups using baseline measurements: normal weight (<25 kg/m2), overweight (25-30 kg/m2), and obese (≥30 kg/m2). Survival free from the composite endpoint hospitalization for CV causes or all-cause mortality was compared across the 3 BMI subgroups. A multivariate Cox proportional hazard regression was also performed to determine the independent effect of obesity as well as overweight, with respect to normal BMI as a reference category regarding the study endpoint. Median follow-up time was 36 months. In this population, 49.3% were obese and 38.2% had overweight. The composite endpoint rate was 70.9%, 67.5% and 57.6% for obese, overweight and normal weight patients respectively (log rank test; p=0.02). An inverse association of obesity with a favorable prognosis persisted even after multivariate adjustment: HR 0.668; 95% CI, 0.449-0.995; p=0.0047. HR of overweight, however, was 0.741; 95% CI, 0.500-1.098; p=0.096.

Finally, in a recent study, Juan Wang et al[45] also found an obesity paradox in patients with AF and heart failure. They enrolled 806 patients with AF who were divided into 4 different BMI categories according to Chinese Obesity Working Group: underweight (<18.5 kg/m2, n=101 [12.5%]), normal weight (18.5 to 24 kg/m2, n=230 [28.5%]), obese (≥28 kg/m2, n=102 [12.7%]). The endpoints for current analyses were all-cause death and CV mortality during the 12-month follow-up. Univariate and multivariate Cox regression analyses were performed. A total of 153 deaths and 113 CV deaths occurred. All-cause mortality risk is lower in patients with overweight (HR 0.41, 95% CI, 0.26-0.64, p<0.001) and obesity (HR 0.46, 95%

CI, 0.25-0.83, p=0.011) compared to patients with normal weight. CV mortality risk is lower in overweight (HR 0.43, 95% CI, 0.26-0.73, p=0.002) and obese (HR 0.49, 95% CI, 0.24-0.97, p=0.042) patients. After adjustment for multiple relevant co-variables, as a continuous variable, BMI was not a risk factor for all-cause mortality (HR 0.91, 95% CI, 0.87-0.95, p<0.001), and for CV mortality (HR 0.91, 95% CI, 0.86-0.96, p<0.001). As a categorical variable, obesity (HR 0.50, 95% CI, 0.26-0.94, p=0.032) and overweight (HR 0.40, 95% CI, 0.25-0.63, p<0.001) were significantly associated with a lower risk of all-cause mortality, and overweight also with a lower CV death (HR 0.45, 95% CI, 0.26-0.76, p=0.003) compared to normal weight patients.

Obesity Paradox Controversies

On the basis of previously named studies, a better prognosis in overweight and obese patients with AF has been demonstrated. Nervertheless, the potential mechanism of this obesity paradox has not been fully elucidated. Several hipotheses had been proposed in this regard.

Inflammation and increased inflammatory markers are believed to cause AF initiation and maintenance.[46] It seems that the cell signaling protein called Tumor Necrosis factor alpha (TNFα), can increase the pulmonary vein arrhythmogenicity thereby causing inflammation-related AF. Because adipose tissue produces TNFαtype I and II receptors, this could result a anti-arrythmogenic milieu in obese patients with AF.[47,48]

The called "Endotoxin-Lipoprotein hypothesis", states that obese patients have higher cholesterol and lipoprotein levels, which could remove proinflammatory toxins causing a subsequent inflammatory state reduction, although the applicability of this hypothesis in AF is not clear.[49] Atrial natriuretic peptide levels are importantly increased in AF and predict mortality in advanced heart failure patients with AF.[50,51] Low circulating natriuretic peptide levels found in obese patients could be also related with better outcomes.[52]

The activation of renin-angiotensin system has been associated with atrial fibrosis and electrical remodeling in AF.[53] Obese people with AF may have diminished levels as compared with lean patients, which may improve long-term CV outcomes.[54]

The higher blood pressure levels seen in overweight and obese patients may allow for a greater and fast uptitration of therapies such as αblockers and angiotensin-converting enzyme inhibitors, drugs with demonstrated life-extending properties in AF patients.[55]

On the other hand, it is well known that higher body fat and especially higher lean mass index (LMI) may be associated with muscular strength, linked to favorable prognosis and better survival. Many epidemiological studies were unable to show a higher risk for adverse events in overweighed patients. This could be explained by the limited ability of BMI to differenciate body fat from lean mass.[56-58]

Studies Limitations

Based on its design, we cannot relate the results of the epidemiological studies with the proposed theories previously discussed. It will deserve further investigation in order to explain the mechanism why this particular subgroups of patients, despite the higher rates of diabetes and hypertension, presented better outcomes. These positive results can create doubts about whether current recommendations for CV prevention should be extrapolated to populations with established CVD.

Finally, it should be highlighted that the results of these studies should be considered in light of its potential limitations. First, conclusions are based in the BMI, a parameter that it is known does not differenciate body fat from lean mass. Second, they were ultimately unable to account for fat distribution (peripheral versus abdominal obesity) and other measures of adiposity such as body fat percentage. Besides, information regarding the proinflammatory and nutritional status were not collected, and potential changes in BMI over the study follow-up were not considered.

Conclusions

Overweight, defined as a BMI 25-30 kg/m2, and obesity, defined as a BMI ≥30 kg/m2, according to the WHO, were found to be associated with a better prognosis in terms of CV hospitalizations, global and CV mortality risk in previous studies which included an important number of AF patients. These results should be analyzed under de BMI parameter limitations. Thus, further prospective and randomized studies specifically designed to address this point will be needed to explain the etiopathogenic mechanisms underlying the called "obesity paradox in AF".

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Review And Insights Into The Bleeding Mechanism Incited By Antithrombotic Therapy: Mechanistic Nuances Of Dual Pro-Hemorrhagic Substrate Incorporating Drug-Induced Microvascular Leakage

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Abstract

In patients with atrial fibrillation antithrombotic prophylaxis for stroke is associated with an increased risk of bleeding. Cerebrovascular risk-benefit ratio for oral anticoagulation therapies continues to be debated. Macro and/or microhematomas as well as visible or cryptic ones may appear unexpectedly in any anatomic region.

The diagnostic and prognostic value of subcutaneous hematomas (petechia, ecchymosis, bruise) potentially predisposing intracerebral micro- or macrobleeding might be reconsidered. Hypothetically, subcutaneous hemorrhagic events are "transparent" signs and reflect the coexistence of remote vulnerable sites that are potential bleeding sources. Obviously vigilance is needed for early signs of drug-related petechiae evaluation to determine whether it is a local/superficial subtlety or a systemic problem. Any bleeding complication, regardless of its scale and anatomical location, might be treated as a worrisome clinical symptom requiring subtle correction of antithrombotic regimen. The focus of this article is to review the current knowledge of drug-related hemorrhage with special emphasis on underlying mechanisms and links between the visible bleeding (predominantly subcutaneous) and remote (such as cerebral) hemorrhagic sources. To mitigate inappropriate therapy, we should consider new conceptual insights and more individualized approaches to achieve an optimal balance of efficacy and safety. We hypothesize that bleeding complications occur as a result of two factors – impact of antithrombotic drugs and related detrimental effect on microvascular network. Most likely the microvasculature undergoes pro-hemorrhagic medication stress leading to unfavorable vascular wall "fenestration" with ensuing consequences. If so, it suggests the presence of dual substrate responsible for hemorrhagic events.

Introduction

Atrial fibrillation (AF) is the most common rhythm disturbance worldwide. As a non-life threatening arrhythmia it carries a great risk of ischemic stroke along with severe hemorrhagic events, especially when oral antithrombotic drugs (OAD) are instituted. Untreated, AF increases the risk of ischemic stroke fivefold making stroke the leading complication of AF.[1] Eighty percent of strokes are caused by arterial occlusion of cerebral arteries, whereas the remaining twenty percent are caused by intracerebral hemorrhages.[2] However, although clinically intriguing, antithrombotic therapy can act like a double edged sword with both beneficial and adverse effects.

Meanwhile oral antithrombotic therapy (OAT) remains the best treatment option to prevent cardioembolism in AF.[3] Drug-related hematomas as a concomitant "metastatic ectopy" may simultaneously occur subcutaneously, in the brain or in any other topographic location of the human body. Cutaneous or subcutaneous hemorrhagic areas may cover lower extremities, neck, buttocks and may also affect large areas. Such therapeutic endpoints should not be interpreted as "innocent" symptoms. Spontaneous bruising is important but the bruise should be over 3 cm in size to be significant.[4]

We would like to focus on conspicuous subcutaneous hematomas appearing as a result of antithrombotic treatment. These hematomas as precursors may herald more severe bleeding in other locations, predominantly in the brain. Thus, such correlation likely raises the risk of bleeding expansion. For this reason intracerebral microbleeding and subcutaneous hemorrhage may represent a peculiar clinical relationship. Regarding the mechanism of hemorrhage the OADs presumably affect both blood coagulation parameters and microvascular/angiogenic factors. Thus, better understanding is needed to avoid excessive out-of-control bleeding.

This review is part of the ongoing efforts to improve clinical results in patients undergoing antithrombotic therapy.

Background And Reflections

The prevention and containment of bleeding is a major

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therapeutic goal in patients suffering from AF. Recently Fischer et al.[5] have offered a new term – mixed cerebrovascular disease which incorporates clinical and subclinical syndromes including ischemic stroke, intracerebral hemorrhage and cerebral microbleeds. The balance between the risk of bleeding and the risk of stroke needs to be estimated for each patient based on patient's values and preferences, as well as awareness of the prognostic implications of bleeding.[3]

Hematomas range from small and relatively benign to severe, including life-threatening ones. Numerous reports have amply demonstrated clinical emergency due to acute or subacute intracranial, intracerebral, retropharyngeal or intramuscular hemorrhagic outbreaks resulting in serious brain damage, life-threatening suffocation, anemia and/or death.[6-14] The findings of Risch and colleagues.[15] confirm that intracranial, muscular and soft-tissue hemorrhagic events exclusively occur in patients who receive OADs.

Underlying mechanisms of coagulation-bleeding physiology implicate very complex biological interactions between blood and tissue factors.[16] even without interference of OADs. Sporadic reports suggest that microhemorrhages are preferential focuses of intracerebral hemorrhage (ICH) in patients receiving OAD, most likely because the drug unmasks ICH that would otherwise remain asymptomatic.[17] Extensive anticoagulant effect is well-established as a powerful risk factor for ICH.[8] Fortunately the menace of AF-related stroke and hemorrhage in most cases is amenable to medical control at least when conventional OAD medication is applied.

Ubiquity of multiple hemorrhagic foci actually alerts clinicians and their patients as well. However, it is still unclear where the bleeding starts first – subcutaneously (superficially), intracerebrally, selectively anywhere or uniformly in the whole body. In general, unnoticed or ignored subcuticular hemorrhage may negatively influence the clinical course of AF therapy. Moreover, there is a concern that patients as well as their physicians may become reconciled to the trivial petechiae, eventually paying no attention to alarming abnormality. Aspirational target of medical community is zero hazard ratio – an ideal bleeding-free as well as stroke-free clinical course of AF.

With regard to bleeding substrate one can hypothesize that we deal with the integral bleeding circuit with individual components of favorable/prohemorrhagic conditions. Responsible mechanisms are not clear and may relate to individual effects of local vasculopathy subtlets - bleeding per diapedesis in proportion to medication, microvascular disintegration, capillary fragility, etc. Recently Altman .[19] has emphasized that bleeding is an eventuality that occurs in places of "locus minoris resistentiae". This might serve as a starting point for some clinical revelations, specifically to verify the etiology of the hemorrhage. It seems, at least hypothetically, that OADs activate microvascular "weakest links" residing in the soft tissues.

Clinical Reality

Under physiological circumstances the concerted action of platelets, active biological blood components, and tissue factors influence the coagulation cascade and maintains hemostasis.[3] Interfered by specific drugs the coagulation system is affected significantly; that is why antithrombotic therapy faces many challenges.

Any bleeding events are categorized as major and minor by anatomical site.[20] Major bleeding is defined as an intracranial hemorrhage, a decrease in blood hemoglobin level of more than 5.0 g/dL, the need for a transfusion of two or more units of blood, the need for corrective surgery, or any combination of these events ;[21] minor bleeding is defined as a subcutaneous ecchymosis or hematoma, gastrointestinal bleeding, or bloody sputum.

The study of Guo and colleagues.[21] demonstrated that there were no thromboembolic events in elderly patients taking OAD, but 33% of them had bleeding complications. According to Goldstein and Greenberg[12] while bleeding is the major risk, not all bleeding events are equally damaging. Recently Jacobs and colleagues[22] have suggested that anticoagulation with inherent period of supratherapeutic and subtherapeutic effects provoke both chronic microemboli and microbleeds; patients with prior ischemic cerebral injury may be more likely to experience repetitive or worsened injury with longer anticoagulation use.

There are disparities in efficacy between pharmacologic groups of OADs. Regarding the intracerebral bleeding there is a perception that aspirin is effective and is safer than warfarin.[23] The incidence of major hemorrhage with aspirin monotherapy is approximately 1.5% per year.[24] In general, antiplatelet treatment is likely safer, as antiplatelet agents carry a substantially lower risk of bleeding.[25, 26] Conversely, vitamin K's antagonist warfarin therapy has been shown to be more effective than aspirin for the prevention of stroke in patients with AF.[27] Unfortunately, there is no absolutely "safe" INR (international normalized ratio) even with the conventionally therapeutic range.[8] New anticoagulant dabigatran is associated with a surprisingly enhanced risk for both thrombo-embolism and bleeding disorders clearly indicating the importance of accurate follow-up of AF patients.[28] However, the only reversal option for dabigatran is emergency dialysis which can be a challenge when it comes to patients with a threatening ICH.[29] This procedure takes time which is why the therapeutic efficacy may be overtaken by intense bleeding. Several OADs, i.e. dual or triple therapy and their interactions have been shown to increase the risk of serious bleeding.[6, 30] Warfarin interaction with at least one drug was considered in a retrospective study as the main contributor to bleeding in almost half of the cases.[31]

Controversies Of Intracerebral Microbleeding

The increasing use of antithrombotic drugs in an aging population is associated with a dramatic increase in the incidence of intracerebral hemorrhage.[15,32] A group of clinicians[33] have stated that the count of microbleeds or macrobleeds predicts an increased risk of hemorrhagic stroke in survivors of ICH. With anticoagulation, however, the benefit has to be balanced against an increased risk of ICH, which is the most feared complication of anticoagulation, causing death or severe disability in up to 75% of patients.[13] Increasing use of warfarin to prevent cardioembolic stroke due to AF has led to a fivefold increase in the incidence of anticoagulant-related ICH, which now accounts for approximately 15% of all ICH.[34] It is a paradox that many of these patients at the highest risk of cardioembolic stroke are also at the highest risk of ICH.[35] Recent work in the field.[29] has recognized that OAT related intracerebral hemorrhage rises up more questions than answers.

Cerebral microbleeds (CMB) are small chronic brain hemorrhages which are likely caused by structural abnormalities of the small vessels of the brain.[31] Yates et al.[36] declared that microscopic hemorrhages occur in the setting of impaired small vessel integrity, commonly due to either hypertensive vasculopathy or cerebral amyloid angiopathy. Recently Shoamanesh and colleagues.[37] have demonstrated that microbleeds on magnetic resonance imaging were associated

with evidence in prior bleeding in 81% (e.g. hemosiderin-laden macrophages or old hematoma).

Vascular release of blood components in the absence of trauma in orally anticoagulated patients defines the clinical entity being of great interest. In literature, the risk/benefit ratio of anti-thrombotic drugs in individuals with CMBs is controversial.[31] Microbleeds which have long been perceived as harmless and irrelevant in disease development, were found in 23 percent of patients with Alzheimer's disease in the review of five studies;[38] a previous study showed that 6.5% of healthy 45-to 50-year olds have microbleeds, whereas 35.7% of people 80 and older have them. Some investigators have concluded that CMBs are not just an incidental finding revealed by new neuroimaging technology.[39] From a pathophysiological standpoint, CMBs appear to be the expression of a hemorrhage-prone state of the brain, which might carry greater risk of ICH.[31]

There are some controversies related to whether the intracerebral microbleeding is harmful or not. The presence of cognitive decline symptoms in anticoagulated patients is also debated. Most cerebral microhemorrhages identified by gradient-echo imaging are clinically silent.[39, 40] Some investigators, however, have shown that microvascular damage plays a key role in cognitive impairment, especially in older patients.[31] Because CMBs reflect small areas of hemorrhage, and are common in both ischaemic and intracerebral hemorrhage,[41] they have caused concern regarding the risk of future intracerebral hemorrhage.[39] Kakar and colleagues[39] have postulated that CMBs develop over time and are common in populations likely to be exposed to antithrombotic drugs. Anti-platelet agents, traditionally safer than anticoagulants, are associated with an increased risk of ICH, especially in subjects with high number of CMBs.[42, 43] Apparently every anticoagulated individuum possesses its own hemorrhagic scenario. The ability to concentrate or disseminate the hemorrhagic foci in specific anatomic regions represents the phenomenon to yet be elucidated.

The rate of intracerebral hemorrhage in patients given OADs has been hypothesized to be the inherent risk multiplied by a factor determined by intensity of anticoagulation.[44] It looks like weak points are or provoked with the anticoagulation as a parent material which activates a bleeding cascade. Specifically, increase in dose often leads to exacerbation of hemorrhage or to proliferation of "weakest points". When collated, multilateral interrelationship of "high anticoagulation - high vulnerability - high risk" might be traced.

Clinical Importance Of Subcutaneous Bleeding

In individuals under antithrombotic treatment clinicians often observe multiple hemorrhages scattered across the patient's body. Anatomical distribution of bleeding sites varies within wide range allowing the hemorrhagic foci to overlap several territories. Hemorrhagic events sometimes are represented by simultaneous appearance of subcutaneous and intraorganic/intraparenchymal hematomas, both overt and/or cryptic. It is still unclear whether subcutaneous hemorrhage is strongly associated with systemic bleeding. Again, it is worth to discuss whether the subcutaneous bleeding is a clinically remarkable symptom or not. Also the recurrence of subcutaneous bleeding is to be estimated mostly in terms of its diagnostic and prognostic value. No doubt, we deal with the plural, i.e. loci minores resistentiae which, according to the manifestation pattern might be defined as sporadic, multiple, migrans, cryptic and/or visible. In theory, the patient without visible hematomas is not free from supposed hemorrhage. If so, petechia likely coexists with other bleeding sources, e.g. intracerebral microhematomas. Literature sources available do not provide a distinct relationship in this regard.

Some investigators[31, 35, 39] have declared that CMBs are potential predictors of future intracerebral hemorrhage. In turn, by extrapolation, clinical significance of CMBs likely is comparable to subcutaneous hemorrhage as far as their etiological similarity. In other words, subcutaneous bleeding foci are important not per se, but may reflect the presence of intracerebral hemorrhage and vice versa. Thus, any bleeding events wherever they are most often reflect the common anticoagulation status and increased bleeding risk in any possible anatomical site. If so, the entire body of the patient comprises the feasibility of hemorrhagic outbreaks at any time and in any topographic area, especially under excessive anticoagulation.

There are no recommendations related to clinical strategy and how to care for the noticed subcutaneous bleeding, particularly when it is extensive. Physical removal of OADs even provisionally might be a risky maneuver unless worsening signs do appear. Reduced anticoagulation particularly in repeat bleeding events and subsequent monitoring of blood markers is beneficial. Some clinical reports suggest that optimal antithrombotic therapy selection for patients with AF must be mainly accomplished based on individual and accurate risk stratification for both thromboembolism and hemorrhage during therapy, not based only on the risks before treatment.[21] The cautious approach to OAT in patients with bleeding risk is suggested by many clinicians.[31, 44]

Co-Participation Of Anticoagulation And Vascular Disintegrity: New Insights

The precise mechanism by which anticoagulation increases the incidence of intracerebral bleeding is unclear.[7] Immediate precipitants could be as trivial as an interval of relatively higher blood pressure or minor mechanical stress such as the shear forces of vigorous head shaking;[8] one idea is that the anticoagulation may cause subclinical brain hematomas to grow to clinical importance. Classical bleeding supportive causes might be taken into account, e.g. per diapedesis or per microvascular rupture resulting in extravasation of blood components. Bleeding likely evolves from both the intensity of medication and individual characteristics of small vascular peculiarities. Herein we do not analyze the subclinical or clinical injuries originating from physical impact.

Meanwhile the hypothesis of "locus minoris resistentiae" provides the best explanation of the behavior of bleeding-prone locations. However, this approach fails to disclose the cause and the mechanism of hemorrhagic foci migration across the anticoagulated human body. We can observe sporadic, multiple or single hemorrhagic spots (bruises) which may appear or reappear in the same site or in alternating regions. Likely the local architectonic and structural tissue specificities along with "anticoagulant-induced vasculopathy" reflect the clinical threats which might be construed and incorporated into the discussion. Seemingly, unique tissue/vascular conditions may determine different bleeding intensity in specific vulnerable/susceptible anatomic sites.

Under physiological conditions the breakage of the endothelial barrier leads to exposure of extravascular tissue factor which provides additional hemostatic protection.[16] Consequently, drug-induced vascular disintegration conjoined and reinforced by the loss of blood's clotting capability eventually cause blood spillage into surrounding

tissues most often in a form of imbibition. So, it is reasonable to suspect that dual substrate, i.e. both the antithrombotic agent and microvascular abnormality most likely are responsible for the bleeding event. Conceptually AODs open the bleeding sources which were tightly closed before the therapy. These gates likely resist until the crucial shift in concentration of AOD's is reached; then bleeding of non-traumatic origin is launched. In other words the extravasation of clotting-free blood is impossible without vasogenic component. Findings of Charidimou and Werring[35] have shown that OADs provide direct evidence of blood leakage from pathologically fragile small vessels. The contributing role of local vascular disease, such as cerebral amyloid angiopathy, is favored by observation of a high frequency of this angiopathy in individuals with warfarin-related ICH.[29] Negative influence of OADs on capillary or pre-capillary endothelial cells, including their disintegration, might be conceivable. However, individual characteristics of small vascular peculiarities as an indispensable cofactor presumably influence the bleeding intensity from patient to patient under the same antithrombotic regimen. Taken together it could be suspected that AODs, especially in high-doses, may have direct impact on microvascular damage, at least enhanced capillary or precapillary permeability.

Despite percolation of blood's "corpuscles" and plasma through the capillary the cardiovascular system represents a unique, securely sealed and well-organized entity. From a purely mechanical point of view functional harmony of the closed circulatory system might be characterized by an axiom: no vascular leakage, no sanguination regardless of the presence of blood thinners.

Epilogue And Conclusions

As stressed by Yates et al.[36] microscopic hemorrhages occur due to impaired small vessel integrity. It supports our conceptual viewpoint. It could be suspected that anticoagulant milieu do facilitate capillary fragility and potentiate microvascular damage, most likely its auto-rupture. Deductively, the microvasculature undergoes pro-hemorrhagic medication stress. The exposure to critical dose of OADs, in the absence of physical impact, might explain the mechanism of sanguination. Eventually, the higher the serum drug concentration is the greater risk of blood eruption. Figuratively speaking the vascular "fenestration" (of iatrogenic origin), abundantly adverse, is a critical condition, otherwise the bleeding will not be evoked by any blood thinner even when using maximum dosage.

In a metaphorical sense, loss of coagulability as such covers just a half or two thirds of the "distance" until bleeding is initiated. The remaining "distance" – up to the bleeding manifestation - is surmounted and finalized by drug-dependent microvascular changes.

Clinical observations demonstrate the potential presence of multiple hemorrhagic sources in different anatomic regions. In reality these focal points are dormant unless OADs are introduced. More surprising is the fact that bleeding foci may change their topographic areas, as if migrating occasionally with a period of clinical latency eventually related to anticoagulation regimen.

Despite the fact that almost all subcutaneous hematomas resolve spontaneously without clinical consequences their presence and reappearance should not be underestimated or ignored. Therapeutic vigilance is needed to eliminate two risks – bleeding and cardioembolism. Hence, OAD's dose re-adjusting strategy in response to anticoagulation fluctuations should be the best solution of clinical problem. An ideal approach – treatment lege artis with painstaking control of both bleeding and cardioembolism is the goal of clinical practice. In summary, the following methods should be considered:

1) Enhanced surveillance for visible bleeding sites in patients during their routine visits should be taken into account.

2) To maintain adequate anti-coagulated status the risk/benefit ratio should be considered and care should be individualized, especially in those patients with visible subcutaneous hemorrhage.

3) Dose re-adjusting strategy to reach ne plus ultra therapeutic condition is highly recommended.

4) Under the thromboprophylaxis the bleeding likely stems from dual substrate – impact of antithrombotic drug which, in turn, evokes detrimental effect on microvascular network.

5) Further studies are needed to improve the understanding of the mechanism of drug-related hemorrhage.

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Atrioventricular Junction Ablation In Atrial Fibrillation: Choosing The Right Patient And Pacing Device

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Abstract

Atrial fibrillation (AF) is the most common cardiac arrhythmia and despite advancements in rhythm control through direct catheter ablation, maintaining sinus rhythm is not possible in a large proportion of AF patients, who therefore are subject to a rate control strategy only. Nonetheless, in some of these patients pharmacological rate control may be ineffective, often leaving the patient highly symptomatic and at risk of developing tachycardia-induced cardiomyopathy and heart failure (HF). Catheter ablation of the atrioventricular junction (AVJ) with subsequent permanent pacemaker implantation provides definite rate control and represents an attractive therapeutic option when pharmacological rate control is not achieved. In patients with reduced ventricular function, cardiac resynchronization therapy (CRT) should be considered over right ventricular apical (RVA) pacing in order to avoid the deleterious effects associated with a high amount of chronic RVA pacing. Another group of patients that may also benefit from AVJ ablation are HF patients with concomitant AF receiving CRT. In this patient cohort AVJ ablation ensures near 100% biventricular pacing, thus allowing optimization of the therapeutic effects of CRT.

Introduction

Atrial fibrillation (AF) is the most prevalent arrhythmia and has during recent years experienced significant advancements, with pulmonary vein isolation through direct catheter ablation becoming a cornerstone therapy in drug refractory AF.[1,2] Despite this, a significant proportion of AF patients are resistant to rhythm control and in some instances pharmacological rate regulation is also insufficient, often leaving the patient highly symptomatic and at risk of developing tachycardia-induced cardiomyopathy and heart failure (HF).[3] In such patients, catheter ablation of the atrioventricular junction (AVJ) represents an attractive, and often the only, therapeutic option.[4] Since the patient is left with a junctional escape rhythm, implantation of a permanent pacemaker is warranted and when left ventricular (LV) systolic function is reduced cardiac resynchronization therapy (CRT) should be considered in order to avoid the deleterious effects associated with right ventricular apical (RVA) pacing.[5] Another group of patients that may also be eligible for AVJ ablation are those with AF who require CRT as part of their HF therapy and during follow-up present low percentage of biventricular pacing secondary to insufficient rate control and irregular RR intervals.[6,7] In this cohort AVJ ablation ensures near 100% biventricular pacing thereby optimizing the therapeutic effects of CRT.[8] The aim of this review is to discuss the existing evidence regarding the role of AVJ ablation in the two mentioned AF patient groups – AF with rapid ventricular rates and HF patients with concomitant permanent AF receiving CRT – as well as the preferred type of pacing device (RVA pacing vs. CRT) following AVJ ablation.

Key Words:
Atrial Fibrillation, AV Junction Ablation, Cardiac Resyncrhonization Therapy, CRT, Pacing.

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Ablation Technique

On the 9th of April 1981, the first AVJ ablation in humans was carried out, using high-energy direct current shock (300-500 J) from a portable defibrillator which was delivered over a standard electrode catheter, positioned at a site where His bundle potential was recorded.[9] However, given the high complication rates, in particular cardiac perforation, direct current energy was replaced by radiofrequency energy towards the end of the 1980s.[10]

The aim of AVJ ablation is to ablate the compact AV node with resultant AV block and a stable junctional escape rhythm. Normally,

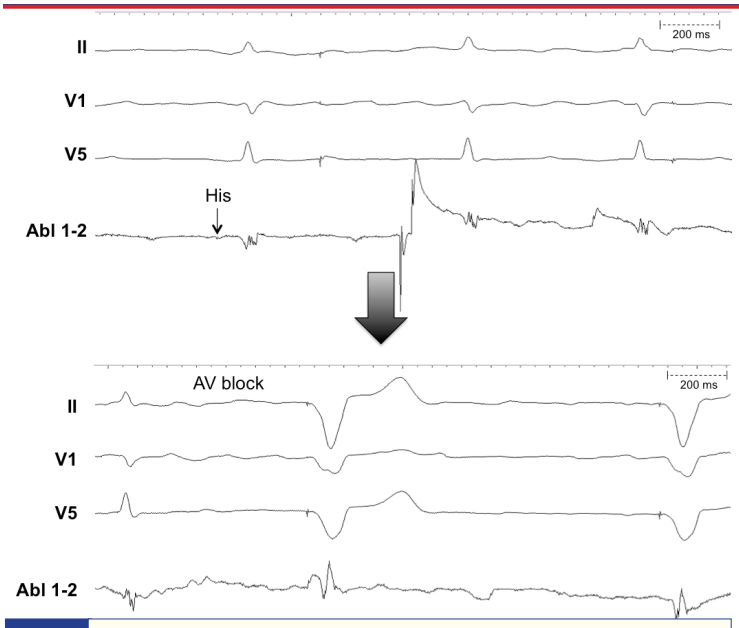

Figure 1: Surface electrocardiogram (lead II, V1, and V5) and intracardiac radiofrequency ablation (Abl) catheter electrodes (distal 1-2) of a 78-year-old woman with symptomatic permanent fast atrial fibrillation refractory to pharmacotherapy. Top panel shows recordings at the start of ablation and bottom panel 25 seconds later when atrioventricular (AV) block is achieved. Note the asynchronous ventricular pacing spikes due to the permanent pacemaker programmed in V00 mode at 50 ppm.

radiofrequency ablation is performed in the right atrium through femoral venous access with the ablation catheter advanced across the tricuspid valve annulus and withdrawn until it lies over the compact AV node, typically identified by a definite His signal, and a large atrial and smaller ventricular electrogram. Radiofrequency energy, with maximum power of 60W, is administered for 30-60 seconds at a temperature of 60-70ºC (Figure 1).[11] Overall success rate have been reported over 97%.[12] Occasionally, in patients with cardiomyopathy and ventricular remodeling the recoding of a stable His potential from the right side can be difficult and a left-sided ablation may be necessary. In those instances the ablation catheter is placed across the aortic valve over the upper left ventricular septum where a His bundle potential is recorded, through a retrograde aortic approach.[13] The permanent pacemaker options include a single chamber (VVIR) for permanent AF, dual chamber (DDDR) for paroxysmal AF, and in case of ventricular systolic dysfunction, a CRT device. The device is usually placed 4-6 weeks prior to ablation with the advantage of stable pacing lead(s) at the time of ablation, although a combined procedure, obviating the risk of lead dislodgement during the manipulation of the ablation catheter, is advocated by some.[14]

Complications include those related to femoral venous access, (venous thrombosis, ateriovenous fistula, infection and bleeding), cardiac perforation or tamponade, tricuspid valve regurgitation and death.[11] Specific procedure related complications include hemodynamic deterioration and development of severe mitral regurgitation secondary to mitral valve leaflet apposition due to RVA pacing,[15] and sudden cardiac death (Figure 2).[16] The latter has been described to occur more frequently in patients with certain comorbidities (diabetes mellitus, aortic valve lesions, ventricular rhythm disturbances, and chronic obstructive pulmonary disease).[16] Although the exact mechanisms of sudden death following AVJ ablation is not fully elucidated, several factors that contribute to repolarization disturbances have been identified, creating a substrate for pause-dependent polymorphic ventricular arrhythmia (similar to acquired long QT syndromes). These predisposing factors include decreased heart rate, increased sympathetic activity, hypokalemia, antiarrhythmic drugs and change in myocardial activation sequence from the native conduction system to RV apical pacing. Therefore, in order to minimize the risk of ventricular arrhythmia it is recommend to program a relatively high pacemaker lower rate limit (80-90 ppm) for the first 4-6 weeks following AVJ ablation.[17] More recently, reports of Gerbode defect (LV to right atrium shunt) has been described as a rare complication following AVJ ablation.[18] This is due to unfortunate ablation at the thin superior atrioventricular portion of the membranous septum which separates the right atrium from the LV. Given that a permanent pacemaker is necessary complications related to its placement should also be included. Overall, the incidence of procedure-related complications is around 3%, with the majority being related to femoral venous access.[11] In a European survey from 88 institutions including 900 patients a 3.2% complication rate was reported with major complications of 1.8%.19 The NASPE Prospective Voluntary Registry, which included 646 patients, had a 0.8% severe complication rate.[12] Finally, an observational study of long-term survival of 350 patients with AF undergoing AVJ ablation and permanent pacemaker insertion found that this strategy does not adversely affect patient survival when compared to general population (adjusted for underlying heart disease) or patient with AF who received drug therapy.[20]

AF With Rapid Ventricular Rates

This represents the largest group of patients with AF who undergo AVJ ablation, which is normally considered as a last resort when both rhythm (direct catheter or surgical ablation and/or pharmacotherapy) and pharmacological rate control have failed and the patient remains symptomatic. Worth mentioning are a subgroup of patients with left atrial flutter following AF ablation, often significantly more symptomatic and more difficult to control pharmacologically than when the patient was suffering AF. Although, in the majority of cases a repeat ablation of the flutter is successful, in some instances ablation is unsuccessful and the only remaining option is AVJ ablation to manage the symptoms.[4]

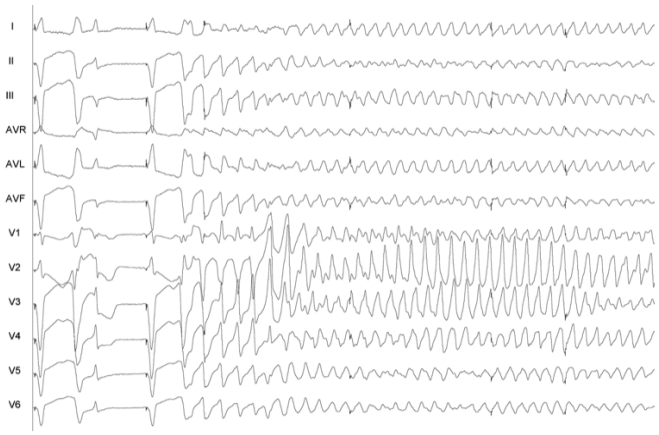

Figure2: Ventricular tachycardia (Torsade de Pointes) recorded 60 minutes after atrioventricular junction ablation in a patient with mitral valve disease and atrial fibrillation with rapid ventricular response. Adapted from Rodríguez-Mañero M. et al.[35] with permission.

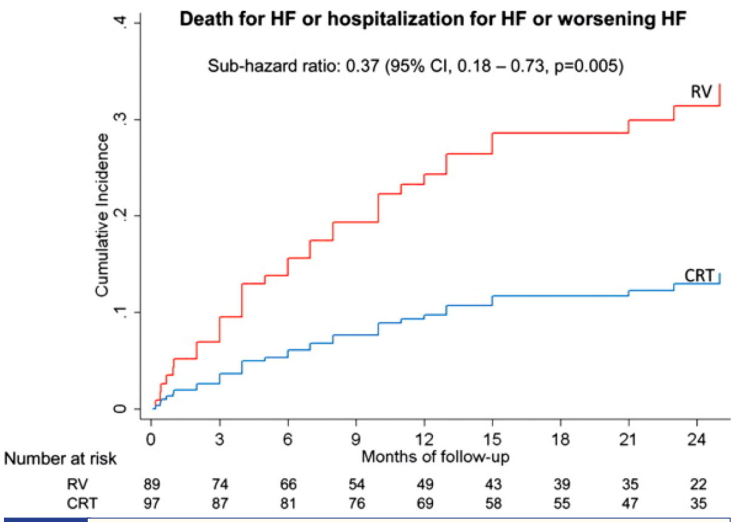

Figure 3: Corrected cumulative incidence of the composite primary outcome of death from heart failure, hospitalization due to heart failure, or worsening heart failure, comparing cardiac resynchronization therapy (CRT) vs. right ventricular (RV) pacing following atrioventricular junction ablation for permanent atrial fibrillation in the APAF trial.[44] Reproduced with permission.

Tachycardia-Induced Cardiomyopathy

The rapid ventricular rate is the main source of symptoms in this patient group and, if occurring for a prolonged period of time, increases the risk of tachycardia-induced cardiomyopathy, consisting of reversible ventricular dilatation, systolic dysfunction and symptoms of heart failure. The entity may be divided into 2 types: pure (tachycardia being the chief mechanism of LV deterioration); and 2) impure (tachycardia worsens a pre-existing cardiomyopathy of a different cause). Although described in 1913 in a patient with AF, and during the last 3 decades extensively studied in both animal models and in humans, its pathophysiological mechanisms have not been fully elucidated although interplay of several mechanisms clearly exists.[3]

In animal models sustained atrial or ventricular pacing leads to severe biventricular systolic dysfunction which is characterized by increased ventricular filling pressures, diminished cardiac output and increased systemic vascular resistance.[21] At a microscopic level there is myocyte loss, myocyte elongation, effacement of the interface between the basement membrane and sarcolemmal surface, depletion of T-tubules associated with decreased density of L-type calcium channels and beta-adrenergic receptors, resulting in abnormal excitation-contraction coupling which may impair contractile function.[22] Diastolic function is impaired by tachycardia with impaired relaxation secondary to a disproportionate increase in sarcoplasmic reticulum calcium content that manifests as diastolic contracture.[23] Other mechanisms include exhaustion of high energy stores in the myocardium due to augmented metabolism from the tachycardia, mitral regurgitation secondary to annular dilatation, reduced myocardial blood flow, oxidative stress, and neurohormonal changes.[3]

Both in animal and human studies, normalization of the rapid heart rates results in recovery of myocardial function with improvements in LV ejection fraction (LVEF) typically observed after 3 to 4 months. In a metaanalysis of 21 studies with a total of 1181 patients with drug refractory AF, an overall improvement in LVEF of 4.4% was observed as well as in a broad range of clinical outcomes including symptoms, number of hospital admissions and New York Heart Association (NYHA) functional class.[24]

AVJ Ablation: Symptomatic, Echocardiographic, And Functional Benefits

As AVJ ablation became a more widespread therapeutic option for drug refractory fast AF during the 1990s, several studies were published evaluating the potential beneficial aspects of this procedure. Initial uncontrolled studies in highly symptomatic patients with drug refractory permanent AF established that AVJ ablation provides symptom relief[25] and improved cardiac function,[26,27] the latter attributed to the reversal of tachycardia-induced cardiomyopathy and the favorable hemodynamic effects of regularization of RR intervals.[28] For example, The Ablate and Pace Trial,[25] a prospective multicenter study including 156 patients with drug refractory fast AF undergoing AVJ ablation and pacemaker implantation, reported after a 12-month follow-up an significant improvement in NYHA class (2.1 to 1.8), quality of life and arrhythmia related symptoms and frequency. The LVEF at 12-month was not different from baseline, however in those with reduced LVEF at baseline a significant improvement was observed (31±2% vs. 41±3%; P=0.0001).

Subsequently, the results of a few randomized trials were reported comparing pharmacological rate control with AVJ ablation in AF patients (Table 1).[29-33] Of note, the patient profile was different to the previous uncontrolled studies, in particular since an acceptable pharmacological heart rate control was a pre-requisite. Brignole et al.[31] studied 66 patients with AF lasting >6 months, clinically manifest heart failure, evidence of structural heart disease, and heart rate >90 bpm, randomized to AVJ ablation and pacemaker implantation or pharmacological treatment. At 12 month the ablation group showed significantly lower scores in palpitations and exertional dyspnea and a non-significant favorable trend for exercise intolerance, Living with Heart Failure Questionnaire, NYHA class, and Activity Scale when compared with the drug group. No difference in echocardiographic parameters between the 2 groups was observed at the end of the study, perhaps due to the presence of structural heart disease having more of an impact on the depressed cardiac function than tachycardia induced cardiomyopathy. In a similar way, The Australian Intervention Randomized Control of Rate in Atrial Fibrillation Trial (AIRCRAFT)[33] compared AVJ ablation and pacemaker

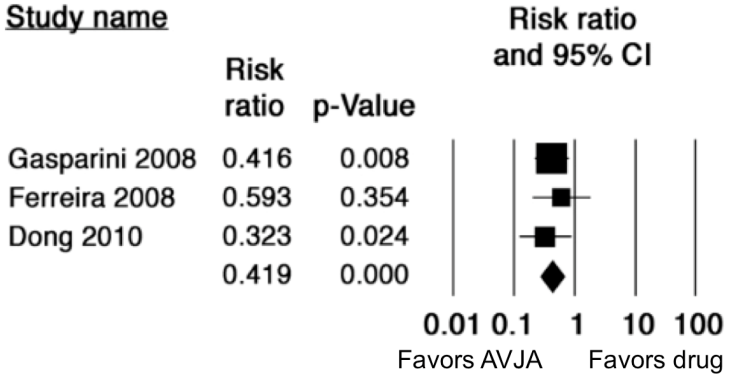

Figure 4: All-cause mortality meta-analysis data from 3 studies,[8] comprising 450 patients, comparing pharmacological rate control (drug) vs. atrioventricular junction ablation (AVJA) in heart failure patients with concomitant permanent AF receiving cardiac resynchronization therapy. CI = confidence interval. Figure content under Elsevier user license.

Table 1: Randomized controlled trials comparing pharmacological rate control (drug) vs. AVJ ablation + pacemaker implantation (Abl+Pm) in patients with rapid AF

Study	Patients (n)	Age (y), Abl+Pm/ drug	AF duration (y), Abl+Pm/ drug	Baseline LVEF (%), Abl+Pm/drug	Follow-up (m)	Inclusion criteria	Results
Brignole[29] 1997	43	66±10/ 64±10	9±8/ 8±5	58±11/60±10	6	-Symptomatic paroxysmal AF -Refractory to 3 AAD	Abl+Pm group showed significantly better scores in LHFQ, palpitations, effort dyspnea, exercise intolerance score, and easy fatigue. -AF was documented in 25% (Abl+Pm group) and 8% (drug group) -No differences in echocardiography parameters
Brignole[31] 1998	66	72±9/ 72±9	5.7±6.9/ 4.1±5	43±12/44±15	12	-AF duration >6m -HR >90 bpm + clinical HF	- Abl+Pm group showed significantly better scores in palpitations and effort dyspnea - No differences in echocardiography parameters nor exercise test
Marschall[30] 1999	56	65±8/ 60±10	7.1±6.3/ 9.8±8.0	NR	4	-Symptomatic paroxysmal AF -Refractory to 2 AAD	-Abl+Pm group showed significantly better scores for overall symptoms, palpitations and dyspnea -DDDR was better than VVIR pacing for overall symptoms and dyspnea -More patients developed persistent AF in the Abl+Pm group
Ueng[32] 2001	50	68±6/ 65±8	14±7/ 12±8	45±6/45±8	12	-Symptomatic lone AF >6m -Normal HR (60-100 bpm) -LVEF ≤50%	-Abl+Pm group showed significantly better scores for overall symptoms, overall activity scale -Abl+Pm group presented significantly higher LVEF than drug group (49±5% vs. 44±6%)
Weerasooryia[33] (AIRCRAFT Study) 2003	99	68±9/ 68±9	4.8±5.5/ 6.5±10.9	55±16/57±14	12	-Symptomatic AF >12m -HR controlled by drugs (<80 bpm)	-Abl+Pm group showed significantly improved QoL and less symptoms -No differences in echocardiography parameters nor exercise test

AAD = antiarrhythmic drugs; AF = atrial fibrillation; AVJ = atrioventricular junction; LHFQ = Living with heart failure questionnaire; LVEF = left ventricular ejection fraction; QoL = Quality of life.

implantation with pharmacological rate control in 99 patients with mild to moderately symptomatic permanent AF, normal LVEF, and a ventricular rates that was adequately controlled by medication (<80 bpm and <150 bpm at rest and exercise, respectively). After 12 month of follow-up no difference in echocardiographic parameters or exercise tolerance was observed, however quality of life was significantly improved in the AVJ ablation group. Finally, Ueng et al.[32] studied 50 patients with permanent symptomatic AF, reduced LVEF and no evidence of structural heart disease, and normal ventricular rates (60 – 100 bpm). Assignment to AVJ ablation and pacemaker implantation was according to patient preference and after 12 months the ablation group showed significant improvements in quality of life, symptoms and LVEF, the latter likely due to the regularization of R-R intervals when compared to the drug group. A metaanalysis of randomized or prospective trials, including the previously commented studies,[31-33] found that AVJ ablation when compared with pharmacotherapy was associated with significant improvement in several symptoms (palpitations, dyspnea) but no significant difference in exercise duration or LVEF.[34] In subgroup analysis of patients with reduced LVEF this parameter was significantly improved after AVJ ablation. Importantly, the same metaanalysis reported a low incidence of procedure-related mortality(0.27%) and malignant arrhythmia (0.57%).

Our group aimed to determine the change in LVEF after AVJ ablation and RV apical pacing and the clinical predictors of LVEF deterioration in a sample of 104 consecutives patients referred for AVJ ablation.[35] After 2 years of follow up there was a decrease in the rate of hospital admission (from 0.9 admission/year to 0.35, P<0.001), an increase in the functional status in at least one NYHA class in 58 patients, and an increase in the global LVEF (from 48.9% to 54,1%; P<0.001). Valvular replacement and LVEF <50% were independently associated with a decrease in the LVEF. Therefore, we hypothesized that the mechanical ventricular dyssynchrony induced by long-term RVA apical pacing may have more impact in patients with mitral disease, which as is known, plays an important role in the cardiac mechanics. Scarce information in this subgroup is currently available and it is our belief that it warrants further investigations

RVA Pacing vs. CRT After AVJ Ablation

RVA pacing produces electrical and mechanical ventricular dyssynchrony, similar to left bundle branch block, with subsequent detrimental effects on cardiac structure and function.[36] During the last 2 decades the clinical relevance of the negative effects of long-term RVA pacing has gained recognition following the publication of large pacemaker and implantable cardiac defibrillator (ICD) trials where a high amount of chronic RVA pacing was associated with increased risk of AF, HF and death.[36-38] Subanalyses from these trials suggest that patients with reduced LVEF subject to >40-50% of RVA pacing are at high risk.[39,40] Such findings are also relevant for patients who undergo AVJ ablation and conventional pacemaker implantation since they will receive near 100% of pacing for the rest of their life. Importantly, the vast majority of patients studied (including all studies commented in the previous section) received an RVA pacing system (typically VVIR), and it is therefore likely that some of the benefits associated with the AVJ ablation procedure were offset by the detrimental effects of chronic RVA pacing, especially after years of chronic pacing. This was observed by Tops et al[41] who retrospectively evaluated 55 patients with medically refractory AF and preserved LVEF who had undergone AVJ ablation. After a relatively long follow-up of 3.8±1.7 years, 49% had developed LV dyssynchrony and in this subgroup LVEF was significantly worsened (from 48±7% to 43±7%; P<0.05) as well as NYHA class (from 1.8±0.6 to 2.2±0.7; P<0.05). On the contrary, a retrospective study[42] of 286 patients with baseline LVEF of 48±18% with a shorter follow-up (1.7±1.6 years) than the Tops et al.[41] who had undergone AVJ ablation showed short-term improvement in mean LVEF with no significant change compared to baseline at the end of the study follow-up. Differences in the prevalence of patients with tachycardia-induced cardiomyopathy, duration of exposure to RVA pacing (i.e. study follow-up), and baseline LV dysfunction are possible explanations for the contradictory study results.

During the 2010s several studies compared RVA pacing with

cardiac CRT in patients undergoing AVJ ablation for AF (Table 2). This was first studied in the randomized controlled trial Post AV Nodal ablation Evaluation (PAVE) study[43] where 184 patients with drug refractory AF and baseline LVEF of 46±18%, who had undergone AVJ ablation were randomized to CRT or RVA pacing. At 6 months postablation, the LVEF remained stable in the CRT group but had deteriorated by 3.1% at 6 weeks and 3.7% at 6 months in the RVA pacing group. Similar results were reported in the more recent Ablate and Pace in Atrial Fibrillation (APAF)[44] randomized controlled trial, which included 186 patients with impaired cardiac function (mean LVEF 37.5±14%) and AVJ ablation for symptomatic AF. After a mean follow-up of 20 months, the primary composite endpoint of death from HF, hospitalization due to HF, or worsened HF occurred more frequently in the RVA pacing group than the CRT group (26% vs. 11%; P=0.005), principally driven by the latter 2 endpoints (Figure 3). Of note, 50% of the patients had a QRS duration ≥120ms, however patients benefited equally from CRT independent of QRS duration. A meta-analysis of 5 RCTs[43-47] that compared RVA pacing with CRT following AVJ ablation in patients with drug refractory fast AF and at least mildly depressed LVEF (<45%) found a significant reduction in hospitalization for HF and increase in LVEF but no effect on exercise capacity, quality of life or mortality.[5] Taken together, in patients with reduced LVEF and drug refractory fast AF who undergo AVJ ablation, RVA pacing is associated with deterioration of LV function and increase risk for hospitalization for HF and in this cohort CRT confers significant clinical and cardiac functional benefits. Given the lack of clinical studies, there is currently no evidence to support CRT after AVJ ablation for AF when LV function is normal.

Clinical Guidelines

Both the North American and the European AF clinical practice guidelines recommend AVJ ablation followed by permanent pacemaker implantation in patients with AF when rate is not controlled pharmacologically and rhythm control is not achievable (when antiarrhythmic therapy is ineffective or associated with intolerable side effects and direct catheter-based or surgical ablation of AF is not indicated, has failed or is rejected) (recommendation Class IIa; Level B).[1,2] When it comes to device selection the European clinical practice guidelines on cardiac pacing recommends CRT in those with reduced LVEF (without a specific cutoff value) (recommendation Class IIa; Level B)[48] and the North American clinical practice guidelines recommends CRT when LVEF is ≤35% but state that it should also be considered for patients with less severe dysfunction.[2]

HF Patients with Concomitant Permanent AF Receiving CRT

Almost all randomized controlled trials that have established the clear clinical benefits of CRT in patients with symptomatic HF, prolonged QRS duration and reduced LVEF included only patients in sinus rhythm.[48] However, a large proportion of HF patients present AF and despite the limited evidence the available results suggests that CRT is also useful in these patients,[46,49] for which reason it shares the same indications as for patients in SR (when in NYHA class III-IV).[48,50] Nonetheless AF in itself is linked to a poorer prognosis in HF patients,[51] and there is substantial data that CRT is associated with a higher risk of non-responders in patients with AF undergoing CRT.[52] This is most likely due to the absence of atrioventricular optimization benefit and a high intrinsic ventricular rate with irregular RR intervals, which leads to reduction in fully captured biventricular pacing beats through fusion and pseudo-fusion beats. Indeed, the greatest magnitude of reduction in mortality is observed when biventricular pacing is >98%.[6] Furthermore, it is important to note that device counters have been found to overestimate the degree of effective biventricular pacing in patients with AF due to fusion and pseudo-fusion beats, in which instances a 12-lead Holter monitor is helpful to assess the presence of effective pacing.[7] Therefore, in order to optimize the CRT derived benefits in patients with AF, rate regulation is paramount, either pharmacologically or by AVJ ablation (after pharmacological and/or direct catheter ablation rhythm control has been deemed unsuitable).[48,50]

Medical Rate Control vs. AVJ Ablation

Although there is no randomized controlled trial data available, most observational studies indicate that AVJ ablation is associated with significant clinical benefits when compared with medical rate control in patients with AF who undergo CRT implantation (Table 3). A metaanalysis published in 2012 that included 768 CRT patients with AF, from 4 retrospective and 2 prospective cohort studies, reported that AVJ ablation in CRT-AF patients was associated with significant risk reduction in all-cause mortality (risk ratio 0.42; 95% confidence interval [CI]: 0.26 to 0.68; P<0.001), cardiovascular mortality (risk ratio 0.44; 95% CI: 0.24 to 0.81; P=0.008), and

Table 2: Randomized controlled trials comparing RVA pacing versus CRT after AVJ ablation in symptomatic AF

Study (year)	Patients (n)	Follow-up (months)	Baseline LVEF (%)	Study endpoints	CRT benefits
MUSTIC AF[46] 2002	59	3 (cross-over)	25 ± 10	6 min walk distance* Peak oxygen uptake, hospitalization for HF, QoL, and mortality	Improved 6 min walk distance, peak oxygen uptake and QoL.** Non-significant reduction in hospitalization for HF. No difference in mortality.
OPSITE[45] 2005	56	3 (cross-over)	38 ± 14	6 min walk distance*, NYHA* and QoL* LVEF, LVESD and LVEDD	Improved NYHA, LVEF and LVESD. No differences in other endpoints.
PAVE[43] 2005	184	6	46 ± 16	6 min walk distance* QoL and LVEF No difference in QoL	Improved 6 min walk distance and LVEF. No difference in QoL.
AVAIL[47] 2010	127	6	56 ± 9	6 min walk distance*, NYHA* and QoL* LVEF, LVESV, LVEDV and LA volume	Improved NYHA, LVEF, and LV and LA volumes. No differences in 6 min walk distance or QoL.
APAF[44] 2011	186	20	38 ± 14	Composite of death due to HF, hospitalization for HF or worsened HF* Total mortality, hospitalization for HF, worsened HF, LVEF, LVESD, or LVEDD	Reduction in composite endpoint. No difference in mortality. Non-significant improvement in LVEF and LVEDD.

*Primary endpoint; **Significant improvement was only observed in the 37 patients where therapy was delivered and not in the intention-to-treat analysis; AF = atrial fibrillation; AV = atrioventricular; CRT = cardiac resynchronization therapy; HF = heart failure; NYHA = New York Heart Association functional class; LA = left atium; LVEF = left ventricular ejection fraction; LVEDD/V = left ventricular end diastolic diameter/volume; LVESD/V = left ventricular end systolic diameter/volume; QoL = quality of life; RCT = randomized controlled trial; RVA = right ventricular apex. (Adapted from Akerström F et al.[36] with permission.)

improvement NYHA class (mean difference -0.34; 95% CI: -0.56 to -0.13; P=0.002) (Figure 4).[8] Of the studies included, 3 consisted solely of permanent AF patients, 1 of persistent AF lasting >3 months and 1 did not report data on AF subtype. One year later the results from the prospective, multicenter, international, observational Cardiac Resynchronization Therapy in Atrial Fibrillation Patients Multinational Registry (CERTIFY) study were published.[53] The study reported the clinical outcome of CRT patients with permanent AF undergoing CRT implantation followed by AVJ ablation (n=443) or pharmacological rate control (n=895) compared with patients in SR (n=6046). After a median follow-up of 37 months total mortality (6.8 vs. 6.1 per 100 patient-years) and cardiac mortality (4.2 vs. 4.0) were similar for those with AF+AVJ ablation. On the contrary, the AF+drug group had a significantly higher total and cardiac mortality than the sinus rhythm (SR) group (11.3 and 8.1 respectively; P<0.001). The biventricular pacing capture (by means of device counters) in the AF + AVJ ablation group was significantly higher than the AF+drug group (96±6% vs. 87±14%; P<0.001), reinforcing the importance of achieving a high percentage of biventricular capture, particularly in AF patients (the SR group presented 92±13% biventricular pacing). Interestingly, in the same year a single-center prospective observational study,[54] including 155 patients with permanent AF treated with CRT, found that AVJ block (either spontaneous or ablation induced) did not improve survival at a mean follow-up of 30 months. The contradictory results could be explained insufficient statistical power with a study population of only 155 patients and a lower baseline LVEF.[55] Future randomized controlled trials, comparing the 2 rate-control strategies, are in great need and if such trials would prove AVJ ablation superior to medical rate-control we might see an ablate and CRT pace strategy becoming increasingly prevalent for HF patients with concomitant AF and CRT indication. Finally, it should also be noted that rhythm control through direct catheter ablation might be an option in selected HF patients with paroxysmal/persistent AF receiving CRT, although there is currently no data available to supports this strategy.

Clinical Guidelines

Both the North American and European clinical practice guidelines underline the importance of ensuring a near 100% biventricular pacing in patients with AF undergoing CRT implantation.[48,50] The European guidelines further states that, since most studies favor AVJ ablation over pharmacological rate control in most AF patients, this should be considered in most patients always taking into account the risks associated with creating pacing dependency.

Conclusions

AVJ ablation with subsequent permanent pacemaker implantation represents an effective and safe therapeutic option in patients with fast AF refractory to pharmacotherapy when rhythm and rate control are not achievable. It provides symptom relief through lowering of ventricular rates and regularization of RR intervals, and reversal of tachycardia-induced cardiomyopathy when present. Due to the deleterious effects caused by RVA pacing induced electro-mechanical dyssynchrony in patients with reduced LVEF, CRT is the preferred pacing strategy and should always be considered in this patient group. Nonetheless, data on predictors of poor response to RVA pacing and potential benefit of CRT is scarce and warranted. HF patients with concomitant AF receiving CRT is another patient group that may benefit from AVJ ablation since this guarantees a near 100% of biventricular pacing. So far, multiple cohort studies indicate that in this patient group AVJ ablation is associated with improved LV function, functional class, cardiac and total mortality when compared

Table 3: Clinical cohort studies comparing pharmacological rate control vs. AVJ ablation (AVJA) in HF patients with concomitant permanent AF receiving CRT (NYHA II-IV, LVEF ≤35% and QRSd ≥120ms)

Study (year)	Intervention groups (n)	Follow-up (months)	AVJA criteria	%BVP	Results
Gasparini[56] 2006	CRT-SR (511) CRT-AF-AVJA (114) CRT-AF-drug (48)	Prospective 25.2±18 months	BVP <85% at 2 months follow-up	CRT-SR: 98.5±1.8% CRT-AF-AVJA: 98.4±2.1% CRT-AF-Meds: 88.2±3.1%	-CRT significantly improved LVEF, LVESV, NYHA class, functional capacity score in both CRT-SR and CRT-AF-AVJA/Meds groups -CRT-AF-AVJA group, and not CRT-AF-drug group, showed significant improvements in LVEF, LVESV and functional capacity score -Significantly higher rate of responders in CRT-AF-AVJA group (68%) than CRT-AF-drug group (18%)
Ferreira[57] 2008	CRT-SR (78) CRT-AF-AVJA (26) CRT-AF-drug (27)	Retrospective 6 months	Not specified	CRT-SR: 95±13% CRT-AF-AVJA: 98±6% CRT-AF-Meds: 87±19%	-CRT significantly improved NYHA class in both CRT-SR and CRT-AF-AVJA/drug groups -Significantly higher rate of responders in CRT-AF-AVJA group (85%) than in CRT-AF-drug group (85% vs. 52%; P<0.008) -CRT-AF-drug was independently associated with higher mortality (HR 5.22; CI: 1.60-17.01; P=0.006)
Gasparini[58] 2008	CRT-SR (1042) CRT-AF-AVJA (118) CRT-AF-drug (125)	Retrospective 34 (10-40) months	BVP <85% at 2 months follow-up	CRT-SR: not reported CRT-AF-AVJA: 98.7±1.8% CRT-AF-Meds: 89.4±2.4%	-CRT-AF-AVJA/drug and CRT-SR groups showed similar total mortality (8.4 vs. 8.9 per 100 person-year) -CRT-AF-AVJA group showed significantly higher overall survival compared to CRT-AV-drug, primarily by reducing HF death (4.3 vs. 15.2 per 100 person-year; P<0.001)
Dong[59] 2010*	CRT-AF-AVJA (45) CRT-AF-drug (109)	Retrospective 2.1 (1.4-3.0) years	Not specified	CRT-AF-AVJA: 99.0% CRT-AF-Meds: 96.5%	-CRT improved LVEF (8.1% vs. 6.8%) and LVEDD (-0.7 vs. -0.4) in both CRT-AF-AVJA and CRT-AF-drug groups with no significant intergroup differences -Improvement in NYHA class was significantly greater in CRT-AF-AVJA group than CRT-AV-drug group (-0.7 vs. -0.4; P=0.04) -CRT-AF-AVJA was associated with increased survival (HR 0.13; CI 0.03-0.58; P=0.007)
Gasparini[53] 2013	CRT-SR (6046) CRT-AF-AVJA (443) CRT-AF-drug (895)	Prospective 37 (14-58) months	BVP <85% and/or inadequate clinical response at 3 months follow-up	CRT-SR: not reported CRT-AF-AVJA: 96±6% CRT-AF-Meds: 87±14%	-CRT-AF-AVJA/drug and CRT-SR groups showed similar total mortality (6.8 vs. 6.1 per 100 person-year) and cardiac mortality (4.2 vs. 4.0) -CRT-AF-drug was associated with significantly higher total mortality (HR 1.52; CI 1.26-1.82; P<0.001) and cardiac mortality (HR 1.57; CI 1.27-1.94; P<0.001)
Tolosana[54] 2013**	CRT-AF-AV Block*** (76) CRT-AF-drug (79)	Prospective 30 (13-51) months	BVP <85% at 45 days follow-up	CRT-AF-AVJA: 97±4% CRT-AF-Meds: 94±5%	AV Block did not improve overall and cardiovascular mortality in CRT-AF patients

*88% permanent AF; **Only NYHA class III-IV; ***72% AVJA and 28% spontaneous AV block; BVP = biventricular pacing; CI = confidence interval; CRT = cardiac resynchronization therapy; HF = heart failure; HR = hazard ratio; LVEDD = left ventricular end-diastolic diameter; LVEF = left ventricular ejection fraction; LVESV = left ventricular end-systolic volume; NYHA = New York Heart Association functional class; QRSd = QRS complex duration; SR = sinus rhythm.

to pharmacological rate control. Future randomized controlled trials, comparing AVJ ablation vs. pharmacotherapy in CRT-AF patients are needed in order to establish the definite role of AVJ ablation in this patient group.

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Outcomes Of Cryoballoon Ablation Of Atrial Fibrillation: A Comprehensive Review

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Abstract

Over the last decade, cryoballoon ablation has emerged as an effective alternate strategy to point-by-point radiofrequency ablation for treatment of symptomatic atrial fibrillation. There are several reasons for this. First, the acute and long-term safety and efficacy associated with cryoablation appear comparable to that of radiofrequency ablation in patients with both paroxysmal and also persistent atrial fibrillation. Second, cryoablation offers certain advantages over conventional radiofrequency ablation including a gentler learning curve, shorter ablation and procedure times as well as lack of need for costly electroanatomical mapping technologies commonly utilized with radiofrequency ablation. Lastly, with the recent advent of the second-generation cryoballoon, the effectiveness of cryoablation has further improved dramatically. This comprehensive review examines the gradual evolution of the cryoablation tools as well as the rationale and data in support of the currently-available cryoballoon technologies for catheter ablation of atrial fibrillation.

Introduction

Catheter ablation has emerged as a practical approach for treatment of symptomatic atrial fibrillation (AF) in those who fail membrane-stabilizing antiarrhythmic drug (AAD) therapy.[1] AF ablation has been shown to improve patient quality of life[2] and reduce hospital readmission.[3] Additionally, the observed benefits even persist in patients in whom complete freedom from AF cannot be achieved.[2] As the role for catheter ablation in the management of AF has evolved within the last 2 decades, so have the ablative techniques and strategies. To date, a variety of energy modalities have been utilized for catheter ablation of AF including unipolar radiofrequency (RF),[4] irrigated[5] and non-irrigated bipolar RF,[6] laser,[7] cryothermy,[8] and high-intensity focused ultrasound.[9] While the long-term safety and efficacy of RF energy has rendered it the mainstay of arrhythmia ablation therapy, there are certain practical and theoretical advantages to using cryoenergy.

The principles of cryobiology were first established with investigations on the treatment of frostbite and tumor destruction.[10] Current data suggests that a temperature of –30°C to –40°C is necessary to induce cell death.[10] Ice formation is the cornerstone of cellular injury with cryotherapy which occurs both intracellularly and extracellularly. Hypothermy-induced cellular and tissue destruction occurs through immediate and delayed mechanisms.[10] The immediate effects including hypothermic injury and cellular freeze rupture are mediated through tissue freezing/thawing, whereas delayed injury results from vasculature damage and apoptosis or programmed cell death.[11]

Rationale For Using Cryoenergy For AF Ablation

As a result of technological advances, evolutions in catheter design, and improved energy delivery that have come about in the last two decades, cryoablation is now routinely used in cardiac electrophysiology laboratories. Cryotherapy exploits the Joule–Thomson effect[12] to achieve temperatures between –30°C to –90°C at the catheter–tissue interface.[13] Furthermore, the use of cryoablation for pulmonary (PV) vein isolation may offer certain advantages. First, tissue-catheter adhesion during cryoablation can result in improved catheter stability. Second, cryoablation is associated with reduced pain and discomfort since the afferent pain fibers are 'frozen' as opposed to stimulated thermally.[14] Third, cryoablation carries a lower risk of thrombus formation and consequently systemic thromboembolization and stroke, since it is associated with decreased activation of platelets and the coagulation cascade as compared with RF.[15] Fourth, cryoablation leaves the connective tissue matrix intact and also avoids the risk of steam pops.[14] Fifth, the lack of circulation, vascular disruption, and endothelial injury at the center of the cryolesion results in uniform tissue necrosis.[14] As a result, unlike with RF, cryolesions consist of a smooth, sharply-demarcated necrotic core corresponding to the frozen volume within the zone of lethality, and they are thought to be associated with reduced likelihood of ulceration, stenosis, and formation of fistulas

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Atrial Fibrillation, Catheter Ablation, Cryoablation, Cryoballoon, Outcome.

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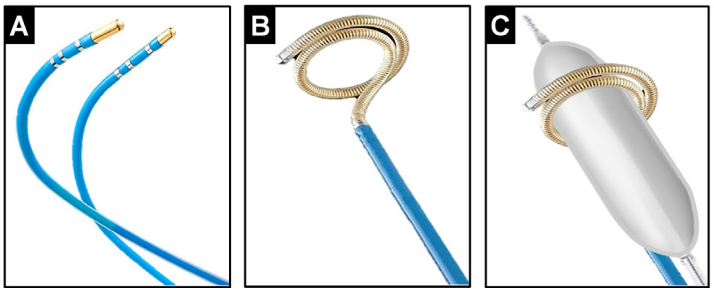

Figure 1: **Cryoablation tools originally used for catheter ablation of AF. Panel A, shown, are a 6-mm and a 4-mm tip focal cryoablation catheter. Panel B, illustrates a curvilinear cryoablation catheter with a 64-mm freezing segment and the ability to expand to a diameter of 18 to 30 mm. This was the first cryoablation catheter specifically designed for PV isloation. Panel C, illustrates the 'block the vein' strategy – through this approach the PV is mechanically occluded using an angioplasty balloon catheter, advanced through the curvilinear cryoablation catheter to diminish PV blood flow and to further enhance the efficacy of cryoablation.**

and strictures.[14] Nonetheless, cryoablation can still pose a significant threat to collateral structures such as the esophagus, lungs, coronary arteries, and phrenic and vagus nerves.[13] Another disadvantage relates to the impact of blood flow on lesion size. That is, increased blood flow surrounding the ablation catheter can significantly attenuate the size of cryolesions. As such, cryoablation is generally more effective in 'low-flow' areas.[12] Meanwhile, thaw time continues to remain the most important determinant of acute and long-term efficacy associated with cryoablation.[16,17]

Focal Cryoablation Of AF

The safety and feasibility of focal cryoablation (Figure 1-A) for PV isolation was initially studied in 52 patients with paroxysmal and persistent AF who underwent PV isolation using this approach.[18] While 97% of the targeted PVs were successfully isolated, freedom from AF was only 56% at 1 year. Though in this study the long-term clinical efficacy appeared to be lower than conventional RF ablation, post-procedural computed tomographic (CT) surveillance demonstrated no evidence of PV stenosis. Hoyt et al.[19] also reported on the feasibility of focal cryoablation in a cohort of 31 paroxysmal AF patients. Acute PV isolation was attainable in 94% of patients, but freedom from AF was only 58% at 6 months. Once again, no cases of PV stenosis were encountered on serial CT surveillance. Similarly, Kenigsberg et al.[20] found that in fact focal cryoablation up to 15 mm inside the PV ostium was not associated with increased risk of PV stenosis. Furthermore, endoscopic studies have reported lack of esophageal ulcerations following focal cryoablation as compared with the cryoballoon or RF.[21] Nonetheless, the practical application of focal cryoablation for PV isolation appears limited by prolonged ablation times and reduced long-term efficacy. Additionally, there are no data currently on the clinical efficacy of linear focal cryoablation within the left atrium. While clinical studies in patients with atrial flutter (AFL) have shown that linear lesions can be effectively created by point-by-point cryoablation, long-term recovery of cavotricuspid isthmus conduction is generally higher using the latter approach as compared to RF.[22] Recently, the feasibility of a novel cryoablation system designed for catheter ablation of AF/AFL using a liquid refrigerant in place of nitrous oxide (used traditionally in catheter-based cryoablation systems), was described in vivo.[23] The latter is capable of achieving lower nadir temperatures and seems to hold promise for both PV isolation and linear ablations.

Cryoballoon Ablation Of AF

In order to overcome the challenges associated with focal cryoablation for PV isolation, a curvilinear catheter was initially developed in early 2000s. This catheter consisted of a 64-mm freezing segment with the ability to expand to a diameter from 18 to 30 mm (Figure 1-B). Skanes et al.[24] reported on the use of this circular cryoablation catheter. Although using this ablation tool, complete PV isolation proved possible in 91% of patients without any cases of PV stenosis, only 22% exhibited freedom from AF at 6 months. On the other hand, in 44% of patients who underwent a repeat procedure, PV reconnection was evident in 93% of the previously isolated PVs. The poor efficacy associated with this catheter was attributed largely to the undesirable effects of PV blood flow on cryoablation using this technology and its suboptimal catheter design. As a result, the 'block the vein' strategy was proposed (Figure 1-C). Eventually, based on this scheme, the first cryoballoon ablation catheter was introduced and subsequently tested in vivo.[25,26]

First-Generation (Arctic Front) Cryoballoon

The cryoballoon (Arctic Front, Medtronic, Inc, Minneapolis, MN) is a steerable, over the wire, 12-French double-walled balloon catheter system (Figure 2-A). Two sizes are available – a 23 and

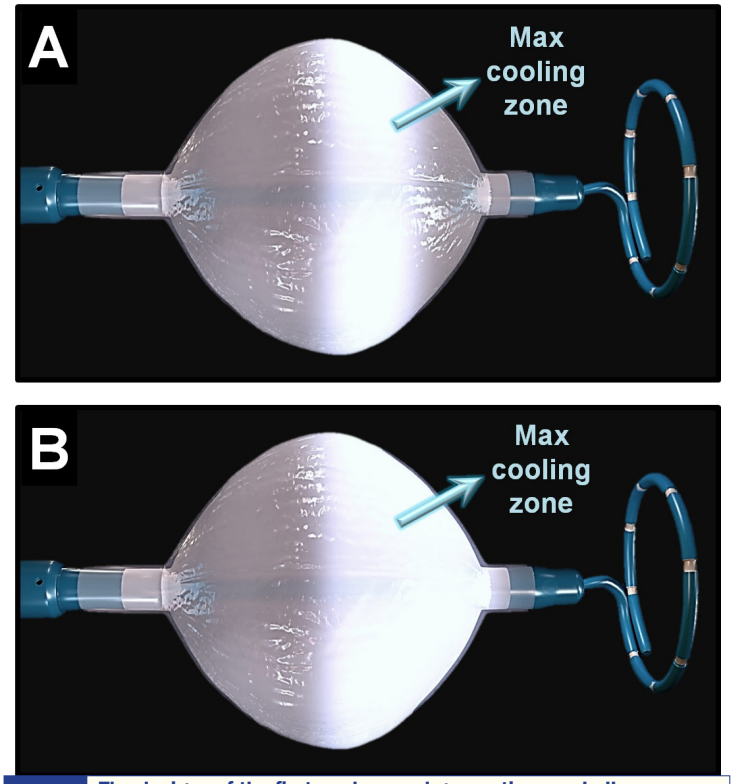

Figure 2: **The designs of the first- and second-generation cryoballoon catheters, both advanced over an octapolar spiral mapping catheter specifically designed for recording PV potentials to guide real-time PV isolation. Panel A, in the first-generation cryoballoon, the maximal cooling zone (arrow) consists of an equatorial band. Accordingly, optimal balloon alignment would be vital to ensure proper circumferential contact between the PV antra and the cooling zone on this balloon. Panel B, due to design modifications made to the second-generation cryoballoon, the maximal cooling zone on this catheter (arrow) now spans the entire distal half of its surface including the distal tip. This in turn offers a greater cooling surface area while minimizing the impact of balloon orientation on optimal tissue contact.**

Table 1: Acute and long-term efficacy and safety of PV isolation using the first-generation cryoballoon in non-randomized studies.

Study	n	Paroxysmal AF, n	Acute PV isolation	Procedure time, min	Fluoroscopy time, min	Transient PN palsy	Persistent PN palsy	Freedom from AF during follow-up
Malmborg, et al.[28]	43	34 (79%)	91%	239 ± 48	57 ± 21	4.7%	2.3%	52% at 9 months
Neumann, et al.[29]	346	293 (85%)	97%	170	40	7.5%	0%	74% at 12 months (paroxysmal AF) 42% at 12 months (persistent AF)
Klein, et al.[30]	21	21 (100%)	95%	165 ± 35	39 ± 9	14.3%	4.8%	86% at 6 months
Van Belle, et al.[31]	141	141 (100%)	99%	207 ± 79	50 ± 28	2.8%	0%	55% at 15 months
Chun, et al.[32]	27	27 (100%)	98% (single application)	220	50	11.1%	0%	70% at 9 months
Defaye, et al.[33]	117	92 (79%)	87% (single application)	155 ± 43	35 ± 15	0.9%	0%	69% at 12 months (paroxysmal AF) 45% at 12 months (persistent AF)
Vogt, et al.[34]	605	579 (96%)	91%	156	25	2%	0%	62% at 30 months
Ferrero-de Loma-Osorio, et al.[35]	63	40 (63%)	95%	180 ± 32	31 ± 22	4.8%	0%	72% at 2 years (paroxysmal AF) 36% at 2 years (persistent AF)
Aytemir, et al.[36]	236	188 (80%)	99%	72 ± 5	14 ± 3	4.6%	0%	81% at 18 months (paroxysmal AF) 50% at 18 months (persistent AF)
Rao, et al.[37]	51	51 (100%)	97%	151 ± 30	49 ± 12	5.9%	0%	57% at 36 months

a 28 mm balloon catheter. Early on, a small study comparing the outcomes between the curvilinear cryoablation catheter and the cryoballoon pointed to the superior efficacy associated with the use of the latter in patients with paroxysmal AF.[27] Subsequently, acute and long-term safety and efficacy of PV isolation using the cryoballoon was evaluated in several non-randomized studies in patients with paroxysmal AF (Table 1), reporting long-term success rates ranging between 55 and 86%.[28–37] Neumann et al.[29] reported on a prospective, 3-center experience of cryoballoon ablation in 346 patients with symptomatic, drug refractory paroxysmal and persistent AF. Acute PV isolation could be achieved in 97% of the targeted PVs, and freedom from AF was 74% in patients with paroxysmal and 42% in those with persistent AF. No PV stenosis was again encountered during follow-up. However, transient phrenic nerve (PN) palsy occurred in 7.5% of patients; though they all resolved within 1 year. The Sustained Treatment of Paroxysmal Atrial Fibrillation (STOP AF) trial is the only published multicenter, prospective, randomized-controlled trial that evaluated the safety and efficacy of cryoballoon ablation for treatment of AF.[8] In this study, 245 patients with paroxysmal (78%) or early persistent AF (22%) were randomized to cryoballoon ablation or AAD therapy in a 2:1 randomization scheme. Cryoablation achieved electrical isolation in 98.2% of PVs, in 97.6% of patients. Following a 3-month blanking period, freedom from AF was achieved in 69.9% of patients treated with cryoablation as compared to only 7.3% using AAD therapy ($p<0.001$). Transient PN palsy was encountered in 11.2% which ultimately persisted in 1.5% of patients at 1 year. Stroke occurred in 2.2% and PV stenosis (defined as a reduction of >75% in cross-sectional area or a 50% reduction in PV diameter) in 3.1% of patients treated with cryoablation. Two patients with PV stenosis were symptomatic and one required PV stenting. Subsequently, a systematic review of 23 studies published on the outcomes of cryoballoon ablation among 1,308 patients with paroxysmal and persistent AF showed a 97.5% acute procedural success (PV isolation) with freedom from AF in 72.8% at 1 year.[38] These findings were generally consistent with those reported in STOP AF. More recently, Yorgun et al.[39] reported on the additional benefits of cryoballoon-based ablation of AF beyond PV isolation. The authors found that modification of ganglionic plexi as evaluated by occurrence of vagal reactions during cryoablation may serve as an independent predictor of AF recurrence during long-term follow-up.

Second-Generation (Arctic Front Advance) Cryoballoon

Soon after the early experiences with the first-generation cryoballoon it became apparent that ablation using this tool was prone to certain challenges and drawbacks. Due to its number and location of refrigerant injection ports, the maximal cooling zone on the first-generation balloon occurs primarily over its equator (Figure 2-A). Therefore, optimal balloon positioning and orientation at PV antra is often critical when using this catheter, such that balloon mal-alignment can frequently compromise uniform tissue cooling and lesion formation.[40] This is further supported by more recent data showing that durable PV isolation is directly impacted by the degree of PV occlusion and tissue cooling, which in turn is influenced by the distance from the balloon (cooling zone These concerns subsequently led to the development of the second-generation cryoballoon (Arctic Front Advance, Medtronic, Inc). The principal modification in the design of this catheter has to do with the expansion of the cooling zone to the entire distal half of its surface (Figure 2-B). Knecht et al,[42] analyzed the magnitude of ice formation using this new design as compared to the first-generation cryoballoon and found that the mean covered surface areas were significantly different for the 28-mm but not the 23-mm balloons. Where as the first-generation catheter created non-contiguous ice formation, the second-generation cryoballoon exhibited a rather homogenous ice cap covering the entire distal segment of the balloon including its distal pole (the nose of the balloon). The superior efficacy of the second-generation cryoballoon was subsequently validated in vivo.[43,44] That is, it was shown that cryoablation of canine PVs through a single 4-min cryoapplication using the second-generation cryoballoon created transmural and circumferential lesions resulting in electrical isolation in 100% of PVs, as compared to only 60% using the first-generation cryoballoon. A more recent clinical study showed that cryoablation using this balloon was wide and circumferential with the level of PV isolation more antral, resulting in generous posterior left atrial debulking which could in part also account for this balloon's improved efficacy.[45] Furthermore, Reddy et al.[46] evaluated the outcomes of PV isolation using the second-generation cryoballoon in 21 consecutive patients with paroxysmal AF, all of whom subsequently underwent a second remapping procedure to assess for durability of PV isolation at 3 months. The authors found that acute electrical isolation could be achieved in 83% of PVs using a single cryoapplication, with

Table 2: Acute and long-term outcomes of PV isolation using the first- versus second-generation cryoballoons in non-randomized studies.

Study	n	Acute PV isolation	Cryoballoon temperature at PV isolation, at 60 sec or, at nadir temperature, °C	Time to PV isolation or nadir temperature, sec	Ablation Time, min	Procedure time, min	Fluoroscopy time, min	Transient PN palsy	Freedom from AF at 1 year
Martins, et al.[47]	66	81%	−36 ± 10*	52 ± 34**	26 ± 14	120 ± 24	29 ± 10	10.6%	N/A
First-generation balloon	81	90%	−32 ± 10*	40 ± 25**	22 ± 7	107 ± 24	25 ± 9	24.4%	N/A
Second-generation balloon p-value		0.003	0.001	0.001	<0.001	0.002	0.020	0.048	N/A
Fürnkranz, et al.[48]	30	100%	−49 ± 6†	79 ± 60**	N/A	128 ± 27	19 ± 7	3.3%	N/A
First-generation balloon	30	100%	−52 ± 6†	52 ± 36**	N/A	98 ± 30	13 ± 5	3.3%	N/A
Second-generation balloon p-value		1.00	0.005	0.049	N/A	<0.001	0.001	1.00	N/A
Aryana, et al.[49]	140	92%	26 ± 23‡	232 ± 77§	61 ± 17	209 ± 58	42 ± 17	12.1%	80%
First-generation balloon	200	98%	−32 ± 16‡	209 ± 68§	47 ± 12	154 ± 47	27 ± 12	16.0%	84%
Second-generation balloon p-value		0.036	<0.001	<0.001	<0.001	<0.001	<0.001	0.311	0.289
Straube, et al.[50]	364	99%	61¶ / −50#	48†† / 76‡‡	60 ± 16	185 ± 49	34 ± 12	20.6%	85%
First-generation balloon	120	100%	−58¶ / −52#	33†† / 52‡‡	58 ± 12	175 ± 45	29 ± 11	27.5%	85%
Second-generation balloon p-value		0.43	<0.001¶ / 0.074#	<0.001†† / <0.001‡‡	0.007	0.038	<0.001	0.121	1.00
Fürnkranz, et al.[51]	50	98%	N/A	N/A	52 ± 10	137 ± 33	22 ± 10	8.0%	64%
First-generation balloon	55	100%	N/A	N/A	33 ± 6	94 ± 24	13 ± 4	12.7%	84%
Second-generation balloon p-value		0.48	N/A	N/A	<0.001	<0.001	<0.001	0.434	0.008
Di Giovanni, et al.[52]	50	100%	−50 ± 10†	69 ± 25**	N/A	115 ± 39	25 ± 6	8.0%	66%
First-generation balloon	50	100%	−52 ± 5†	43 ± 17**	N/A	90 ± 16	18 ± 6	16.0%	84%
Second-generation balloon p-value		1.00	—	<0.05	N/A	<0.01	<0.01	0.218	0.038
Liu, et al.[53]	57	88%	−42 ± 6†	N/A	37 ± 10	117 ± 26	20 ± 5	0%	60%
First-generation balloon	68	93%	−46 ± 6†	N/A	28 ± 9	103 ± 23	18 ± 5	2.9%	90%
Second-generation balloon p-value		0.352	0.003	N/A	<0.001	0.001	0.011	0.159	<0.001

L*Cryoballoon temperature at PV isolation, **Time to PV isolation, †Nadir cryoballoon temperature, ‡Cryoballoon temperature at 60 sec, §Time to nadir temperature, ¶Cryoballoon temperature at PV, isolation using the 23-mm cryoballoon, #Cryoballoon temperature at PV isolation using the 28-mm cryoballoon, ††Time to PV isolation using the 23-mm cryoballoon, ‡‡Time to PV isolation using the 28-mm cryoballoon

91% of PVs still durably isolated at 3 months. This provides clinical evidence that in fact the improved thermodynamic characteristics of the second-generation cryoballoon seem to be associated with a higher rate of both single-shot PV isolation and also chronic lesion durability, which may translate into improved clinical outcomes.

Meanwhile, several studies have compared the acute and long-term outcomes of PV isolation using the first- and second-generation cryoballoons in patients with paroxysmal and persistent AF.[47–53] These studies collectively point to the superiority of the second- over the first-generation cryoballoon based upon several major benchmark parameters including acute PV isolation, biophysical characteristics, ablation time, procedure time, fluoroscopic utilization, and long-term freedom from AF (Table 2). As previously shown by our group, in addition to faster balloon cooling rates at 30 and 60 sec, shorter time-to-nadir temperature, and longer interval and total thaw times observed with the use of the second-generation cryoballoon, we also found a significantly lower PV reconnection rate at repeat procedure in those with arrhythmia recurrence during long-term follow-up (30% versus 13%; p=0.037).[49] Furthermore, these results were independent of operator experience and learning curve. Furthermore, Bordignon et al.[54] evaluated the magnitude of biomarker release in 66 patients following cryoablation using the first- versus the second-generation cryoballoons and found that despite shorter ablations required using the second-generation cryoballoon, higher levels of cardiac biomarkers such as troponin T, creatine phosphokinase and lactate dehydrogenase could be detected within the first 48 h in patients treated with the latter – possibly suggestive of more effective ablation. Interestingly, these findings also correlated with higher procedural success at 6 months. Table 3, illustrates a summary of mid- and long-term clinical outcomes of AF ablation using the second-generation cryoballoon as assessed by non-randomized single and multi-center studies.[46–58] These studies have consistently reported improved procedural and clinical outcomes associated with the use of the second-generation cryoballoon.

PV Isolation Using The Cryoballoon And Predictors Of AF Recurrence

A more recent feature of cryoballoon ablation of AF is the ability to potentially monitor real-time to PV isolation, also known as time-to-effect via a single transseptal access. That is, the cryoballoon can be advanced into the left atrium either over a conventional guide wire or a specific octapolar spiral mapping catheter/guide wire (Achieve, Medtronic, Inc) designed for monitoring and recording of PV potentials to guide real-time PV isolation (Figure 2). To date, this approach has been validated in several studies.[59–61] Nonetheless, the main limitation of this catheter has to do with its smaller diameter size (either 15-mm or 20-mm), precluding consistent real-time recording of PV potentials in patients with larger PV antra. Additionally, the wider spacing among the electrodes on the catheter further amplifies far-field electrogram sensing. In a recent publication, Boveda et al[61] reported a stepwise approach using this catheter which could accurately assess real-time PV isolation in ~98% of the PVs. Though in our experience, we have been unable to duplicate such a high rate of confirmation of PV isolation during cryoablation using this spiral recording catheter, undoubtedly this remains a highly effective tool for measuring time-to-effect providing overall a simpler method for validation of PV isolation as compared to other single-shot ablation systems such as the nMARQ or the pulmonary vein ablation catheter (PVAC).

Meanwhile several other studies have closely examined the predictors of a successful cryoballoon ablation of AF. One report

found an inverse association between the ovality index and the orientation of PV ostia as determined by cardiac CT angiography with the degree of cryoballoon occlusion during catheter ablation.[62] Similarly, Kubala et al.[63] found that in patients undergoing cryoballoon ablation, presence of normal versus atypical PV anatomy such as a common left PV, was associated with improved freedom from AF during long-term follow-up. With respect to biophysical characteristics of cryoballoon ablation, it seems that balloon thaw time and perhaps its secondary derivative, freeze area-under-the-curve, represent significant predictors of PV reconnection during follow-up and long-term freedom from AF post-catheter ablation.[64,65] On the other hand, cryoablation time and cryoballoon temperature served as poor and unreliable predictors of such endpoints.[65] It should be emphasized that the freeze area-under-the-curve signifies a comprehensive metric to assess the magnitude of cryoablation.[49] As such, the computed value collectively reflects a multitude of parameters including duration of cryoapplication, rate of cooling, nadir temperature, and thaw-time. Meanwhile, another study has suggested that very cold minimum balloon temperatures (<-51°C) may in fact be predictive of acute PV isolation.[66] Conversely, the same study found that a minimum balloon temperature ≥-36°C (for superior PVs) and ≥-33°C (for inferior PVs) predicted failed acute PV isolation with a relatively high specificity (≥95%). But it should be pointed out that in this study no data on long-term outcomes were reported to further corroborate the acute procedural findings with respect to durability of PV isolation or freedom from AF. Collectively, we believe that these findings underscore the importance of the 'quality' as opposed to the 'quantity' of cryoapplications during catheter of ablation when using the cryoballoon.

In the meantime, there remains a lack of consensus on the appropriate ablation dosing when performing an AF ablation using the cryoballoon – that is, with respect to the ideal freezing duration and the number of freeze-thaw-freeze cycles. The current recommendations suggest a 4-min cryoapplication along with a 'double freeze' approach (freeze-thaw-freeze cycle). Though the 'double freeze' method has been shown to result in more extensive tissue destruction and deeper, larger lesions due to the repeated freeze/thaw effects on the cell membrane,[14] it has been argued that this data may largely pertain to the less potent cryoablation tools such as the focal cryoablation catheter. Indeed, there is cumulative evidence in support of improved acute and long-term efficacy associated with a single PV cryoapplication using the second-generation cryoballoon. Ciconte et al.[57] recently reported their results of a single 3-min cryoapplication using the second-generation cryoballoon in 143 consecutive patients. The authors achieved acute PV isolation in 94% of PVs using a single application and in 100% after 1.1 ± 0.4 freezes. After a 3-month blanking period, freedom from atrial arrhythmias was achieved in 80% of patients at 1 year (82% with paroxysmal versus 73% with persistent AF). Additionally, 10% of patients underwent a repeat procedure. Though this data is subject to selection bias, among these patients 43% of PVs exhibited conduction recovery at redo ablation. Now it should be called to attention that it would be extremely difficult to meaningfully compare such data against those derived from other non-matched series. However, as previously reported by our group,[49] the same outcome of PV reconnection in patients undergoing repeat procedures following an initial second-generation cryoballoon ablation using ≥2 applications (≥1 freeze-thaw-freeze cycle) was found to be 13%. In the long run, whether a second 'bonus' freeze will in fact prove necessary still needs to be determined.

A recent study has also evaluated the predictive value of early AF recurrence following catheter ablation using the first-generation cryoballoon by analyzing data from the STOP AF trial.[67] The authors found that over half of the patients (51%) experienced an early recurrence post-ablation within the first 3 months. Moreover, of these recurrences the great majority (85%) had occurred within the first month. Though nearly half of these individuals (44%) remained free of long-term atrial arrhythmias, early recurrence did in fact correlate with late recurrence of AF. Conversely, only 13% of those with early recurrences were found to have recurrent AF during long-term follow-up.

Comparison Of Cryoballoon Versus RF

Though there is limited data on prospective head-to-head comparisons between cryoballoon versus RF catheter ablation of AF, several non-randomized comparative studies[58,68–76] have been published on the use of the first-generation cryoballoon as compared to open-irrigated, non-force sensing RF (Table 4). The results have

Table 3: Acute and long-term efficacy and safety of PV isolation using the second-generation cryoballoon in non-randomized studies.

Study	n	Paroxysmal AF, n	Acute PV isolation	Ablation time, min	Procedure time, min	Fluoroscopy time, min	Transient PN palsy	Persistent PN palsy	Freedom from AF during follow-up
Kenigsberg, et al.[46]	43	34 (79%)	100%	22 ± 4	126 ± 23	16 ± 8	N/A	N/A	95% at 6 months
Martins, et al.[47]	81	81 (100%)	90%	22 ± 7	107 ± 24	25 ± 9	3.3%	0%	N/A
Fürnkranz, et al.[48]	30	23 (77%)	100%	29 ± 12	98 ± 30	13 ± 5	3.3%	0%	N/A
Aryana, et al.[49]	200	143 (72 %)	98%	47 ± 12	154 ± 47	27 ± 12	16.0%	0.5%	84% at 1 year
Straube, et al.[50]	120	63 (52%)	100%	58 ± 12	175 ± 45	29 ± 11	27.5%	1.7%	85% at 1 year
Fürnkranz, et al.[51]	55	55 (100%)	100%	33 ± 6	94 ± 24	13 ± 4	12.7%	5.4%	84% at 1 year
Di Giovanni, et al.[52]	50	50 (100%)	100%	N/A	90 ± 16	18 ± 6	16.0%	2%	84% at 1 year
Liu, et al.[53]	68	50 (74%)	93%	28 ± 9	103 ± 23	18 ± 5	2.9%	0%	90% at 1 year
Bordignon et al.[54]	33	26 (79%)	100%	33 ± 6	N/A	N/A	6.1%	0%	85% at 6 months
Chierchia, et al.[55]	42	42 (100%)	100%	31 ± 4	95 ± 16	20 ± 12	19.0%	0%	83% at 1 year
Metzner, et al.[56]	50	36 (72%)	100%	35 ± 6	140 ± 28	25 ± 8	2.0%	0%	80% at 1 year
Ciconte, et al.[57]	143	113 (79%)	100%	13 ± 5	95 ± 16	13 ± 8	6.3%	3.5%	80% at 1 year
Aryana, et al.[58]	633	472 (75%)	98%	40 ± 14	145 ± 49	29 ± 13	7.6%	1.1%	77% at 1 year

been largely mixed without any apparent, significant differences between the two modalities. However, two of the larger series by Kojodjojo et al.[69] and Mugnai et al.[75] did in fact illustrate subtle trends towards improved 1-year outcomes with the first-generation cryoballoon as compared to RF (77% versus 72% and 63% versus 57%, respectively). Xu et al.[77] reported the outcomes from a meta-analysis of 1,104 patients from published studies, who underwent AF ablation using the cryoballoon (n=469) or RF (n=635). They found cryoablation to be associated with a significantly shorter procedure time (by a weighted mean of 30 min) and fluoroscopy exposure (by a weighted mean of 14 min), whereas ablation time was non-significantly longer with cryoablation (by a weighted mean of 12 min). Moreover, cryoablation was also found to be associated with a non-significantly higher rate of long-term success as compared with RF. Recently, our group has reported on the acute and long-term outcomes from a large, non-randomized, multicenter study comparing the second-generation cryoballoon to open-irrigated, non-force sensing RF.[58] The study included 1,196 patients with AF (76% paroxysmal), and it found that cryoablation was associated with a superior primary endpoint of freedom from atrial arrhythmias at 12 months following a single catheter ablation procedure without the use of AAD therapy (76.6% versus 60.4%; p<0.001), and overall a reduced need for AADs (16.7% versus 22.0%; p=0.024) and fewer repeat ablations (14.6% versus 24.1%; p<0.001) , as compared to non-contact force sensing RF. In addition, at redo procedure, fewer patients exhibited PV reconnection if previously ablated using the cryoballoon (44.2%) as versus RF (65.7%); p=0.002. Cryoablation was also associated with shorter ablation and procedure times, but greater fluoroscopic utilization. Both transient and persistent PN palsy occurred exclusively with cryoablation, whereas all other adverse event rates were similar between the two groups. These findings coupled with the relative safety associated with the use of cryoablation using the second-generation cryoballoon, reproducibility of the results across a number of different centers with variable procedural volume, and suggestion of a similar magnitude of benefit in patients with both paroxysmal and persistent AF, evoked the second-generation cryoballoon a more favorable ablation tool as compared to non-force sensing RF with an AF ablation score[78] notably greater than that computed for RF. Additional investigations to evaluate the safety and efficacy related to the use of cryoballoon ablation in comparison to the recently made available force-sensing RF ablation catheters seems necessary to identify the most optimal approach to AF ablation. Along these lines, Jourda et al.[79] reported on a prospective comparison between force sensing RF and the second-generation cryoballoon. The study found that both procedural and fluoroscopic times were shorter with force sensing RF but with similar ablation times, adverse events, and long-term freedom from AF as compared to cryoablation using the second-generation balloon. At this point, a larger, multicenter comparison of these two diverse types of ablation techniques with respect to cost, safety, and efficacy seems relevant.

In addition, Juliá and colleagues[76] recently reported on the incidence and mechanism of atrial tachycardias following catheter

Table 4: Acute and long-term outcomes of PV isolation using RF versus the cryoballoon in non-randomized studies.

Study	n	Paroxysmal AF	Acute PV isolation	Ablation Time, min	Procedure time, min	Fluoroscopy time, min	PN palsy	Other adverse events	Freedom from AF during long-term follow-up
Linhart, et al.[68]									
RF	20	20 (100%)	100%	N/A	200 ± 67	55 ± 23	0%	0%	45% at 6 months
Cryoballoon	20	20 (100%)	81%	N/A	166 ± 39	41 ± 13	15%	0%	50% at 6 months
Kojodjojo, et al.[69]									
RF	53	53 (100%)	99%	N/A	208 ± 58	62 ± 36	0%	3.8%	72% at 1 year
Cryoballoon	90	90 (100%)	83%	N/A	108 ± 28	27 ± 9	2.2%	1.1%	77% at 1 year
Tayebjee, et al.[70]									
RF	25	25 (100%)	100%	N/A	35	0%	0%	4%	52% at 1 year
Cryoballoon	25	25 (100%)	76%	N/A	45	8%	4%	4%	56% at 1 year
Kühne, et al.[71]									
RF	25	25 (100%)	00%	47	197 ± 52	46 ± 22	0%	4%	92% at 1 year
Cryoballoon	25	25 (100%)	100%	45	166 ± 32	61 ± 25	4%	4%	88% at 1 year
Sorgente, et al.[72]									
RF	29	20 (69%)	100%	N/A	N/A	N/A	0%	13.8%	66% at 1 year
Cryoballoon	30	24 (80%)	100%	N/A	N/A	N/A	10%	3.3%	66% at 1 year
Herrera Siklódy, et al.[73]									
RF	30	17 (57%)	100%	52 ± 21	200 ± 46	37 ± 16	0%	0%	80% at 1 year
Cryoballoon	30	21 (70%)	100%	44 ±6	177 ± 30	38 ± 12	6.7%	6.7%	63% at 1 year
Schmidt, et al.[74]									
RF	2,870	2,870 (100%)	98%	33	165	24	0%	4.6%	N/A
Cryoballoon	905	905 (100%)	97%	45	160	34	2.1%	2.7%	N/A
Mugnai, et al.[75]									
RF	260	260 (100%)	100%	43 ± 6	192 ± 49	36 ± 14	0%	14.2%	57% at 23 months
Cryoballoon	136	136 (100%)	100%	45 ± 4	112 ± 58	31 ± 17	8.1%	11.0%	63% at 23 months
Juliá, et al.[76]									
RF†	186	186 (100%)	98%	N/A	190 ± 57	35 ± 19	N/A	N/A	80% at 1 year
Cryoballoon*	100	100 (100%)	100%	N/A	117 ± 59	27 ± 16	N/A	N/A	81% at 1 year
Aryana, et al.[58]									
RF	422	319 (76%)	99%	66 ± 26	188 ± 42	23 ± 14	0%	2.6%	60% at 1 year
Cryoballoon**	633	472 (75%)	98%	40 ± 14	145 ± 49	29 ± 1	7.6%	1.6%	77% at 1 year
Jourda, et al.[79]									
RF†	75	75 (100%)	100%	2 ± 13	111 ± 32	21 ± 8	0%	2.7%	88% at 1 year
Cryoballoon**	75	75 (100%)	100%	32 ± 3	134 ± 48	25 ± 10	17.3%	1.3%	85% at 1 year

*Combination of first- and second-generation cryoballoons, **Second-generation cryoballoon only, †Force sensing RF

ablation of paroxysmal AF in 286 consecutive patients using the cryoballoon versus RF. The authors found that the incidence of post-ablation atrial tachycardias was significantly lower with cryoablation as compared to RF (3.0% versus 11.3%; p= 0.028). This difference was driven largely by the larger (28-mm) second-generation cryoballoon. Though not entirely clear, the mechanism is believed to be related to the overall reduced atrial ablation and perhaps larger and more homogeneous lesions created using the latter balloon.

Cryoballoon Ablation Of Persistent AF

Since the STOP AF study which originally evaluated the outcomes of cryoablation in patients with paroxysmal and 'early' persistent AF, several non-randomized first-/second-generation cryoballoon studies have evaluated this therapy in those with both paroxysmal and persistent AF.[46,48–50,53,54,56,58] Specifically, a few additional studies have explicitly examined the efficacy of cryoablation of non-PV triggers using the second-generation cryoballoon.[80–82] In a recent multicenter study, the second-generation cryoballoon was shown to be a safe and effective tool for electrical isolation of the superior vena cava and ablation of the left atrial roof, the left lateral ridge and the base of the left atrial appendage throughout both atria in 110 patients with persistent and long-standing persistent AF.[82] Complications were rare and at 1 year, 78% of patients remained free of AF recurrence following a 3-months blanking period. Obviously, additional data is currently needed to further validate the acute and long-term outcomes using this approach.

'Hybrid' Approach

Recently, a 'hybrid' approach involving a thoracoscopic surgical and a concomitant endocardial cryoballoon PV ablation has been described in patients with persistent AF or in those with paroxysmal AF and a failed prior catheter ablation.[83] While in two small studies this approach proved safe and feasible, the long-term efficacy of this strategy has yet to be evaluated.[83,84] For now, the precise role, applicability and specific advantages of the above-mentioned approach over each of the individual strategies alone, remain unclear.

Safety

Several studies have established the overall safety of cryoballoon ablation of AF,[8,38,85] While some have suggested fewer major adverse events associated with the use of cryoballoon versus RF including fewer cardiac perforations and fatalities,[85] these observations have not been entirely consistent. Aside from PN palsy which remains the most frequent complication related to the use of cryoballoon,[8,85] the same adverse events that in general complicate RF ablation also occur with cryoablation of AF.[38,58] These consist of groin complications, bleeding, thromboembolism, pericardial effusion, gastroparesis, and atrioesophageal fistula.[8,38,85] Though thromboembolism remains rare in the setting of cryoablation,[15] most embolic events as a consequence of cryoablation are believed to represent air embolism related to the handling of the larger sheath inside the left atrium. Neumann et al.[86] investigated the incidence of micro-embolization immediately after catheter ablation of AF with the cryoballoon versus RF in 89 patients using cerebral magnetic resonance. The authors discovered presence of asymptomatic cerebral lesions one day post-ablation in 8.9% of patients ablated with cryoballoon versus 6.8% with RF. These outcomes did not differ statistically. Meanwhile, PV stenosis may also complicate cryoablation of AF. Thought this adverse event has historically been thought to be a rare sequela of cryoablation,[14] there is sufficient evidence to suggest that cryoballoon ablation is not immune to this type of complication.[8] Nonetheless, a recent meta-analysis documented the overall incidence of PV stenosis resulting in symptoms or requiring intervention at only 0.17% in patients who underwent cryoballoon ablation of AF.[38] Chierchia et al. investigated the incidence and outcomes of pericardial effusion following cryoballoon versus RF ablation, and found no significant difference between the two modalities (11% versus 16%).[87] The authors concluded that this complication was generally asymptomatic and mild with a benign self-limiting course in nearly all cases. Lastly, persistent iatrogenic atrial septal defect (iASD) following cryoablation has also been described.[88–90] Specific concerns surrounding this complication have been raised due to the use of the larger, 15-French transseptal sheath which is required for delivery of the cryoballoon catheter into the left atrium. The incidence of iASD in cryoablation studies varies between 16–31% during short-term follow-up[88,89] and has been reported as high as 20% at 1 year.[90] Not surprisingly, this incidence seems to be higher than that which is reported for RF which generally utilizes a smaller transseptal sheath for performing the ablation.[89] Though most patients with persistent iASD seem to tolerate this entity rather well and without apparent adverse events,[88–90] additional studies on larger patient populations with longer follow-up are needed to reach a firm conclusion.

Meanwhile, some of the more important and specific adverse events complicating cryoballoon ablation of AF are reviewed in the ensuing sections.

PN Palsy

PN palsy is by far the most common complication of cryoballoon ablation of AF.[8,38] Anatomical studies have revealed the close proximity of the right PN to the superior vena cava and the anterior-inferior aspect of the right superior PV, and also the left PN to the left atrial appendage.[78] Hence, catheter ablation in the vicinity of these structures can potentially yield collateral injury to the adjacent PN. However, PN injury is not unique to cryoablation. In fact, it can also occur as a consequence of catheter ablation using RF as well as other energy modalities.[91,92] Overall, the prevalence of PN palsy due to AF ablation is estimated between 0.37% and 1.6%.[91] A recent study suggested that the mechanism of PN injury as a result of cryoablation seems to be axonal in nature and characterized by Wallerian degeneration, with great potential for regeneration and neuronal recovery.[93] Consistent with this, the short-term outcome of patients with post-ablation PN palsy appears to be favorable with >80% achieving complete resolution by 1 year.[91] As such, PN palsy may be classified as either transient or persistent. While the incidence of transient right PN palsy as a consequence of cryoballoon ablation of AF can reach ≈20%, persistent PN palsy remains uncommon with a reported incidence of only 0–4% in most studies.[29,31,34,36,49,50,58,74,75] Moreover, transient but not persistent right PN palsy has been shown to occur more frequently using the second-generation as compared to the first-generation cryoballoon.[47,49,52,94] This is likely due to the second-generation catheter's increased potency. Furthermore, PN palsy has also been shown to occur more frequently with the use of the 23-mm cryoballoon.[44,94] In most cases, the latter is believed to be related to the deployment of a relatively undersized cryoballoon deeper inside the PV.[95] In addition to minimizing the physical distance between the cryoballoon and the PN, cryoablation at a relatively more distal position inside the right PVs may be more conducive to enhanced 'cold' transfer to deeper tissues such as the PN due to reduced convective heating of the balloon by atrial blood

flow.[94–96] Hence, this may result in deeper penetration of cryoenergy, thereby increasing the risk of collateral injury.

Esophageal Injury

Esophageal thermal injury seems to occur with left atrial ablation virtually using any type of energy modality,[97,98] including also cryoenergy.[99–102] Furthermore, it is believed that in some patients this may represent a precursor to atrioesophageal fistula.[103] Early experiences using the first-generation cryoballoon suggested possibly a lack of esophageal thermal injury associated with cryoablation as assessed on post-procedural endoscopy, despite steep luminal esophageal temperature drops during catheter ablation.[104] Nonetheless, esophageal thermal injury and ulceration were subsequently demonstrated in other clinical studies,[105] particularly with the use of the second-generation cryoballoon which can be associated with esophageal ulcerations in as many as ≈20% of patients.[106,107] It should be emphasized that this incidence generally remains similar and possibly lower than that reported with RF.[108] Though as with ablation using other energy modalities no precise measures have been identified to mitigate esophageal thermal injury, Fürnkranz et al.[107] found that a luminal esophageal temperature ≤12°C during cryoballoon ablation predicted esophageal ulceration with 100% sensitivity and 92% specificity. In a subsequent study,[111] these authors reported that by adopting a strategy of luminal esophageal temperature-guided cryoablation through interruption of ablation with esophageal temperatures ≤15°C, the esophageal ulceration rate decreased to 3%. As such, avoidance of ultra-cold luminal esophageal temperatures during cryoablation seems prudent.

Lung Injury

Both cough and hemoptysis have been reported following cryoablation of AF.[112–118] A persistent dry cough can be detected more commonly in some patients following cryoballoon ablation. However, hemoptysis remains rather uncommon with an incidence ranging between 0–2.1%.[114–116] Though hemoptysis can also occur in the setting of PV stenosis, most cases of hemoptysis following cryoablation do not seem to accompany such a complication.[112–118] Furthermore, most overt cases of hemoptysis seem to manifest within hours to days following cryoablation,[112–114,116] rendering the possibility of PV stenosis once again less likely. Instead, it has been postulated that transient interruption of vascular integrity, perhaps within the pulmonary capillary system due to cryoinjury, may serve as a possible culprit.[113,114,116] Accordingly, some investigators have attributed this to colder balloon temperatures (<55°C) and deeper balloon positioning inside the PVs during cryoablation.[112–114,116,117] CT imaging of patients with hemoptysis frequently demonstrates presence of edema surrounding the PV tissue sometimes with erosion,[112] with[118] or without[113,114,117] luminal narrowing. Mucosal hyperemia and erosion can also be detected during bronchoscopy.[113,114] Some investigators have ascribed these findings to pulmonary infarction.[116] While this remains unclear based on the reports to date, both the clinical symptoms and findings appear to be self-limiting with a gradual resolution over time.[112–116] Furthermore, none of these cases have been associated with catastrophic complications such as formation of a fistula.

Conclusions

Over the past decade, cryoballoon ablation of AF has emerged as a practical, alternative strategy to point-by-point RF ablation. There seem to be several reasons for this. First, the acute and long-term safety and efficacy associated with cryoablation appear to be similar to RF, in patients with both paroxysmal and also persistent AF. Second, this technology also offers certain advantages over conventional RF ablation including a gentler learning curve and relative ease of use, shorter ablation and procedure times, and lack of need for costly electroanatomical mapping equipment commonly used with RF ablation. More recently, with the advent of the second-generation cryoballoon, the effectiveness of cryoablation has further improved remarkably. Given that results from several cryoablation studies strongly suggest a greatly improved efficacy associated with the use of the second-generation cryoballoon, a prospective head-to-head comparison between the latter and force sensing RF seems appropriate. As such, we eagerly await the results of ongoing studies that are currently investigating this topic.

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Diagnosis and Therapy of Atrial Fibrillation: the Past, the Present and the Future

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Abstract

Atrial fibrillation (AF) is the most common age-related cardiac arrhythmia. It is a progressive disease, which hampers successful treatment. The progression of AF is caused by the accumulation of damage in cardiomyocytes which makes the atria more vulnerable for AF. Especially structural remodeling and electrical remodeling, together called electropathology, are sustainable in the atria and impair functional recovery to sinus rhythm after cardioversion.

The exact electropathological mechanisms underlying persistence of AF are at present unknown. High resolution wavemapping studies in patients with different types of AF showed that longitudinal dissociation in conduction and epicardial breakthrough were the key elements of the substrate of longstanding persistent AF. A double layer of electrically dissociated waves propagating transmurally can explain persistence of AF (Double Layer Hypothesis) but the molecular mechanism is unknown. Derailment of proteasis –defined as the homeostasis in protein synthesis, folding, assembly, trafficking, guided by chaperones, and clearance by protein degradation systems – may play an important role in remodeling of the cardiomyocyte. As current therapies are not effective in attenuating AF progression, step-by-step analysis of this process, in order to identify potential targets for drug therapy, is essential. In addition, novel mapping approaches enabling assessment of the degree of electropathology in the individual patient are mandatory to develop patient-tailored therapies. The aims of this review are to

1) summarize current knowledge of the electrical and molecular mechanisms underlying AF,

2) discuss the shortcomings of present diagnostic instruments and therapeutic options and

3) to present potential novel diagnostic tools and therapeutic targets.

Introduction

The first electrocardiogram (ECG) of atrial fibrillation (AF) was recorded by Einthoven in 1906.[1] Nowadays, AF is one of the most common arrhythmias with a prevalence varying from <0.1% to >12% in the elderly which is expected to be doubled in patients over 55 years by 2060.[2,3] AF is originally known as a disease of the ageing population. However, an increasing prevalence is seen in young adults, especially in endurance athletes[4] and patients with congenital heart disease.[5] Hence, a continuous rise in the number of AF associated hospitalizations and healthcare costs is to be expected.[6] Several treatment modalities have been developed, but all are associated with high recurrence rates or negative side effects. The aims of this review are to

1) summarize current knowledge of the electrical and molecular mechanisms underlying AF,

2) discuss the shortcomings of present diagnostic instruments and therapeutic options and

3) to present potential novel diagnostic tools and targets for future therapy.

Key Words:
Atrial Fibrillation, Heat Shock Protein, Diagnosis, Therapy.

Disclosures:

None

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Deficiencies in Diagnostic Tools of Atrial Fibrillation

AF is usually diagnosed by a surface ECG or Holter recording. However, diagnosis of new onset, paroxysmal or asymptomatic AF

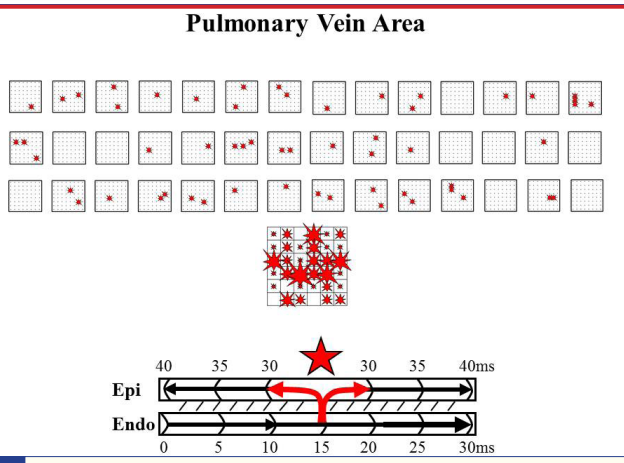

Figure 1: **Epicardial breakthrough**
Upper panel: beat-to-beat variation in spatiotemporal distribution of epicardial breakthrough waves ('focal waves') during 6 seconds of persistent AF in a small area of 1.25 X 1.25cm between the pulmonary veins. Each asterisk indicates a breakthrough site. The large map shows all 55 epicardial breakthroughs sites. The size of the asterisk is proportional to the number of epicardial breakthroughs occurring at that site. The breakthrough map demonstrates a wide distribution of these focal waves; none of these breakthrough waves occurred, however, repetitively.
Lower panel: schematic presentation of excitation of the endo- and epicardial layer explaining how transmural conduction from the endocardium to the epicardium gives rise to an epicardial breakthrough wave. Hence, the endocardial layer serves in this case as a source for 'new' fibrillation waves in the epicardial layer.[22]

can be challenging. An ECG only captures several seconds of the heart rhythm and episodes of AF can therefore be easily missed. The use of long-term ambulatory electrocardiography devices or implantable loop recorders increases the chance of detecting AF paroxysms. In addition, these devices also allow determination of the total duration of all AF episodes within a specific time frame, the so-called AF burden. However, electrocardiographic recordings do not provide any information on the mechanism underlying AF. Recent studies[7-10] suggest that body surface mapping arrays, containing 252 electrodes, may be useful to identify driver regions in patients with AF. Yet, none of the currently available recording techniques can determine the degree and extensiveness of atrial electropathology. Hence, when a patient presents with AF, we have no diagnostic tool available for evaluating the mechanism underlying AF and determining the stage of the disease at any time in the process.

Mechanisms Of Atrial Fibrillation: From Past To The Present

Experiments performed by Gordon Moe[11] nearly 60 years ago, provided the basis for the ongoing debate on the underlying cause for AF. In isolated canine atria, he showed that AF could be due to either fibrillatory conduction (AF caused by an ectopic focus with a high frequency discharge resulting in non-uniform excitation of the atria) or true fibrillation (AF persists independently from the site where it was initiated). In 1959, Moe[11] introduced the so-called Multiple Wavelet Hypothesis which further described the features of true fibrillation. In this hypothesis, Moe postulated that persistence of AF depended on the average number of wavelets. With the total number of wavelets being increased, the probability of extinguishment and thus termination of AF would become smaller. Twenty-six years later, Allessie et al.[12] performed the first experimental evaluation of Moe's multiple wavelet hypothesis. In a canine right atrium, during 0.5 second of acutely induced AF, he demonstrated in series of consecutive excitation maps that there was a continuous beat-to-beat change in activation pattern. The critical number of wavelets in both right and left atria necessary to perpetuate AF was estimated to be between three and six. Ever since, numerous experimental and clinical mapping studies,[11, 13-21] reporting on perpetuation of AF, are supportive on either a focal (repetitive ectopic discharges) or reentrant mechanism (mother-wave, rotor, multiple wavelets). In the past years, most clinical studies reported on the presence of rotors in patients with various types of AF.[20]

Electropathology Associated With Persistence Of Atrial Fibrillation

High-resolution wavemapping studies[22] of AF in patients with valvular heart disease and longlasting persistent AF, demonstrated that a large proportion of fibrillation waves were so-called focal waves. These waves appeared in the middle of the mapping area and could not be explained by fibrillation waves propagating in the epicardial plane. Focal fibrillation waves appeared scattered throughout the mapping area and were not repetitive (Figure 1). The coupling interval was longer than the dominant AF cycle length, and unipolar electrograms at the epicardial origin of these waves exhibited R-waves.[22] Hence, characteristics of these focal fibrillation waves strongly suggest that they originated from endo-epicardial breakthrough. These findings were supported by a report from Lee et al.[23] who observed that more than one third of the fibrillation waves in patients with persistent AF were of 'focal' origin without any area sustaining focal activity.

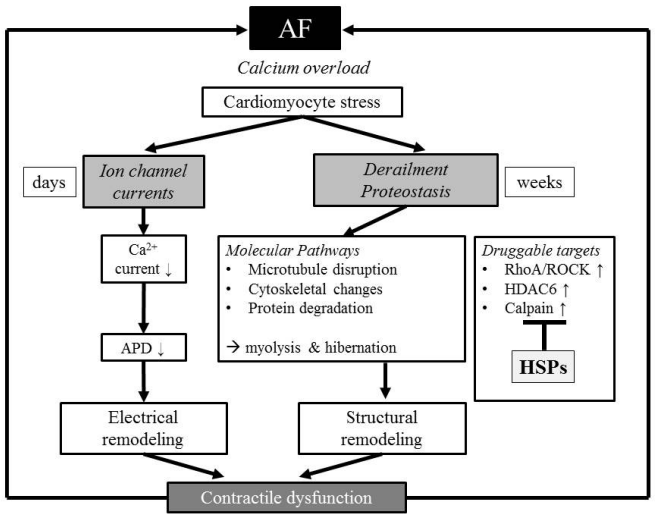

Figure 2: **Overview of AF-induced cardiomyocyte remodeling**
AF induces time-related progressive remodeling. First, AF causes a stressful cellular Ca^{2+} overload, which results in a direct inhibition of the L-type Ca^{2+} channel, shortening of action potential duration and contractile dysfunction. These changes have an early onset and are reversible. The early processes protect the cardiomyocyte against Ca^{2+} overload but at the expense of creating a substrate for persistent AF. When AF persists derailment of proteostasis occurs, which results in microtubule disruption, cytoskeletal changes and degradation of proteins. The targets involved in proteostasis are RhoA/ROCK, HDAC6 and calpain. In addition, HSP induction has been found to counteract these targets. Derailment of proteostasis results in structural remodeling, myolysis/ hibernation, and consequently impaired contractile function and AF persistence. Thus drugs that normalize proteostasis via inhibition of RhoA/ROCK, calpain, and HDAC6, but also via induction of cardioprotective HSPs are of therapeutic interest for future treatment of clinical AF.

Based on our observations, we recently introduced a new mechanism explaining persistence of AF independently of the presence of foci or re-entrant circuits in our Double Layer Hypothesis.[22,24] The "Double Layer Hypothesis" states that the substrate of longstanding persistent AF in humans is caused by progressive endo-epicardial dissociation, transforming the atria into an electrical double layer of dissociated waves that constantly 'feed' each other (Figure 1). Whereas in patients with short-lasting episodes of AF, the endo- and epicardial layers are still activated synchronously, in patients with longstanding persistent AF, the endo- and epicardial layers of the atrial wall are activated asynchronously. Over time, due to electrical and structural remodeling of the atria, the atrial wall is gradually transformed into a double layer of narrow anatomically delineated pathways. The exact molecular mechanisms underlying electrical dissociation are, however, unknown.

Molecular Mechanisms Underlying Electropathology AF

As mentioned above, AF is a progressive disease, which can be explained by the fact that AF itself induces alterations in both function and structure of the cardiomyocyte. These alterations induce an arrhythmogenic substrate which facilitates perpetuation of AF episodes.[25]

During the last decennia, various researchers aimed to identify the molecular mechanisms that underlie cardiomyocyte remodeling and AF progression. Although several pathways, especially related to ion channel remodeling, have been described, the exact molecular mechanisms driving AF remodeling and progression are still unidentified. The general concept is that during AF, cardiomyocytes are subjected to rapid and irregular excitation causing calcium overload in the cells which leads to fast and reversible electrical remodeling and slower, irreversible structural remodeling (figure 2). The cardiomyocyte responds to a calcium overload by the functional downregulation of L-type Ca^{2+} current channels, which causes the shortening of action potential duration (APD) and electrical

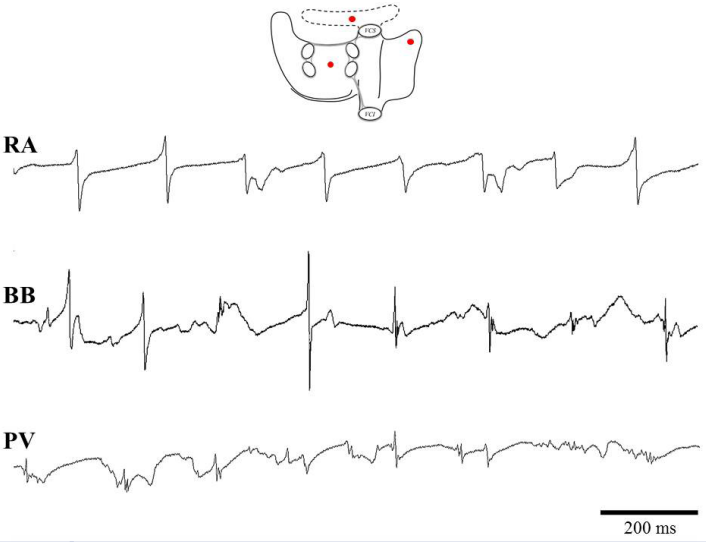

Figure 3: Intra-individual variation in electrogram morphology. Typical examples of unipolar fibrillation electrograms recorded from the middle of respectively the right atrial appendage (RA), Bachmann's Bundle (BB) and the pulmonary vein area (PV) obtained from a patient with mitral valve disease and persistent AF. In the right atrium, the fibrillation potentials contain a single deflection whereas fibrillation potentials recorded from Bachmann's Bundle and the pulmonary vein area contain multiple deflections.

remodeling, thereby providing a further substrate for AF.[26-30] Also, several other ion channel currents are affected either on the expression level or phosphorylation and redox status.[31-33] In addition,

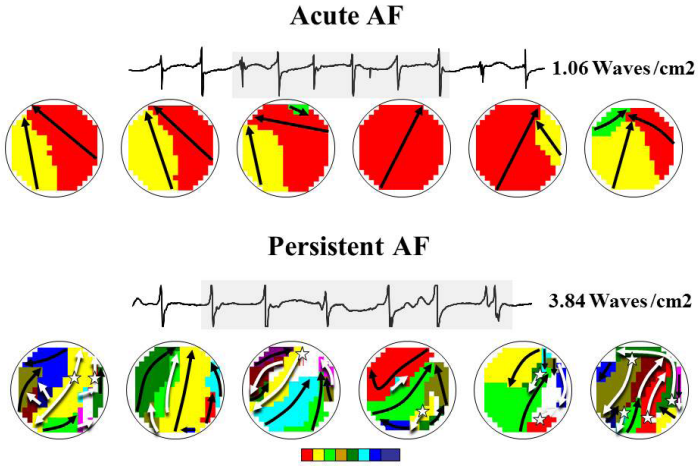

Figure 4: Inter-individual variation in characteristics of fibrillation waves. Examples of six consecutive wavemaps obtained from the right atrial free wall constructed during acute AF (upper panel) and persistent AF (lower panel); unipolar fibrillation electrograms recorded in the middle of the mapping area are shown on top. The mapping area activated by each individual fibrillation is represented by a color; every color indicates the moment of entrance in the mapping area (from red to purple); the arrows indicate the main trajectory of the fibrillation wave (black: peripheral fibrillation wave, white epicardial breakthrough wave). During acute AF, there are a fewer number of fibrillation waves and the patterns of activation are less complex, compared to persistent AF. In addition, 'focal fibrillation waves' occur more frequently during persistent AF.

various kinases and phosphatases become activated and regulate the function of ion channels and other downstream target proteins, for example transcriptions factors, various calcium handling proteins (such as RyR2, Sarcoplasmic Reticulum Ca^{2+} ATPases (SERCA), or Na^{+}/Ca^{2+} exchanger) and the actin cytoskeleton.[34-38]

When AF persists beyond a few days, irreversible structural remodeling occurs, especially hibernation[39] (figure 2). Various research groups[39-41] showed that hibernation is a form of tissue adaptation. It is defined as the ability of the cardiomyocytes to turn into a non-functional phenotype featuring irreversible degradation of the myofibril structure (myolysis), which leads to loss of atrial contraction.

While the early electrical remodeling is reversible[30] a 'second factor' underlies the persistence of AF, having a time course comparable to AF-induced structural changes (hibernation/myolysis) in the atrial cardiomyocytes.[42] Thus, the prevention of structural remodeling represents a key target to attenuate cardiomyocyte remodeling and dysfunction and may improve the outcome of (electrical) cardioversion to normal sinus rhythm. We have strong indications that derailment of proteostasis represents this 'second factor' that underlies AF progression.[38,39,43-46]

Derailed Proteostasis Novel Concept Of Cardiomyocyte Remodeling

Proteostasis is defined as the homeostasis in protein synthesis, folding, assembly, trafficking, guided by chaperones, and clearance by protein degradation systems.[47-50] Healthy proteostasis is controlled by an exquisitely regulated network of molecular components and cellular pathways, the protein quality control (PQC) system.[47,51]

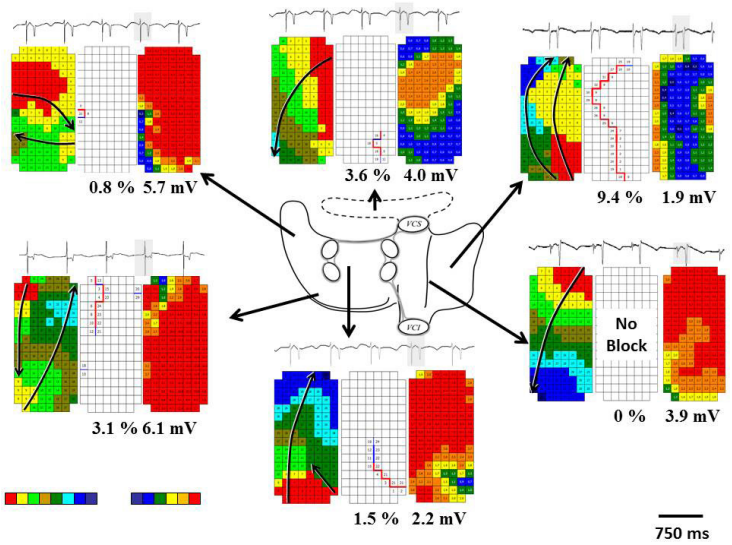

Figure 5: **Atrial epicardial mapping**
Activation -, conduction block- and voltage maps constructed from Bachmann's Bundle, right atrium, crista terminalis, pulmonary vein area, left atrioventricular groove, left atrial appendage during sinus rhythm, obtained from a patient with coronary artery disease. Electrograms recorded from the middle of the mapping area are shown on top. Arrows in the color-coded activation maps show the main trajectory of the excitation wave. Areas of slow conduction (<18cm/s) and conduction block (<30cm/s) are represented by respectively blue and red lines. Voltage maps show the peak-to-peak amplitude of the atrial potentials.

Cells, including cardiomyocytes, are very sensitive to changes in the intra- and extracellular environment, induced by stressors, including AF. Stressors can cause derailment in the proteostasis by altering the stability of proteins, leading to protein damage, unfolding and breakdown, as observed for cardiac troponins and structural proteins.[38, 43] In the heart, various chaperones, especially Heat Shock Proteins (HSPs), are expressed to ensure a healthy cardiomyocyte proteostasis and optimal function of the heart. For example HSP27, cvHSP, HSP20 and HSP22 are important members of the PQC system and attenuate derailment of proteostasis in AF by assisting in the refolding of unfolded proteins,[38,51] prevention of AF-induced damage to contractile proteins[44,52] and attenuation of protein breakdown.[43] In this way, HSPs normalize the proteostasis and protect the cardiomyocyte against remodeling and AF progression.

Table 1: **Novel therapeutic targets**

Drug	Target	Phase	Indication	Ref (clinical trials.gov identifier)
GGA	HSP induction	Phase IV	Gastric ulcers Gastritis Gastric lesion	NCT01190657 NCT01547559 NCT01284647 NCT01397448
NYK9354	HSP induction	Pre-clinical	Atrial Fibrillation	(HoogstraBerends et al., 2012)
Leupeptin ALLN MDL-28170 A-705239 A-705253	Calpain induction	Pre-clinical		reviewed in Cardiovascular Research (2012) 96, 23–31
Tubastatin	HDAC6	Pre-clinical	Arthritis Anti-inflammatory	(Vishwakarma et al., 2013)
ACY-1215	HDAC6	Phase I/II	Myeloma	NCT01323751 NCT01583283
Fasudil Ezetimibe AR-12286	ROCK	Phase III Phase II Phase II Phase IV Phase II	Raynaud's Phenomenon Vascular function study Atherosclerosis Atherosclerosis Glaucoma	NCT00498615 NCT00120718 NCT00670202 NCT00560170 NCT01936389
CCG-1423 Rhosin	Rho	Pre-clinical		(Evelyn, et al., 2007) (Shang, et al.,2012)

Molecular Pathways Underlying Derailed Proteostasis

Recently, several molecular pathways were found to induce derailment of proteostasis. These pathways include the persistent activation of calpain, activation of RhoA/ROCK pathway and the activation of HDAC6.

Investigators found proof for a role of persistent activation of the calcium overload-induced protease calpain to underlie impairment of proteostasis and AF progression in experimental cardiomyocyte, and Drosophila model systems for AF,[43,52,53] but also in human permanent AF.[39] In experimental studies it was observed that calpain activation causes the degradation of contractile and structural proteins, and subsequently contributes to structural cardiomyocyte remodeling (myolysis) and dysfunction and AF progression.[43,53] The role of calpain was confirmed in human AF. Here, a significant induction in calpain activation was observed in patients with permanent AF, compared to patients with paroxysmal AF and controls in sinus rhythm.[39] Furthermore, patients with permanent AF revealed induced amounts of myolysis which correlated significantly with calpain activity levels, suggesting a role for calpain in derailment of cardiomyocyte proteostasis, structural remodeling and AF progression.

Also, during AF, RhoA-GTPases are activated. RhoA-GTPases represent a family of small GTP-binding proteins that are involved in cell cytoskeleton organization, migration, transcription and proliferation. They have an important role as regulators of the actin cytoskeleton in cardiomyocytes[54] and trigger the initiation of AF.[55, 56] RhoA-GTPases activation results in conduction disturbances and cardiac dysfunction.[57, 58] Recent studies[38] revealed that in AF, RhoA-GTPase become activated resulting in the activation of its downstream effector ROCK and thereby stimulate the polymerization of G-actin to filamentous F-actin stress bundles. These stress bundles impair calcium homeostasis and contribute to contractile dysfunction, cardiomyocyte remodeling and AF progression.[38]

Furthermore, recently it was found that histone deacetylases (HDACs), such as HDAC6, are implicated in AF-induced cardiomyocyte remodeling.[43] HDACs affect cardiomyocyte proteostasis by epigenetically regulating protein expression and modulating various cytoplasmic proteins, including α-tubulin, a structural protein from the microtubule network.[59-61] By using mutant constructs, AF-induced contractile dysfunction and structural remodeling was proven to be driven by HDAC6 via de-acetylation of α-tubulin and finally breakdown of microtubules by calpain. This effect of HDAC6 was observed in tachypaced HL-1 atrial cardiomyocytes, Drosophila, dogs and confirmed in patients with permanent AF.[43] HDAC6 inhibition by tubacin conserved the microtubule homeostasis and prevented depolymerized α-tubulin from calpain-mediated degradation. These results indicate a key role for HDAC6 in the derailment of cardiomyocyte proteostasis in experimental and clinical AF.

So, three key pathways in AF-induced structural and functional remodeling have been identified, and all these pathways impair a healthy proteostasis of the cardiomyocyte.

Induction Of HSPs Normalize Proteostasis

To maintain a good functioning PQC system, numerous chaperones are expressed to ensure a healthy cardiomyocyte proteostasis.[38] HSPs are under the control of heat shock transcription factor 1 (HSF1), and represent important chaperones in proteostatic control.[47, 62] During excessive stress situations such as AF, HSP levels were found to become exhausted.[44] This finding suggests that upregulation of HSP levels might normalize proteostasis and improve cardiomyocyte function in AF. In clinical studies, induced HSP levels showed protection against AF initiation and progression. HSP70 atrial expression levels were found to correlate with reduced incidence of post-operative AF in patients in sinus rhythm undergoing cardiac surgery.[63,64] In another clinical study,[65] a potent Heat Shock Response (HSR) and high HSP27 levels have been associated with restoration of normal sinus rhythm in patients with permanent AF after mitral valve surgery. Higher atrial HSP27 levels were found to be related to shorter AF duration and less myolysis when comparing paroxysmal versus persistent AF and sinus rhythm.[44, 66] These findings suggest that HSPs become activated after AF episodes, and exhaust in time in a stress related manner.[44] Consequently, PQC is lost and incorrect/damaged proteins accumulate in cardiomyocytes, inducing or accelerating remodeling, in turn resulting in AF progression and recurrence. Next to AF, also a loss of PQC is recognized to contribute to the deterioration of heart function, reduction of stress tolerance, and the possibility of reducing the threshold for manifestation of cardiac disease.[67]

Various in vitro and in vivo models for tachypacing-induced AF identified HSPs to protect against AF initiation and against the derailment of proteostasis and cardiomyocyte remodeling. HSPs increase SERCA activity and stimulate both the reuptake of Ca^{2+} into the sarcoplasmic reticulum and the removal of Ca^{2+} out of the cardiomyocyte via Na^{+}/Ca^{2+} exchanger,[68] suggesting that HSPs attenuate AF progression by protecting against (tachypacing-induced) changes in calcium handling proteins. Several HSPs (including HSP27) were shown to reduce oxidative stress, thereby potentially preventing or restoring the redox status of the ion channels[69] and preventing damage to the actin cytoskeleton. This protective effect of HSP27 was found via direct binding to actin filaments and indirectly by preserving the redox status.[43, 44, 70-73] Reducing oxidative stress preserves proteostasis and electrophysiological and contractile function of the cardiomyocyte in AF. Moreover, HSPs prevent calpain activation[39, 53] and thereby attenuate contractile protein degradation and conctractile dysfunction.

Deficiencies Of Present Therapy Of Atrial Fibrillation

Therapy of AF is aimed at either rhythm or rate control. Since AF induces electrical, structural, and contractile remodeling, therapy aimed at prevention or restoration of remodeling and consequently restoration of sinus rhythm should be the strategy of first choice.[74] The different AF treatment modalities include pharmacological therapy, electrical cardioversion (ECV), pacemaker implantation combined with His bundle ablation or surgical isolation of the pulmonary veins with or without additional linear lesions/substrate modification (endovascular or surgical). According to the Multiple Wavelet Theory, the stability of the fibrillatory process is determined by the number of simultaneously circulating wavelets. Anti-fibrillatory effects of class IA, IC and III drugs are based on widening of the excitable period (difference between AF cycle length and refractory period). When the excitable period widens, it is less likely that a fibrillation wave encounters atrial tissue, which is still refractory. This in turn decreases the degree of fractionation of fibrillation waves and subsequently also the number of fibrillation waves. It is most likely that when patients with AF have a variable degree of remodeling due to e.g. dissimilar underlying heart diseases or AF episodes of different durations anti-arrhythmic drugs will also widen the excitable gap to a variable degree. This in turn may explain differences in inter-individual responses to anti-arrhythmic drugs. The acute success rate of intravenous chemical cardioversion (CCV) using various drugs including amiodarone and flecainide is 58-75%[75,76] for patients with paroxysmal or persistent AF and is highest when performed in AF <48 hours.[76] Immediate (prior to discharge) AF recurrences were observed in 3%[76] and AF relapsed in 30-40% of patients within one year with continuation of anti-arrhythmic drugs.[76] When CCV is unsuccessful, ECV is next treatment in line. Immediate restoration of sinus rhythm is achieved in 88-97%.[76-78] Comparable to CCV, AF recurrences are common; sinus rhythm is maintained for one year in only 40-60% of the patients.

Circumferential Pulmonary Vein Isolation (PVI), endovascular or surgical, is aimed isolating ectopic foci within the myocardial sleeves of the pulmonary veins. Endovascular PVI can be achieved with radiofrequency current, laser or cryothermal energy. Navigation of the ablation catheters can be performed either manually guided by fluoroscopy or electroanatomical mapping systems, or robotically using remote (non-) magnetic navigation systems.[79-81] Despite the promising acute success rates, one year AF free survival is approximately 40-50% and redo ablations are frequently performed.[79-82] This data is confirmed in a large meta-analysis by Ganesan et al.[83] In this study, the long-term success rate increased to 79,8%, however only after multiple ablation procedures. The overall complication rate associated with endovascular AF ablation is 5% including phrenic nerve palsy, pulmonary vein stenosis, pericardial effusion and cardiac tamponade.[82, 84] From a theoretical point of view, PVI should be an effective treatment modality for patients with paroxysms of AF triggered by ectopic foci within the pulmonary veins. Recurrences of AF after pulmonary vein isolation can be due to incompleteness of circular lesions, conduction or an arrhythmogenic substrate located outside the pulmonary veins.[85] In addition, an arrhythmogenic substrate may also develop over time as a result of a progressive cardiomyopathy. Different ablation approaches targeting the assumed substrate of AF have therefore been developed in the past years[85] including ablation of ganglionated autonomic plexuses in epicardial fat pads or disruption of dominant rotors in the left or right atrium as recognized by high-frequency Complex Fractionated Atrial Electrograms (CFAE).[86] Wu et al.[87] concluded in a meta-analysis that CFAE ablation could reduce the recurrence of atrial tachycardia in patients with nonparoxysmal AF after a single procedure. This effect was not observed in patients with paroxysmal AF. The reported one year AF free survival after the first CFAE ablation is only 29% when performed as a standalone procedure[86] and 74% in CFAE ablation additional to PVI.[86,88] Endovascular ablation of the ganglionic plexi as a standalone procedure in patients with paroxysmal AF is associated with a significantly lower arrhythmia free survival when compared to the PVI.[89, 90] When performed additionally to (repeat) PVI in patients with persistent AF, 16 months success rate rises to 59%.[90] The recurrence rates of these (concomitant) substrate modifications are

thus high, indicating that the arrhythmogenic substrate underlying persistence of AF was still not fully understood. Our Double Layer Hypothesis[22,24] provides the explanation why, in case the endo- and epicardial layers are electrically dissociated, ablative therapy is not successful anymore.

Future Diagnostic Tools

As large numbers of disorders are associated with AF and patients with AF reveal AF episodes of variable duration, it is most likely that there is a large degree of variation in the degree of atrial remodeling. In addition to this, within a patient, it is also likely that there is intra-atrial variation in the degree of remodeling. Examples of regional differences in morphology of unipolar fibrillation potentials are shown in Figure 3. Hence, knowledge of the degree and extensiveness of the arrhythmogenic substrate in the individual patient is essential in order to evaluate a patient-tailored therapy for AF. For this purpose, we developed custom made mapping software ('wave mapping') which enabled visualization of the individual fibrillation waves and quantification of the fibrillatory process. By using this software, we compared electrophysiological properties of fibrillation waves recorded during induced AF in patients with normal atria (physiological AF) with persistent AF in patients with valvular heart disease (pathological AF) and demonstrated that electrical dissociation of atrial muscle bundles and epicardial breakthrough of fibrillation waves play a key role in development of the substrate of persistent AF (figure 4).[24] In order to diagnose the arrhythmogenic substrate of AF in individual patients, we are currently evaluating a real-time, high resolution, multi-site epicardial mapping approach of the entire atria (figure 5) as a novel diagnostic tool which can be applied as a routine procedure during cardiac surgery. An approach like this allows quantification of electrophysiological properties of the entire atria. In such manner, we study electropathology throughout the entire atria in patients with and without AF and with a diversity of underlying structural heart diseases. This novel mapping approach will not only be used to gain further insights into the arrhythmogenic substrate of AF, but will also be used to develop novel therapies or to improve existing treatment modalities. For example, it may guide ablative therapy when the arrhythmogenic substrate is confined to a circumscribed region. In addition, data acquired with this mapping approach will also provide the basis for development of less- or non-invasive mapping techniques.

The Future Novel Therapeutic Targets

Current therapies are directed at suppression of AF symptoms, but are not effective in attenuating AF remodeling , therefore there is a high need to identify novel therapeutic targets which will improve the clinical outcome. Novel targets include RhoA, calpain and HDAC6 inhibition, but also HSP induction. Recent studies revealed the important role of the RhoA/ROCK pathway activation in structural remodeling of cardiomyocytes during AF.[38] To maintain proper cardiac function, RhoA/ROCK inhibitors might be of therapeutic interest. Several RhoA and ROCK inhibitors have been developed. RhoA inhibitors CCG-1423 and Rhosin are studied in the preclinical phase.[91, 92] Fasudil, Ezetimibe and AR-12286 are ROCK inhibitors currently studies in Phase II-IV trials for Raynaud's phenomenon, vascular function study, atherosclerosis and glaucoma (Table 1).

Calpain activation during AF causes the degradation of contractile and structural proteins, resulting in myolysis.[38, 39, 43] In vitro studies showed that inhibitors of calpain conserve the cardiomyocyte structure and function and therefore might have beneficial effects in the treatment of AF.[43, 53] Various calpain inhibitors have been developed and preclinically studied. Disadvantages of the current developed inhibitors are that they show poor selectivity for subtypes of calpain and often have a high LogP value and therefore are hard to dissolve in aqueous solutions.[93]

HDAC6 inhibition, by tubacin, conserves-tubulin proteostasis, and prevents its degradation by calpain 1 and thereby protects against loss of calcium transient and cardiac remodeling in experimental model systems for AF. As tubacin is not suitable for in vivo studies due to low drug-likeness,[94] other promising HDAC6 inhibitors, such as tubastatin A and ACY-1215 have been recently developed[94-96] (table 1). Interestingly, tubastatin A showed to protect against tachypacing-induced cardiac remodeling in a canine model for AF,[52] supporting the use of HDAC6 inhibitors as a novel therapeutic approach in AF.

Promoting maintenance of proteostasis by revitalization of the PQC system may prevent the derailment of proteostasis and structural and functional remodeling in AF. Interestingly, the heat shock response as part of the PQC system can be pharmacologically boosted, and consequently cardiac remodeling may be prevented, halted or even be restored. Indeed, as depicted earlier, increasing HSP expression, by either pharmacologic compounds or molecular biological means, displays cardioprotective effects in various models for AF and in patients. HSP induction provided protection against loss of actin proteostasis by reducing RhoA-GTPase-induced remodeling[38] and against activation of calpain.[38, 43, 44, 46, 52, 53] Furthermore, in canine models for AF progression, treatment with geranylgeranylacetone induced HSP expression and prevented AF initiation and progression by inhibition of the prolongation of the effective refractory period (ERP), shortening of APD and reductions in L-type Ca^{2+} current and it revealed protective effects against atrial conduction abnormalities.[44, 97]

Whether HSP induction also protects via HDAC inhibition is currently unknown. Of all HSP inducing compounds, GGA represents the most efficacious compound for the pharmacological induction of HSPs. GGA has already been applied clinically in Japan since 1984 as an antiulcer drug with no reported serious adverse reactions.[98-102] Due to high LogP value for GGA, high dosages might be needed, therefore, GGA derivatives are developed with improve pharmaco-chemical properties[103] (table 1). Induction of HSP is suggested to be the most promising therapeutic approach with pleiotropic protective effects.

HSPs As Biomarkers

Following stress, HSPs get expressed intracellular, but can also be presented on the cell surface or released to the surroundings.[104] HSPs in serum may act as a biomarker to reveal the stage of AF. Elevated serum HSP60 levels were found in patients with acute myocardial infarction and seemed to be predictive for post-AMI adverse events.[105] Elevated serum HSP70 and HSP60 have found to correlate to the severity of metabolic syndrome-associated factors in postmenopausal women.[106] HSP60 and HSP70 were found to positively associate with severity of cardiovascular disease.[107-112] Patients with coronary artery disease (CAD) have revealed antibodies to HSP27 in serum,[113] but a correlation between antibody titers to HSP27 and the extent of CAD could not be found. Several studies have reported increased serum levels for HSP27 several hours after myocardial infarction[114, 115] In another study, anti-HSP27 levels were found to be higher in patients

with more advanced cardiac artery disease, making the authors to conclude that serum anti-HSP27 titers may be associated with the presence and severity of cardiac artery disease.[116] Anti-HSP27 titers measured in patients with stroke were found significantly elevated.[117] These findings suggest that the measurement of HSP levels in serum, may be useful as biomarkers of disease initiation, and progression.

Conclusions

AF naturally tends to progress from trigger dependent paroxysmal AF to a more substrate mediated (longstanding) persistent or permanent AF. Trigger focused treatments (endovascular or surgical PVI) might be successful in patients with paroxysmal AF, however this approach will not be sufficient for patients suffering from more advanced types of AF, who require substrate modification. Even treatments aimed at substrate modification, such as CFAE ablation, Cox maze III and ganglion ablation, are associated with AF recurrences. This implies insufficient understanding of the electrophysiological and structural changes which form a substrate underlying AF. Hence, as long as the electropathological substrate remains poorly understood, and the stage of electropathology cannot be evaluated, it is challenging to define the optimal approach per individual patient. Therefore, research is focused on the dissection of molecular mechanisms underlying electropathology. New findings indicate a role for derailment of cardiomyocyte proteostasis in AF progression and identified novel innovative targets for drug therapy. These targets are directed at the attenuation of electropathology and prevention of clinical AF progression. Since various drugs are already on in clinical phase II/III for other indications, it seems worthwhile to test some in clinical AF.

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Left Atrial Appendage Ligation And Exclusion Technology In The Incubator

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Abstract

Stroke is the most feared complication of atrial fibrillation (AF). Targeting the left atrial appendage (LAA) mechanically is attractive as a means to simultaneously reduce stroke risk, the need for anticoagulation, and hemorrhagic complications in patients with non-valvular AF. The results of the PROTECT-AF and PREVAIL randomized clinical trials support this approach as a viable therapeutic alternative to warfarin in selected patients and add to accumulating evidence regarding the importance of the LAA in thromboembolism in AF. A number of devices for percutaneous LAA closure are under investigation or development. In this article, key design features of these ligation and exclusion technologies will be discussed, with a focus on aspects of LAA morphology, relational anatomy, thrombosis, and thromboembolism relevant for successful device development and deployment.

Introduction

Left atrial appendage (LAA) closure, by altering the balance of Virchow's triad within the appendicular cavity,[1] is an attractive strategy for stroke prevention in nonvalvular atrial fibrillation(AF).[2-5] An appreciation of the pathophysiological influence of the LAA on stroke risk traditionally hinged on the observation that 15% of patients with nonvalvular AF have intracardiac thrombi, of which 90% are located within the LAA.[6-9] Recent advances in cardiac imaging have allowed investigators to demonstrate that morphological complexity of the LAA significantly influences thromboembolic risk, supporting a structural approach to thromboprophylaxis.[10-16] This principle was tested by the PROTECT-AF and PREVAIL randomized clinical trials, which demonstrated that LAA exclusion using the WATCHMAN percutaneous occlusion device (Boston Scientific, Natick, MA) was not clinically inferior to warfarin in preventing strokes, whilst reducing bleeding risk.[3, 17] Till now, the only percutaneous LAA closure device available in the USA for ameliorating AF-related stroke risk has been the LARIAT appendage ligation system (Sentre-HEART, Redwood City, CA),[18-22] which provides an attractive alternative approach for stroke prevention in patients with a high bleeding risk on systemic anticoagulation. A number of other technologies have received CE (Conformité Européene) mark approval for commercial use in Europe, of which the AMPLATZER cardiac plug (ACP, St Jude Medical, Saint Paul, MN)[23-27] and the now discontinued PLAATO system (eV3, Sunnyvale, CA)[28-30] have been the most widely implemented. Others are currently in the incubator, although reporting preclinical or early clinical results (Table 1).

In this article, aspects of LAA morphology, relational anatomy, thrombosis, and thromboembolism relevant for successful percutaneous LAA closure will be discussed initially, drawing from published observations on devices currently in clinical use. Subsequent focus will be on key design features of devices under clinical investigation or development.

Endpoints For Effective LAA Closure: Epicardial Ligation Versus Endocardial Exclusion

As a broad overview, devices have utilized either an endovascular exclusion-based approach, in which a foreign occlusive body is introduced via atrial transeptal puncture and deployed within the LAA, thereby excluding it from the main atrial chamber (WATCHMAN, ACP, and PLAATO), or an epicardial ligation-based approach where epicardial puncture permits navigating to and tying down a noose over the LAA neck (LARIAT).[4,31-36] Aside from specific variations in device design and application, which translate into important procedural and patient selection considerations, the resulting structural changes that follow are observably dissimilar

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Left Atrial Appendage, Ligation, Exclusion, Technology, Anatomy, Thromboembolism, Device.

Disclosures:
None.

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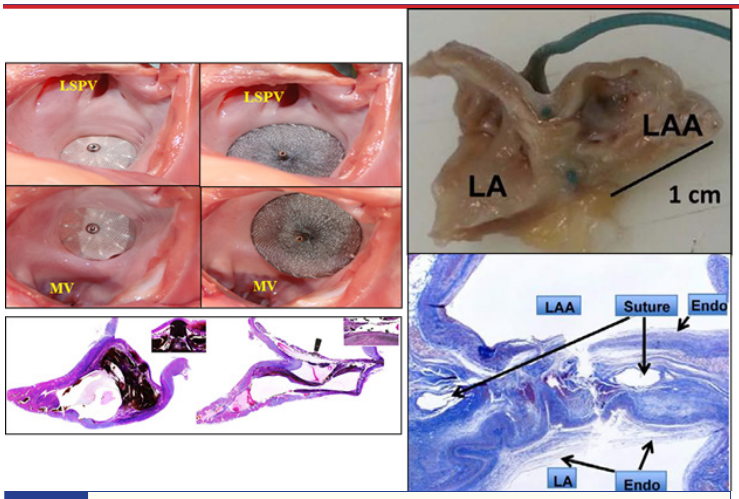

Figure 1: **Left and middle columns: canine specimens demonstrating comparative positioning of the WATCHMAN (left) and ACP (right), with histological sections (bottom) demonstrating cross sectional relationship to ostium and neo-endothelialization (inset). Note the intra-appendicular positioning of the WATCHMAN compared to the external disc of the ACP, and the incomplete endothelial coverage of the ACP mesh wires near the inferior edge of the disk and end-screw hub.[38] Right column: Changes following LARIAT occlusion with suture (green) in the explanted heart of a patient who underwent cardiac transplantation 1 year 11 months after the procedure, with corresponding Mason trichrome staining (bottom) demonstrating extensive scarring (dark blue) within the appendage and suture site that extends into the left atrium .[37]**
LSPV – left superior pulmonary vein. MV – mitral valve. LAA – left atrial appendage. LA left atrium. Endo – endocardial surface.

between these approaches (Figure 1).[37,38] The endpoints for adequate closure are therefore also likely to differ, and whether adequate closure is best defined using anatomical, electrical, or functional criteria[4, 31] will ultimately depend on recognizing the respective association with clinical effectiveness. Data from surgical ligation suggests that both residual leak from incomplete ligation and residual stump from too distal a ligation point predispose to subsequent atrial thrombus.[39-43] Late LAA leakage has been reported in 20% to 25% of patients at 3 months with LARIAT,[21, 22, 44, 45] and a predisposition to subsequent atrial thrombus formation is speculated[46] though not proven. Late thrombus formation at the site of closure has been reported in 5% of patients between 17 to 104 days after LARIAT ligation[22] and both in the presence[46] and absence of a residual leak.[47] Peri-device leaks following endovascular occlusion are also common, being noted in 41%, 34% and 32% at 45 days, 6 months and 12 months respectively in patients from PROTECT-AF after WATCHMAN closure,[48] although the currently published data suggest no associated increase in rates of thromboembolism.[48-51] The velocity of the leak, the degree of residual exposed LAA anatomic complexity, and the ability of the leak to accommodate a thrombus may be quite different between patients with a ligation-related leak versus those with a peri-device leak. Thrombosis mechanisms in device exclusions are often related to the device itself (3.7% of patients in PROTECT-AF receiving WATCHMAN)[32] and more likely to be influenced by seating of the device within the LAA and subsequent device endothelialization,[52] with less complete endothelialization of the ACP compared to WATCHMAN on account of the ACP's larger surfaced extra-appendicular disc and more prominent end-screw hub in a comparative dog study with WATCHMAN (Figure 1).[38] Ligation results in acute appendage ischemia leading to appendage atrophy and cavity obliteration[5, 37, 53, 54] although the contribution of this remodeling to preventing thrombus formation is currently unknown. This is also the case with residual "beaks" where tissues are approximated, residual diverticula or extra-appendicular pectinate ridges.[4, 31]

Key Considerations For Device Design

Epicardial Ligation

The LAA is a tubular projection arising from the free wall of the left atrium, typically extending superiorly to project a variably curvilinear course, bending noticeably in 75% individuals at 98 ± 20 degrees after the initial 14 ± 4 mm, running adjacent and parallel to the left superior pulmonary vein (LSPV), underneath the main pulmonary artery, and draping down over the right ventricular outflow tract, left main coronary artery bifurcation, left atrioventricular groove which houses the left circumflex artery and great cardiac vein, and a portion of the mitral annulus (Figure 2).[55-61] The sinoatrial node artery can be related when it arises directly from the left circumflex artery (30% of individuals) or coursing from the left lateral atrial artery (8% of individuals) rightward between the appendage and LSPV towards the sinoatrial node (Figure 2).[58] The left phrenic nerve runs along the overlaying pericardium[62] traversing the appendage variably from over its tip to over the roof of the ostium.[63]

A transcutaneous epicardial approach to the LAA must therefore first negotiate the anterior pericardial space, with free passage superiorly to engage the appendage whilst avoiding the above mentioned neurovascular structures. Such an approach to the LAA may be restricted in individuals with pericardial adhesions from prior open heart surgery, pericarditis, epicardial VT ablation, or uremia, anatomical distortion such as with pectus excavatum, kyphoscoliosis or severe obesity[58, 64] or congenital abnormalities such as pericardial

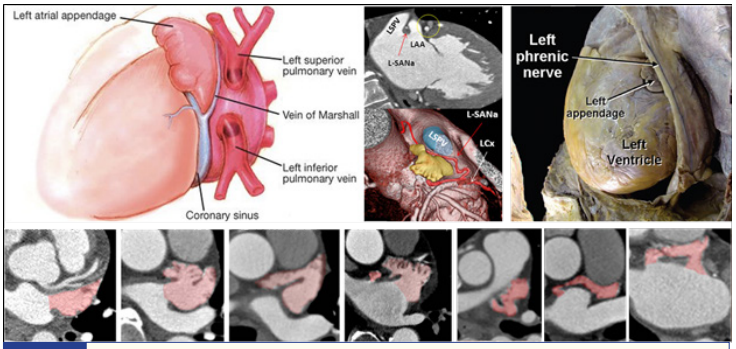

Figure 2: **External anatomy of the LAA. Bottom: CT images with the appendage highlighted in pink, demonstrating variation in morphology and orientation.[55, 63, 58]**
LAA – left atrial appendage; LSPV – left superior pulmonary vein; L-SANa - left sinoatrial node artery; LCx – left circumflex artery.

absence which may additionally be associated with appendage herniation.[65]

Detailed morphological LAA definition on an individual basis is integral to success of epicardial ligation approaches as there is marked inter-individual variation in appendage size, number of lobes, crenelations, and pectinate musculature,[56, 66, 67] with 20 to 70 percent of individuals having a single lobe, 16 to 54 percent having two, and the remainder having up to 4 lobes.[68, 69] Occasionally a second posterior lobe is sandwiched between the right and left ventricular outflow tracts.[55] Although the appendage tip points inferiorly in the majority, usually pointing down in line with the course of the left anterior descending artery, it can sometimes be directed posteriorly or into

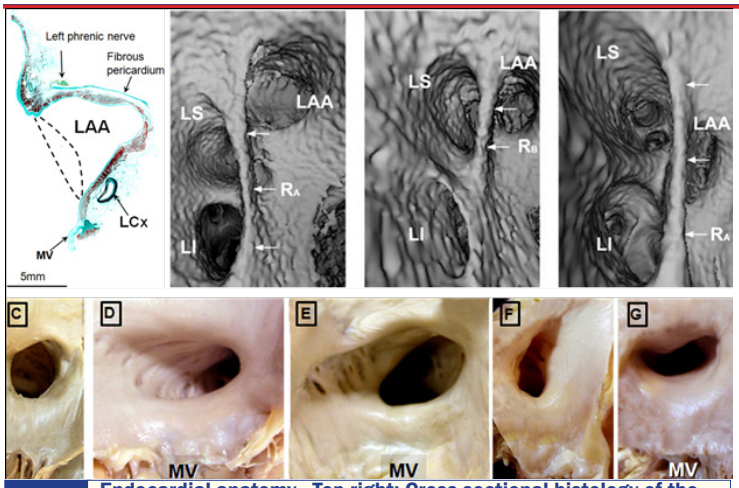

Figure:3 **Endocardial anatomy. Top right: Cross sectional histology of the left atrial appendage. The location of the ostium is denoted by the interrupted line.[58] Top left: CT reconstruction of endocardial anatomy demonstrating the variation in position of the left lateral ridge (arrows, R) and left pulmonary veins.[57] Bottom: Variation in size and shape of the left atrial appendage ostium.[58] LAA – left atrial appendage; MV – mitral valve; LCx – left circumflex artery; LS – left superior pulmonary vein; LI – left inferior pulmonary vein**

the transverse pericardial sinus (Figure 2).[58] These considerations are important as a noose-based ligature has to first engage and be slipped past the appendage tip. Without an effective method to manipulate or re-orientate the appendage tip, the LARIAT is unsuitable for patients with a superiorly oriented LAA or a posteriorly rotated heart.[58] Ensuring the noose is large enough to capture the appendage and any additional lobes is also key; the LARIAT's noose has a maximal diameter of 40 mm.[18] Identifying the relationship of the left main coronary artery and its bifurcation to the neck, and the course of the phrenic nerve, are also important. Appendages may in addition be closely adherent to the underlying left ventricular wall, congenitally aneurysmal,[70] inverted,[71] juxtaposed,[72] or absent altogether.[73]

The above anatomical and pathophysiological constructs present distinct, sequential challenges in executing a successful strategy for percutaneous epicardial LAA ligation.[4] First, in contrast to the ease with which the appendage can be instrumented through transeptal access, negotiating it accurately from within the pericardial space is difficult even when guided by preprocedural CT and intraprocedural TEE. Secondly, once identified, the freely mobile appendage requires stabilization to allow for controlled ligation. LARIAT addresses both these steps simultaneously by using an adjunctive transeptal endocardial approach to first advance one magnet-tipped wire to the appendage tip, and approximate another from the epicardium onto it, thereby grasping the appendage whilst establishing a supporting monorail over which to advance a looped suture.[18] This unique approach does, however, introduce risks from both transeptal and epicardial puncture, risk of appendage puncture from deep intubation of the appendage by the transeptal sheath, risk of appendage laceration, and the procedural complexity of maintaining correct orientation of two curved sheath-based platforms relative to each other and the appendage wall.[64, 74-76] Thirdly, although the optimal ligation site along the LAA is not known, closure is targeted at the ostium based on surgical data implicating persistent leaks and residual stumps for recurrent thrombosis, yet the boundary between the LAA and main atrial chamber is indistinct both anatomically and electrically. To overcome this, both endocardial and epicardial strategies attempt to close the appendage as proximally and snugly as possible,[33] which for LARIAT involves placing an endocardial balloon-tipped catheter at the ostium, overriding it when tying down the epicardial suture, and ensuring a tight seal using contrast fluoroscopy and Doppler TEE.[18, 64] However, the final tightening is reserved for once the endocardial citing balloon is deflated and withdrawn. Despite ensuring an adequate seal, which can be by radiocontrast injection as well as Doppler color flow imaging, recent clinical experience with the LARIAT has reported that leaks reoccur and can be seen in 20% to 25% of patients within a few months,[21, 77] cause or consequence is unknown at present.

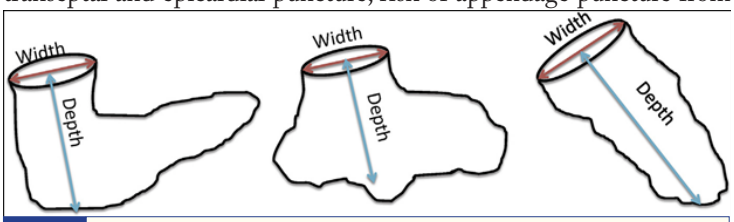

Figure:4 **Appendage width and depth takes precedence to morphology for endocardial device closure.[80]**

Endocardial Exclusion

The LAA can be identified internally by pectinate muscles, which impart the characteristic combed appearance of its endocardial surface, although in a significant proportion of individuals these can extend inferiorly to the vestibule of the mitral valve.[56, 58, 63] The smooth-walled LAA ostium, whilst demarcated by the LLR superiorly and posteriorly, has indistinct borders anteriorly and inferiorly which therefore have to be approximated (Figure 3).[56] Approaches for endocardial exclusion have relied upon TEE-visualization of the left main coronary artery, circumflex artery or mitral annulus to define the plane of the ostium in relation to the LLR.[33, 78-80] The shape of the LAA ostium is usually oval, rather than round, though varies significantly between individuals,[56, 66, 69] and the orientation of the ostium relative to the plan of the mitral annulus is oblique rather than vertical.[56] The ostium can be at the same level as the LSPV (60% to 65% of individuals), superior to it (25% to 30%) or inferior (10% to 15%) (Figure 3).[57, 69] The intervening LLR is formed by an infolding of the lateral atrial wall, is narrow superiorly where it is predominantly muscular, becomes up to 5 mm wide inferiorly and houses the ligament of Marshall (remnant of the left sided superior vena cava), autonomic nerves and a small atrial artery which

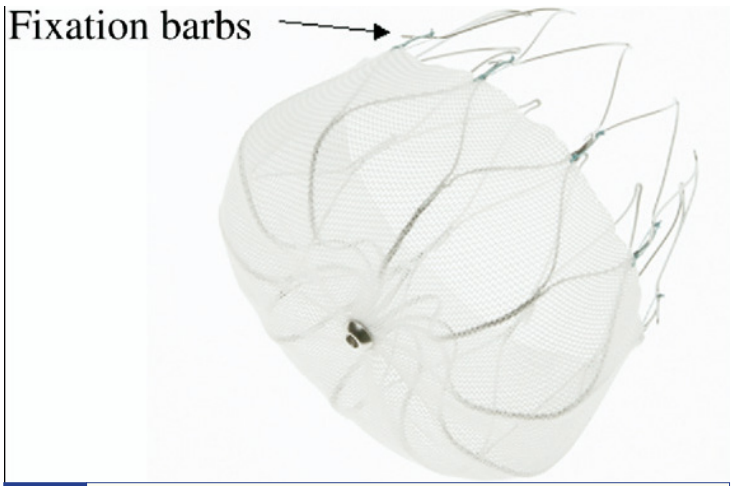

Figure:5 **WATCHMAN device, demonstrating active fixation barbs.[105]**

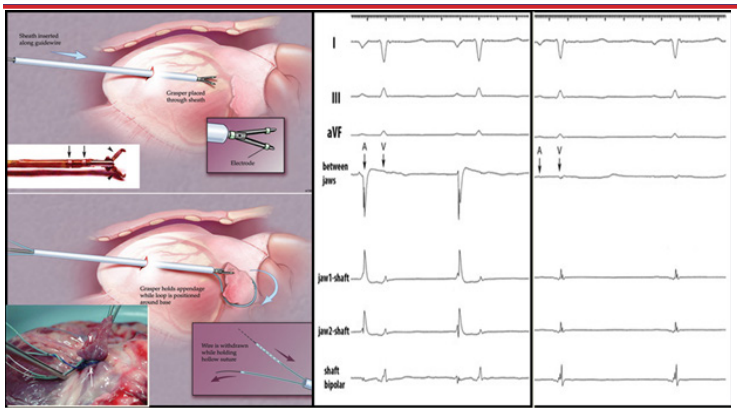

Figure:6 **Aegis electrogram guided intrapericardial ligation approach. Left: Demonstration of intrapericardial navigation to the appendage tip using grabber and shaft electrodes, and preformed looped suture application. Right: From top to bottom on the tracing are shown surface ECG leads I, III, avF, jaw-to-jaw bipolar electrogram (EGM), jaw1-to-shaft EGM, jaw2-to-shaft EGM, and a shaft bipolar recording. Tracings on the left are pre LAA ligation, and on the right are post LAA ligation. Note the disappearance of the atrial signal from the appendage following ligation, and the predominant ventricular signal on the shaft bipolar electrogram.[5]**

sometimes is the sinoatrial nodal artery.[56, 58, 62, 63] Distance from the LAA ostium to the LSPV is 5-10 mm in 45% of individuals, and 10-15 mm in 40%, can be up to 24 mm in the remainder, with distance from LAA ostium to mitral annulus being similar.[56]

By engaging the ostium directly from within, the success of an endocardial exclusion strategy is dependent on the interaction of ostial size and shape with accurate device positioning and adequate exclusion, the internal anatomy of the LAA relied upon by the device for a safe and secure landing, and how well transeptal access orientates engagement with the appendage ostium.[33, 58] Devices design is required to incorporate ways to minimize and compartmentalize thrombosis such as by using resistant materials or minimizing device profile and exposed structures, a delivery platform that facilitates accurate and safe device positioning, a deployment mechanism which can be adjusted for size and position to achieve an adequate seal, a seating mechanism which prevents device embolization, and a profile which does not interact significantly with related structures including the left lateral ridge (LLR), mitral valve, pulmonary vessels and coronary arteries.

The WATCHMAN is designed to be deployed 10 mm below the LAA ostium such that its self-expanding nitinol cage fills the appendicular cavity and its 160 μm thick covering made from microporous polyethylene terephthalate entraps thrombi and promotes endothelialization.[31] The device is unfurled by gradual pullback of the access sheath and delivery catheter while maintaining device position using fluoroscopic and TEE guidance, with Doppler flow to identify adequacy of the seal and the sheath to facilitate partial recapture and adjustment.[33] The ACP has a braided nitinol frame with overlying polyester patch and is designed to cover the ostium with a disc articulated to a distal lobe which anchors within the LAA.[31] The ACP lobe is deployed first by partial unsheathing, followed by the proximal disc by further unsheathing, whilst effectiveness of occlusion is confirmed using distal radiocontrast injection through the delivery system and/or Doppler flow[78] and with partial or full retraction into the sheath for repositioning.[33] Currently available devices are for ostial sizes of 17-31.9 mm for WATCHMAN and 12.6-28.5 mm for ACP.[33]

In contrast to the epicardial approach, accurate and standardized measurement of width of the ostium and depth of the landing zone take precedence to other morphological considerations in ensuring that the device is compatible with the appendage and correctly sized (Figure 4).[33, 80] The WATCHMAN requires the LAA length to be in excess of the maximal ostial diameter and is therefore better suited for long and narrow appendage profiles, whilst the ACP is better suited for short and broad profiles as the anchoring lobe requires the landing zone to be at least 10 mm wide.[33, 80] Challenging morphologies include appendages which taper significantly from ostium to tip, where usual sizing of the ACP landing site may result in an undersized disc at the ostium[33] and "chicken wing" morphologies which can have an excessively early and severe bend.[81] Rarely, there may be an ostial membrane manifesting with elevated gradient across the ostium.[82]

Accurate appendage sizing is also important in ensuring a snug fit and reducing risk of device embolization, and accordingly

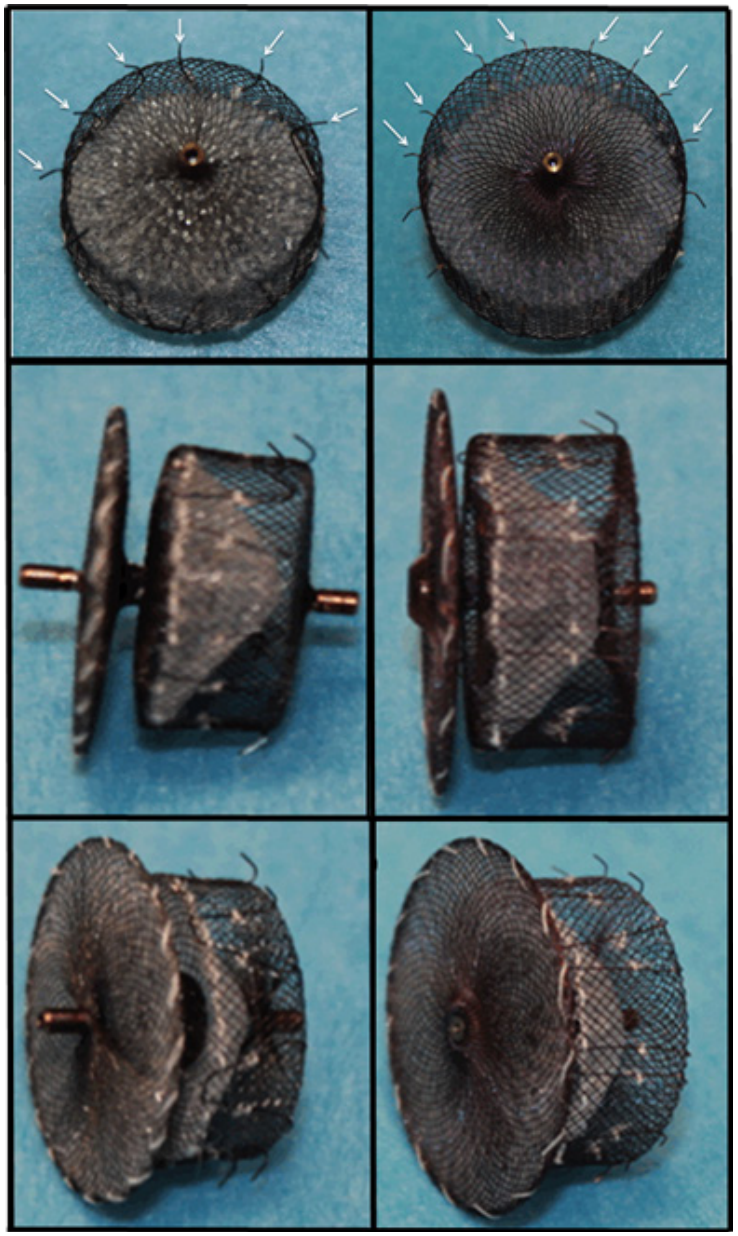

Figure:7 **The Amplatzer first generation ACP (left) comparted to second generation Amulet (right).[84]**

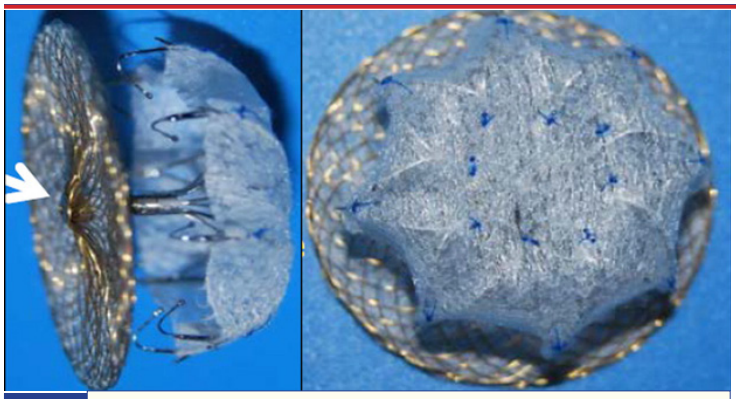

Figure:8 The Lifetech LAmbre device.[97]

WATCHMAN devices are sized 10% to 20% larger and ACP 1.5-3.4 mm larger than the maximal ostial diameter.[33] However, relying on radial expansion forces alone has been shown to be insufficient in ensuring device stability: the very early AMPLATZER septal occluders which relied on this strategy when deployed within the LAA had high rates of device embolization.[31, 78] AF is associated with an increase in appendage size and reduction in the internal trabecular structure due to pectinate muscle atrophy and endocardial fibroelastosis[83] whilst the ostium progressively increases in size and adopts a more rounded shape with increasing AF burden.[79] In addition, with appendages which taper distally, radial forces may paradoxically result in device expulsion as the pressures generated deeper in the appendage will be greater than those at the ostium.[33] Current devices use active fixation mechanisms which are engaged using gentle application of negative traction upon deployment and take advantage of the appendage's trabeculated endocardium (Figure 5).[33, 78] A strategy of oversizing devices serves also to reduce the incidence of peri-device leaks,[84] the significant incidence of which is likely related to the variably oval shape of the ostium[56, 66, 69] in contrast to the uniform and rounded design of devices in current clinical use.[23, 48-51, 84, 85] However, care must be taken not to distend aggressively, as the appendage is paper-thin in areas between the pectinates and may perforate, and the ostium is critically located immediately anterolateral to the left main coronary artery, superior to the great cardiac vein and circumflex artery, and anterior to the LSPV,[56, 58, 63] any of which may become compressed. Reported complications following endovascular exclusion procedures have also included erosion into the overlying main pulmonary artery.[86-88]

All current endocardial exclusion strategies utilize a sheath based delivery platform with access across the interatrial septum.[33, 80] Given the ostium's oblique orientation,[56] a posteroinferior septal puncture allows approaching the ostium at an optimal angle without excessive sheath manipulation and torque, which increases risk of atrial perforation.[33, 58] Slight adjustment of the approach is required for each case to accommodate for the inter-individual variation in the angle adopted by the septum in its left anterior to right posterior course.[58] Puncture should be at the true anatomical septum which is defined by the thin floor of the fossa ovalis, measuring 1-3 mm in thickness, whilst the muscular rim is formed by invagination of the atrial wall, though location and size vary between individuals and in those with kyphoscoliosis and marked left ventricular hypertrophy[63] Echocardiography-guided puncture is to be recommended given the high prevalence of a septal ridge,[57] pouch at the fossa,[63] or other structural abnormalities including atrial septal aneurysm, patent foramen ovale, atrial septal defect, septal flap, thickened interatrial septum, or thrombus.[89]

Device Technology In The Incubator

The ideal AF stroke prevention technique should completely remove any thromboembolic risk and substrate, confer minimal clinical risk, be cost effective and applicable to all.[4] Towards this goal, the experience with WATCHMAN and ACP, and more recently LARIAT, add further insight into determinants of success and current shortcomings of device design and approach, even though no study has to date directly compared one device to the other.[90] With development ongoing, opportunities arise for improving efficacy, universal applicability, safety and simplicity.

Aegis

The Aegis system (Aegis Medical, Vancouver, Canada)[5, 53, 91] is a totally intrapericardial ligation approach which harnesses the appendage as the most inferior site of atrial electrical activity obtained from an anterior subxiphoid epicardial approach.[4] A steerable epicardial sheath, placed via standard subxiphoid puncture, supports the introduction of an appendage grabber with embedded electrodes within the jaws and further electrodes on the shaft proximally. The grabber is electrically navigated onto the atrial appendage, which it then captures and stabilizes, whilst ventricular signals on the proximal shaft electrodes confirms an orientation towards the appendage tip (Figure 6). A hollow suture preloaded with a support wire to permit remote suture loop manipulation and fluoroscopic visualization is advanced to the appendage base and looped around the appendage, with a range of appendage sizes, shapes and lobes enabled by the variable loop size. After loop closure, the wire is removed, leaving only suture behind, which is remotely locked with a clip to maintain closure. If initial closure is unsatisfactory, the loop can be undone and repositioned, or additional loops placed

Figure:9 The Occlutech LAA Occluder.[98]

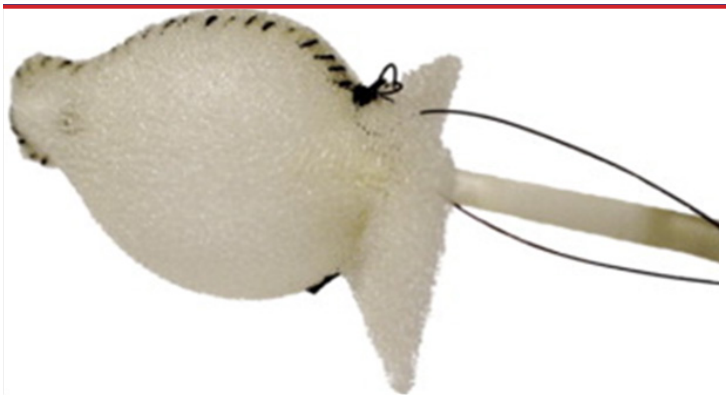

Figure:10 The Transcatheter Patch.[99]

over the first. Successful closure is confirmed within seconds by the elimination of LAA electrical activity, accompanied by shortening of the surface electrocardiographic P wave in dogs[5] and followed by the LAA becoming atretic.[53] As compared to LARIAT, the major advantage offered by Aegis is that transeptal access is not required and, therefore, neither is anticoagulation. Similar to LARIAT, previous cardiac surgery or adhesions from previous pericarditis are the major limitations. Feasibility in humans has been demonstrated,[91] with approximately 50 patients having had the procedure to date.[92]

Amulet

A second generation ACP, the Amplatzer Amulet Left Atrial Appendage Occluder (St. Jude Medical, Saint Paul, MN, USA)[93-95] received European CE Mark approval in 2013 although it is currently voluntarily withdrawn from the USA market by St. Jude. The design is similar to ACP, with a lobe-disc structure made from nitinol mesh covered by polyester patches (Figure 7). In comparison to the ACP, the Amulet is designed for superior seating whilst requiring less oversizing, with a 2-3 mm longer lobe housing stiffer, more evenly distributed and more numerous stabilizing barbs (from six pairs in ACP to 10 pairs), and longer articulating waist between the distal lobe and the proximal disc. Having larger available sizes (31 and 34mm), it is better suited for closure of larger LAA. Aimed at reducing device thrombosis, the screw facing the atrial chamber is now flush to the device, and the larger disc designed to be seated flush to the LLR and less prone to prolapsing into the ostium, which is thought to predispose to thrombus formation with the current ACP by creating a cul-de-sac with the LLR. To facilitate deployment, it now comes pre-mounted on a modified pusher cable inside the delivery system. Recently published non-randomized clinical experience in 25 patients in Europe reported successful implantation in 24, with complications of 1 device thrombosis; there were no leaks >3 mm or other complications.[96]

Table 1:

FDA-approved and CE mark	LARIAT
CE mark only	Amplatzer Cardiac Plug Amplatzer Amulet Transcatheter Patch Watchman (FDA-approval applied for, awaiting decision) Wavecrest
Published preclinical or human studies	Aegis Epitek (withdrawn) LifeTech LAmbre (Phase 0 trial ongoing) Ultrasept
Others	Occlutech (Phase 1 trial registered, not yet recruiting)

Epitek

The Epitek (Medford, NJ, USA) multilumen system utilizes a fiber-optic endoscope, jaws to grasp the LAA visualized endoscopically, a pre-tied suture, and shape-set nitinol wire. Testing in porcine and canine models was performed from December 2006 to February 2008, leading on to early human testing where difficulties were encountered with access (achieved in 78%) and good device positioning (achieved in 41%) with subsequent development halted.[92]

LAmbre

The Lifetech LAmbre device (Lifetech Scientific Corp., Shenzhen, China)[97] has some similarities to ACP, though in place of the lobe there is a nitinol-based, fabric covered, self-expanding umbrella which is introduced into the LAA (Figure 8). The umbrella is secured within the LAA via 8 distal ball-tipped frames with side facing hooks, and articulates via a waist to a disc which orientates onto and seals the ostium. The device is deployed through a sheath, and is retrievable and repositionable. After testing in a dog model,[97] a feasibility and safety human study is underway (clinicaltrials.gov/NCT01920412) and CE Mark is expected in the near future once adequate patient experience is obtained.

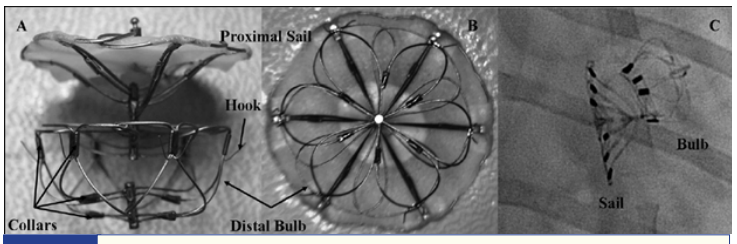

Figure:11 The Cardia Ultrasept LAA Occluder.[100]

Occlutech

The Occlutech LAA Occluder (Occlutech International AB, Helsingborg, Sweden) is based on a braided nitinol frame which is introduced into the LAA (Figure 9).[98] The contour tapers distally to better distribute radial expansion forces and it is anchored distally with closed loops designed to engage the trabeculated LAA whilst avoiding perforation. A polymer covering seals against blood flow and promotes endothelialization. Delivery is via an endocardial sheath, and a ball-shaped connection hub allows the occluder to pivot during delivery. Sizes of 17-39 mm are available. Phase 1 feasibility and safety study has not started enrolling as yet (clinicaltrials.gov/NCT02105584). No published data using this device is available currently.

Transcatheter Patch

The Transcatheter Patch (Custom Medical Devices, Athens, Greece)[99] is also deployed endocardially within the LAA to occlude it (Figure 10). The unique features are that it is frameless, being made from bioabsorbable polyurethane foam and kept inflated by radiocontrast to diameters of 15-25 mm. It is secured within the LAA initially by polyethylene glycol glue, activated by an alkaline solution followed by a prolonged (45 minute) inflation, and over the subsequent 48 hours via fibrin formation. A 2-mm nylon loop is sutured at the bottom of the patch, and a double nylon thread is connected for retrieval purposes. The Transcatheter Patch has CE-Mark approval for the use of occlusion of heart defects in general. Feasibility in LAA occlusion was reported in 17 patients, although in 3 the patch did not attach and in 1 it was placed beyond the LAA ostium, whilst sheath thrombosis was seen in 1 patient.[99] There were

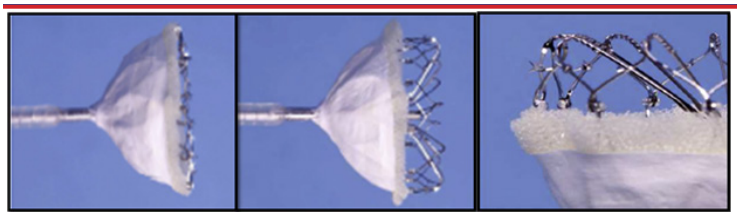

Figure:12 The WAVECREST Left Atrial Appendage Occlusion System. Courtesy of Coherex Medical, Salt Lake City, UT

no strokes at 1 year follow-up.

Ultrasept

The Cardia Ultrasept LAA Occluder (Cardia Inc, Eagan, MN) is made from a nitinol frame with a distal cylindrical anchor which is deployed endocardially within the appendage, secured therein using 12 hooks strengthened onto platinum/iridium collars, thereby providing support via a flexible articulation to a round sail made from polyvinyl alcohol foam which orientates onto and covers the ostium (Figure 11).[100] The stranded design of its frame reportedly increases fatigue resistance and allows fine tuning of the tension applied to the sail and anchor, the long and flexible waist allows increases positional versatility, whilst the sail is reported to be designed to minimize blood flow disturbance within the LAA.[100] Successful deployment in 5 dogs has been reported with complete neointimal coverage on histology at 30 days.[100] The device comes in five sizes for human use, based on the diameter of the distal bulb:[16, 20, 24, 28] and 32mm. No human data is currently published.

Wavecrest

The WAVECREST®[101] Left Atrial Appendage Occlusion System (Coherex Medical Inc., Salt Lake City, UT, USA) is nitinol framed, Gore-Tex covered device (Figure 12) similar in principle to WATCHMAN but with a number of design features to overcome current WATCHMAN limitations.[80, 98] It has an umbrella-shaped frame designed for shallow deployment making it suitable for a wide range of appendage sizes. This is coupled with less stringent sizing criteria allowing for 3 sizes (22 mm, 27 mm, 32 mm), coverage for ostial sizes of 18-30 mm, a completely retrievable and repositionable sheath-based system, and a distal radiocontrast delivery system to guide adequate positioning. Expanded polytetrafluoroethylene (ePTFE), which has low thrombogenecity, covers the occluding cap. Safety features include 20 anchoring nitinol microtines that are extended in a controlled fashion once the device is landed, thereby limiting potential damage from abrupt release, and polyurethane foam surrounding which forms a foamed leading edge when the constrained device is unsheathed.

The WAVECREST I trial (multicenter, prospective, non-randomized registry) recruited 73 patients from Europe, Australia, and New Zealand, with mean CHADS2 score of 2.5, prior cerebral embolism in 34%, and a warfarin contraindication in 49%.[101] After TEE-guided deployment, dual antiplatelet therapy was administered for 90 days and then aspirin continued long-term. Successful deployment with acute closure was seen in 68/73 (93%), with ≤3mm peri-device flow at 6 weeks in 65/68 (96%). Acute tamponade occurred in 2/73 (3%) and there was no procedural stroke, device embolization or device-related thrombosis.

The device has received CE-Mark in 2013. The pivotal US WaveCrest II trial is anticipated in 2014.[98]

The Future

With the evidence supporting LAA occlusion for stroke prophylaxis in AF, the increasingly diverse technologies becoming available for LAA ligation and exclusion, and the parallel development of medical technologies such as novel anticoagulant agents, there is an armamentarium of therapeutic options. Coupled with this, several questions have arisen and remain unanswered, including the role of LAA ligation when used in conjunction with or in place of novel anticoagulant agents, if post procedural antiplatelet agents or anticoagulants are required, the mechanism of recurrent thrombosis and late appearing leaks, the risk attributable to residual or recurrent leaks, structural remnants such as beaks, pits, and side lobes, and what the differences are with ligation versus exclusion.

For now, the current range of products allows for individually tailored therapy. For example, patients with absolute contraindications for any anticoagulation, even temporary, an epicardial technique which does not require adjunctive endocardial access may be better suited, whilst others with pericardial adhesions would be best served with an endocardial approach, and some patients may require combined approaches including with direct surgical visualization.[4] There is evidence that ligation, by silencing the electrical activity of the appendage,[102-104] may provide additional antiarrhythmic benefit in atrial fibrillation. With increased understanding of the interactions between device design, appendage anatomy, clinical risk of thrombosis, and medium to long term success of occlusion, we may recognize how specific strengths can be harnessed and geared towards the patient at hand. Ultimately, through better understanding these determinants, improved device design and deployment technique, and controlled clinical comparisons of strategies, an ideal closure approach may be realized.

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Optimization Of Stroke Prophylaxis Strategies In Nonvalvular AF – Drugs, Devices Or Both?

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Abstract

Atrial fibrillation (AF) is the most common cardiac arrhythmia with the prevalence increasing over time. AF probably afflicts ≥2% of worldwide adult population and increases with age.[1-3] In the Framingham Heart Study, the lifetime risk of having at least one episode of AF for 40-year-old men and women was 26% and 23% respectively.[4]

Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia with the prevalence increasing over time. AF probably afflicts ≥2% of worldwide adult population and increases with age.1-3 In the Framingham Heart Study, the lifetime risk of having at least one episode of AF for 40-year-old men and women was 26% and 23% respectively.[4]

AF is associated with increased morbidity and mortality due to risk of systemic thromboembolism, specifically stroke. In the Framingham cohort, AF was responsible for 14.7% of all strokes, ranging 6.7% in the 50-59 year age-group to 36.2% in the 80-89 year age-group.5 Strokes related to AF are associated with higher mortality and morbidity than strokes in patients without AF.[6-8] Further, among AF related strokes, increasing age and CHADS2 score (Congestive heart failure, Hypertension, Age ≥75 years, Diabetes mellitus, 2 points for history of Stroke/transient ischemic attack) predict worse outcomes.[7, 8] Annual stroke risk in patients with AF across all risk strata is 5%.4 Additionally, subclinical cerebral ischemic events occur in around 15% of patients with AF and are correlated with cognitive dysfunction.[9, 10]

In patients with non-valvular AF, the risk of stroke increases with clinical risk factors. Risk stratification systems include CHADS2 score and its modification CHA2DS2-VASc score (2 points for age ≥75 years, and incorporating additional risk factors of vascular disease [prior myocardial infarction, peripheral artery disease or aortic plaque], age 65-74 years and female sex in conjunction with other predictors).[11, 12]

Mitigation of AF related strokes could have a profound public health impact, but there are many challenges. More than a third of AF patients might be asymptomatic and difficult to identify. The initial presentation of AF might be stroke itself. Stroke can occur even prior to the first episode of AF detected by an implanted pacemaker.[13, 14] On the other hand, in absence of extended cardiac rhythm monitoring the diagnosis of AF can sometimes remain elusive even after a stroke.[15] Even for patients in whom AF is identified upfront and who have adequate access to health care there, is no optimal way of preventing strokes. Anticoagulation is difficult to adhere to and is limited by risk of bleeding complications. An economic analysis in the USA in 2004 estimated that approximately 1.265 million patients with AF not on anticoagulation (55% of all AF patients) suffered 58,382 strokes every year, with $4.8 billion in direct costs to Medicare.16 Non-pharmacologic options like left atrial appendage (LAA) closure are expensive, require operator expertise, have an upfront risk of complications, and have an equivocal evidence base for efficacy and cost-effectiveness in preventing strokes.[17-20]

Mechanisms Of Stroke In Atrial Fibrillation

Over two-thirds of strokes in patients with non-valvular AF who are not on anticoagulation are related to cardioembolic causes.21 In a transesophageal echocardiogram (TEE) study on patients without anticoagulation, an LAA thrombus was identified in 14% acute AF and 27% chronic AF patients.22 When an AF related thrombus is identified within the left atrium, it is in the LAA in 57% of patients with rheumatic mitral valve disease and 91% of

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patients without valvular heart disease.[23] The postulated mechanisms for development of left atrial thrombus in patients with AF include left atrial enlargement, endothelial damage, inflammation, fibrosis, stasis and prothrombotic changes.[19] In addition, stroke risk factors in AF are also correlated with other mechanisms of stroke especially atherosclerotic disease of the aortic arch and carotid arteries.[19, 21]

Anatomic And Mechanical Considerations – Left Atrium And Appendage

AF causes stasis in the LAA (seen as spontaneous echo contrast on TEE) due to loss of atrial systole, dilatation, and fibrosis. The LAA in general is a long, hooked, and narrow-based extension of the left atrium, suitable for stasis and thrombosis.[22, 23] Spontaneous echo contrast and reduced LAA emptying velocity on TEE, left atrial enlargement, and te complex multi-lobulated LAA shape are factors associated with a higher risk of stroke.[17, 24-26] AF leads to structural changes in the LAA characterized by edema, myocyte hypertrophy and necrosis, mononuclear infiltrate, and fibrosis, as well as endothelial denudation and thrombotic aggregation. These changes probably underlie the delay in recovery of mechanical function of the atria despite restoration of sinus rhythm.[17]

Prothrombotic State And Inflammation

AF is associated with an increased expression of prothrombotic markers of endothelial injury including the von Willebrand factor (vWF) and tissue factor, and elevation in the plasma levels of D-dimer.[17, 18, 27] Tissue-plasminogen activator (t-PA) antigen and plasminogen activator inhibitor-1 (PAI-1) are increased and plasmin-antiplasmin complex levels are reduced due to increased thrombolytic activity subsequent to thrombogenesis.[27] Moreover, AF has been described as an inflammatory disorder. Systemic levels of inflammatory markers including interleukin-6 (IL-6) and C-reactive protein (CRP) are increased. Inflammation can mechanistically lead to endothelial dysfunction and expression of tissue factors related to thrombogenesis.[17, 18, 27]

Stroke Unrelated To Left Atrial Thrombus

In a study on TEE evaluation of 72 non-valvular AF patients with ischemic stroke, one-third of patients without spontaneous echo contrast were over twice more likely to have causes of stroke other than AF including proximal aortic arch atherosclerosis, patent foramen ovale, and atrial septal aneurysm (78% versus 36%), suggesting occurrence of strokes unrelated to thrombosis in the left atrium.[28] In the Stroke Prevention in Atrial Fibrillation (SPAF) I–III trials, 32% of classifiable ischemic stroke events were due to non-cardioembolic causes.[21] In SPAF-III, 57% of AF patients had evidence for thoracic aortic atherosclerosis,[29] and absence of atherosclerosis was associated with a lower risk of stroke.[18, 30]

Left Atrial Appendage – Structure And Function

LAA is often thought of as a vestigial remnant.[19, 26, 31] However, LAA has stretch receptors and functions in fluid and electrolyte homeostasis through thirst reflex and production of natriuretic peptides. It contributes to hemodynamic efficiency by functioning as an atrial reservoir and booster.[19, 32] The regional anatomy of the LAA and variability in its shape is relevant when considering mechanical closure of LAA to reduce risk of stroke. LAA lies in the pericardial sac as a superior extension of the left atrial free wall, and is related to the left phrenic nerve. The left aortic sinus and the left main coronary artery are related to the medial aspect of the LAA ostium while the circumflex artery is related to the inferior margin. In some patients the sinus node artery arising from the left circumflex courses adjacent to the LAA ostium. The left superior pulmonary vein is related to the posterosuperior aspect of the LAA ostium and is separated by the ligament of Marshall within the left atrial ridge.[31, 33] Extremely eccentric LAA ostia can be difficult to occlude with an endovascular circular plug, and a multilobar complex LAA may be challenging to fully incorporate within an epicardially placed suture or clip.[19]

Strategies For Stroke Prevention In Atrial Fibrillation

Warfarin anticoagulation has been the mainstay of preventing strokes for over 2 decades. Patients on warfarin therapy have a preferential reduction in cardioembolic strokes, and as a result, two-thirds of the strokes in patients on warfarin are due to non-cardioembolic causes. As reduction in AF-related strokes with anticoagulation is largely due to inhibition of formation of LAA thrombi, it stands to reason that mechanical LAA exclusion would reduce strokes as well.[19, 21]

Chronic Oral Anticoagulation

Warfarin has been available for 6 decades. In a metaanalysis of 29 trials and 28,044 patients with non-valvular AF, warfarin compared to placebo decreased strokes by 64% (95% confidence interval [CI] 49–74%) and mortality by 26% (6% to 35%). Compared to antiplatelet therapy with aspirin, warfarin reduced strokes by 37% (23% to 48%).34 In recent times, drugs with a predictable dose-dependent anticoagulant effect have been developed. Direct thrombin (factor IIa) inhibitor dabigatran was the first such drug approved by the US Food and Drug Administration (FDA) followed by activated factor X (factor Xa) inhibitors rivaroxaban and apixaban.[35-38] Another factor Xa inhibitor edoxaban is awaiting marketing approval.[39] These newer agents have respectively demonstrated non-inferiority to warfarin for stroke prevention in head-to-head randomized controlled trials (RCTs) each enrolling in excess of 14,000 patients. Although overall bleeding rates with the newer oral anticoagulants are similar to warfarin, intracranial and life-threatening bleeding is lower. On the other hand, dabigatran, rivaroxaban, and edoxaban have a higher risk of gastrointestinal bleeding compared to warfarin.[35-39] Apixaban has bleeding rates comparable to aspirin alone and is superior in preventing strokes.[40] Therefore, therapy with warfarin (target INR 2.0-3.0) or the newer anticoagulants is the standard for stroke prevention in non-valvular AF and CHA2DS2-VASc score ≥2. The newer anticoagulants are, however, not recommended in patients with severe renal or hepatic dysfunction nor in those with prosthetic heart valves.[38]

Left Atrial Appendage Exclusion

LAA can be occluded with catheter-based devices implanted using venous access and transseptal puncture, or with epicardial techniques to ligate or clip the LAA. Epicardial exclusion can be done using (i) a mini-thoracoscopic or open surgical approach, (ii) using novel techniques with completely percutaneous pericardial access, or (iii) a hybrid procedure for epicardial closure from percutaneous pericardial access with navigation and deployment facilitated by a transseptal catheter in the LAA.

Endovascular Occlusion Of Left Atrial Appendage

Many observational studies have evaluated percutaneous LAA occlusion in patients with non-valvular AF. In a meta-analysis of 17 retrospective studies and 1052 device implantations, the pooled incidence for stroke at follow-up was 0.7 per 100 patient-years,

and transient ischemic attack (TIA) was 0.5 per 100 patient-years. Access site complications occurred in 8.6% (95% CI 6.3–11.7%) and pericardial effusion in 4.3% (3.1–5.9%).41 Several devices for endovascular implantation have been developed.

• **Plaato** (Percutaneous LAA Transcatheter Occlusion; ev3, Plymouth, Minnesota) was the first device specifically designed for LAA occlusion, but has been abandoned due to lack of financial sponsorship. Plaato sealed the LAA with a polytetrafluoroethylene (PTFE) covered self-expanding nitinol cage (diameter range 15-32 mm).19, 42, 43 A study in CHADS2 ≥1 patients demonstrated successful implantation in 108 of 111 patients and 2.2% annual stroke rate over 9.8 month follow-up. Adverse events included 4 deaths, 2 strokes, 3 pericardiocentesis, and one case each of emergency cardiac surgery, hemothorax, brachial plexus palsy, and deep venous thrombosis.43 Another study in CHADS2 ≥2 patients had successful implantation in 162 of 180 patients, LAA occlusion was confirmed in 126 of 140 patients with 2-month TEE and stroke rate was 2.3% per year. Major adverse events occurred in 12 patients including 2 periprocedural deaths, 6 pericardial tamponades (2 required emergent surgery), and one device embolism.[44]

• **Watchman** (Boston Scientific, St. Paul, Minnesota) is a permeable, polyester covered, self-expanding nitinol frame (diameter range 21-33 mm) with fixation barbs and is positioned in the LAA using transseptal access with a 12-Fr sheath. The entire device sits within the LAA without projecting out of the ostium.[19, 45] Design changes in the fourth generation Watchman include more spines for better radial strength, increased stability, and ability to recapture-redeploy the device.

In the ASA Plavix Feasibility Study With Watchman Left Atrial Appendage Closure Technology (ASAP), 150 non-valvular AF patients with CHADS2 score ≥1 and a contraindication to warfarin underwent Watchman implantation and received dual antiplatelet therapy for 6 months and aspirin thereafter. There were 13 (8.7%) serious adverse events and, during the mean 14.4-month follow-up, there were 3 ischemic and 1 hemorrhagic strokes, while 6 (4%) had device related thrombi.[46] In another study, 59 patients were treated with Watchman (device was oversized by 15% to 30%) and received dual antiplatelet therapy for 45 days followed by aspirin alone – there were 2 pericardial effusions, 3 device thrombi, and 1 thromboembolic event.[47] Two RCTs have evaluated clinical outcomes with the Watchman device

*o **Protect-AF:*** Non-valvular AF patients with CHADS2 ≥1 (mean 2.2)[48] were randomized to Watchman LAA closure (n=463) or long-term warfarin (target INR 2.0-3.0; n=244). Watchman patients were treated with warfarin for 45 days, followed by aspirin and clopidogrel for 6 months and subsequently aspirin alone. The Watchman strategy had 99.9% probability of being non-inferior to warfarin for primary composite outcome of stroke, cardiovascular death, or systemic embolism (3.0 versus 4.9 per 100 patient-years respectively at 18 months; 3.0 versus 4.3 per 100 patient-years on extended mean 2.3 year followup). However, the serious adverse events were higher with Watchman (7.4 versus 4.4 per 100 patient-years) including major bleeding (3.5%), pericardial effusion (4.8%), and device embolization (0.6%).48, 49 Device related thrombus occurred in 20 of 478 (4.2%) Watchman patients.50 Following PROTECT-AF, a non-randomized continued access registry with 460 Watchman implantations showed improved outcomes with increase in operator experience – higher implantation success (from 89.5% to 95.0%) and fewer procedural complications (from 7.7% to 3.7%, including serious pericardial effusions from 5.0% to 2.2% and procedural strokes from 0.9% to 0%).50

*o **Prevail:*** Non-valvular AF patients with CHADS2 score 2.6±1.0 were randomized to Watchman (n=269) and warfarin (n=138). Watchman patients received short-term warfarin followed by dual antiplatelet and then aspirin alone similar to PROTECT-AF. At 18 months, the composite of stroke, systemic embolism, and cardiovascular/ unexplained death was 6.4% in the Watchman group versus 6.3% in the warfarin group (relative risk 1.07, 95% CI 0.57–1.89), though not reaching the non-inferiority criterion. The rate of stroke or systemic embolism >7 days after randomization was 2.5% versus 2.0% (RR 1.6, 95% CI 0.5–4.2). For Watchman implantations, the periprocedural composite safety endpoint of all-cause death, ischemic stroke, systemic embolism, or need for cardiovascular surgery or major endovascular intervention occurred in 6 of 269 (2.2%; 2 device embolizations, 1 cardiac peroration, 1 pericardial tamponade).[51]

• **Amplatzer Cardiac Plug** (St. Jude Medical, St. Paul, Minnesota) is not cleared for use in the USA. It is a nitinol device that comprises a lobe with barbs (shallower than the body of Watchman or Plaato) that lodges in the body of the LAA to prevent migration. This connects across a waist to an interconnecting disk that occludes the LAA ostium (diameter range 16–30 mm). The device can be recaptured and redeployed. Following implantation, dual antiplatelet therapy for 1 month and subsequently aspirin alone is recommended.19 A second generation of the Amplatzer Cardiac Plug called the Amplatzer Amulet (St. Jude Medical, St. Paul, Minnesota) has been designed with the intention to facilitate the implantation process and reduce complications.

There have been multiple retrospective reports showing a 95% to 99% implantations success with Amplatzer Cardiac Plug in patients not suitable for anticoagulation. Procedural complications include stroke (0–2.3%), device embolism (0–2.3%), and cardiac tamponade (0–3.5%). Strokes have been reported in 0–2.8% patients in follow-ups ranging 6-21 months.[19, 45, 52] There was a 16% rate of mild peri-device leak on TEE evaluations among 52 patients from 7 Canadian centers,53 whereas high rates of device-related thrombus were reported from Brazil (6 of 85, 7%)54 and Spain (5 of 35, 14%).55

As opposed to Watchman there are no RCT data available for the Amplatzer Cardiac Plug. The ACP trial (Amplatzer Cardiac Plug clinical trial; NCT01118299) comparing LAA closure versus anticoagulation with warfarin or dabigatran has been withheld after failure to procure the investigational device exemption.[20]

• **Transcatheter Patch** (Custom Medical Devices, Athens, Greece) is used for occlusion of heart defects and comprises a frameless bioabsorbable device. Balloon inflation is used to appose the device within the LAA, which then adheres to cardiac tissues by formation of fibrin over 48 hours. Innovations are being made to accelerate the adhesion process and optimize percutaneous catheter delivery. In the initial report on 17 patients undergoing LAA closure, the patch did not adhere in 3 patients, was placed beyond the ostium of the LAA in one, and led to sheath thrombosis in one although no strokes were reported at follow-up of one year.[56]

• **Lambre** (Lifetech Scientific, Shenzhen, China) device in placed in the LAA and articulates at the waist with a component that can self-orient itself flush with the LAA ostium. The device has been

engineered to be retrievable, and enable repositioning, and it has been tested in canines.[57]

Epicardial Closure Of Left Atrial Appendage

Epicardial LAA closure obviates some of the risks associated with endovascular closure of LAA related to transseptal puncture, thromboembolism (due to exposure of tissue factor from transseptal puncture and foreign material of the catheters and implanted device to systemic circulation), need for intraprocedural and post implantation anticoagulation, and risk of device dislodgement, erosion and infection. Epicardial LAA closure can be performed during open surgery, for example in combination with valve surgery and atrial maze. Dedicated epicardial LAA closure was initially accomplished with video-assisted thoracoscopic access with selective collapse of the left lung and surgical pericardiotomy.[58] Novel approaches using only subxiphoid pericardial access have also been developed.[59]

Surgical Epicardial Left Atrial Appendage Occlusion

AF patients undergoing cardiac surgery can have their LAA ligated. In a series of 205 surgical mitral valve replacements,[58] also had LAA ligation with a reduction in embolic complications independent of other predictors.[60] In a propensity-score matched cohort of patients operated by a cardiac surgeon, LAA ligation was associated with fewer post-operative strokes [0 of 145 (0%) versus 7 of 115 (6.1%) without LAA ligation].[61]

It is not uncommon to have incomplete LAA occlusion with surgical closure. A TEE evaluation published in 2000 showed incomplete LAA occlusion in 18 of 50 (36%) surgical closures. Further, 9 of these (50%) had LAA thrombus, and 4 (22%) sustained a clinical embolic event.58 In another study 94 patients with surgical LAA closure who underwent TEE prior to electrical cardioversion for post-operative AF, left atrial thrombus was much more likely with incomplete LAA occlusion (16 of 34, 47%) versus complete LAA occlusion (7 of 60, 12%). Suture closure as opposed to oversowing and amputation of LAA was more likely to have residual flow in the LAA (51% versus 17%) and have left atrial thrombus (33% versus 14%).[62] The pilot Left Atrial Appendage Occlusion Study (LAAOS) showed suture ligation having a residual leak on TEE in 6 of 11 (55%) cases and staple closure having a residual stump of LAA in 9 of 33 (27%) cases.63 Another study on[137] surgical LAA exclusions similarly showed 77% of suture ligations having residual flow and 27% of LAA excisions having a residual stump.[64]

LAAOS II incorporated measures to improve efficacy of LAA closure (1) amputation or stapling of the LAA instead of simple oversowing or ligation, (2) intraoperative TEE to evaluate successful closure, and (3) goal for any residual LAA stump to be smaller than 1 cm.19, 65 Overall, surgical excision of the LAA appears to be the most successful technique.[45, 66] The inconclusive success of surgical LAA exclusion and the potential for a high risk of thromboembolism with incomplete exclusion makes it difficult to recommend it for all AF patients undergoing cardiac surgery.[38]

LAAOS III is an ongoing Canadian multicenter trial due in 2019 with 4-year follow-up on 4700 cardiac surgical AF patients randomized to LAA occlusion or no occlusion (NCT01561651).[45]

Specifically designed devices can be used to facilitate quick occlusion of the LAA during open cardiac surgery

• **AtriClip Pro** (AtriCure, West Chester, Ohio) can be used to clip the base of the LAA from the epicardial aspect. It has been reported to be effective in LAA occlusion in ≥96% cases in small series, without associated complications.[67, 68]

• **Tigerpaw System II** (Maquet, Rastatt, Germany) uses a delivery forceps to place the device, with an opposing series of barb connectors in a compliant silicone housing, at the base of the LAA. Connectors on one side have a needle that punctures through the LAA tissue and catches the receptor mechanism on the other side. In a prospective 60-patient study, the reported mean application time was 27 seconds, and two patients required adjunctive sutures. No leaks were seen on 90-day TEE among 54 patients, though residual LAA stump was ≥6 mm in 5 patients.[69]

Percutaneous Epicardial Left Atrial Appendage Occlusion

Aegis Medical (Vancouver, Canada) has developed a percutaneous subxiphoid epicardial approach with a tool to record bipolar electrograms from its jaws to identify and grab the LAA. A preloaded suture with a flexible-size loop and a support wire for fluoroscopic visualization is positioned around the LAA and is tightened and locked. Loss of LAA electrical activity on the bipolar electrograms confirms adequate occlusion of the LAA.[70, 71] The loop can be undone and repositioned, or additional loops placed over the first one if needed.[19, 59] Over time the LAA shrinks and atrophies. Epitek (Bloomington, Minnesota) created a fiber-optic endoscope for visualizing the LAA to facilitate grasping and closure, but further development has been abandoned.

Hybrid Epicardial-Endovascular Approach For Left Atrial Appendage Occlusion

Lariat (SentreHeart, Palo Alto, California) suture delivery device uses a hybrid endocardial-epicardial strategy. An endovascular sheath is placed across the interatrial septum in the LAA ostium. Following contrast angiography to define the LAA anatomy, a magnet-tipped wire is positioned in the LAA. Using percutaneous access a second magnet-tipped wire in the pericardial space attaches to this wire to form a rail across the LAA muscle. A preformed suture loop is positioned epicardially and locked down. Lariat is not feasible when the LAA diameter measures ≥40 mm or the LAA has a superiorly directed body or lobe.[19]

A retrospective series showed successful Lariat placement in 85 of 89 (96%) patients who had a favorable LAA anatomy on CT scan. Four patients had ≤3 mm residual leak. Complications occurred related to transseptal puncture in one and pericardial access in 2 patients. Two patients had severe post-procedural pericarditis, one developed late pericardial effusion, 2 had late non-embolic strokes, and there were 2 sudden deaths. Though ineligibility for anticoagulation was the criterion for Lariat, at 1-year follow-up 55% of patients were on warfarin.[72] In another retrospective study Lariat was placed successfully in 25 of 27 patients, and in 22 there was no residual LAA flow at 4-month TEE. There was one LAA perforation, 3 pericarditis, 1 periprocedural stroke, and 1 late non-embolic stroke.[73]

Anticoagulation Versus Left Atrial Appendage Exclusion

Chronic oral anticoagulation is the benchmark for stroke prevention in non-valvular AF. The role of LAA exclusion depends on the safety and effectiveness in excluding the LAA and how it compares to oral anticoagulation in stroke prevention.[18]

Factors Favoring Anticoagulation Over Left Atrial Appendage Exclusion

Contribution of LAA in stroke: Strokes in AF are not completely attributable to thrombi originating in the LAA, and the source of thrombus for embolism can originate in the left atrial chamber itself. This is particularly true for AF in context of valvular heart

disease like rheumatic mitral valve stenosis.[23] AF is also correlated with atherosclerotic causes of stroke. Only a systemic therapy as opposed to targeted LAA exclusion can diminish such non-LAA related sources of stroke. Oral anticoagulation mitigates the systemic prothrombotic milieu, though attenuation of atherosclerotic risk is better dealt with by statin and antiplatelet therapy.[18]

Evidence base: The anticoagulants approved for stroke prevention in AF including warfarin, dabigatran, rivaroxaban, and apixaban have been studied in rigorous large-scale RCTs in thousands of patients, to establish their efficacy and safety profiles.[34-37] These have been vetted by the regulatory agencies such as the FDA prior to marketing approvals. Warfarin has been in commercial use for 6 decades and has a robust long-term safety record.[34, 38] All LAA closure devices have been in clinical use for a limited time, and long-term efficacy and safety profile is not available. Only the Watchman device has been evaluated in prospective RCTs powered for clinical outcomes in approximately 1100 patients.49, 51 It is unclear if demonstration of clinical benefit for such a device can be extrapolated to other devices.[20] The clinical use of other endovascular and epicardial devices relies on poor quality data. Efficacy data limited to successful exclusion of LAA cannot be extrapolated to clinical benefit. Some devices in commercial use such as the Lariat do not have stroke prevention in AF as an approved indication. The largest series on LAA exclusion with Lariat for stroke prevention had only 89 patients.[72]

Procedural And Device Complications With LAA Exclusion: Interventional LAA exclusion is fraught with risk of complications, although with technological improvements and operator experience, procedural outcomes improve over time.[50] All transvenous methods require transseptal puncture and placement of catheters in the left atrium. Complications include vascular trauma, venous thromboembolism, aortic or coronary artery injury, systemic thromboembolism including stroke, pericardial effusion with cardiac tamponade, and device dislodgement, embolism, erosion or infection. The complications might require pericardiocentesis, blood transfusions, or surgical interventions and can be fatal.[44, 45, 49, 51, 54] Cases of pulmonary artery tear with resultant pericardial bleeding and tamponade have been reported from hooks of the Amplatzer Cardiac Plug.[74, 75] Transseptal puncture and catheters/device in the left atrium pose a risk for systemic thromboembolism and full therapeutic anticoagulation is required during the procedure. Disruption of preformed left atrial thrombi and embolism of debris or air confer additional risk of periprocedural strokes. Screening with TEE to exclude any left atrial thrombus prior to such procedures is obligatory. Pericardial access for percutaneous epicardial techniques requires expertise and can have complications like coronary artery injury, myocardial perforation, diaphragmatic bleeding, hemothorax, intra-abdominal bleeding, liver laceration, and right ventricle-abdominal fistula. LAA ligation leads to infarction of the LAA along with consequent pain and pericarditis. Pericardial access and manipulation in itself poses risk for pericarditis with potential for subsequent recurrences or pericardial constriction.[20] As opposed to LAA exclusion, anticoagulants do not have a substantial upfront risk at the time of initiation.

Incomplete LAA Exclusion And Risk For Device Related Thrombus: Leaks around endovascularly implanted LAA occlusion devices like Watchman and Amplatzer Cardiac Plug occur in 30% to 60% of cases due to eccentric oval shape of the ostium, and there can be a residual LAA stump with Watchman and epicardial closure devices.[19, 76] Though retrospective analyses suggest that peri-device leaks are usually small with brisk flow and are not high risk for thromboembolism, these are nonetheless a cause of concern.19, 76 Endocardially placed occlusion devices have a risk of thrombus formation on the exposed device surface, and either warfarin or dual antiplatelet therapy is recommended for 3 to 6 months till endothelialization of the exposed surface is complete. Regardless, there was a 4% rate of Watchman device-related thrombus in the PROTECT-AF trial and ASAP registry,[46, 50] and there have been numerous well-documented reports of thrombus formation on various devices and embolic complications.[47, 54, 55, 77-79] Incomplete epicardial closure of the LAA might have a subsequent higher risk of thromboembolism.[58, 62, 80] Reopening of the Lariat suture has been reported81 as has left atrial thrombus following LAA closure with Lariat.[82-84]

Large-Scale Feasibility: Anticoagulants are easy to prescribe and administer for the providers, and easy to procure and use for the patients without need for any sophisticated operator expertise or technology. LAA exclusion, on the other hand, is a technically complex endeavor that requires expensive medical care including cost of the device, equipment, advanced catheterization lab facility, backup cardiac surgical care, as well as expensive periprocedural and followup testing like CT scans, cardiac MRIs, and TEEs. Further, patients and operators are exposed to radiation with stochastic and cumulative risks.

Candidacy For Laa Exclusion: All LAA closure devices need appropriate sizing to match the LAA anatomy. Due to variability in shape and size of the LAA, some patients with unsuitable anatomy are ineligible for these devices. Percutaneous epicardial techniques might not be feasible in patients with pericardial adhesions due to pericarditis or prior surgery.

Loss of physiologic functions of LAA: LAA exclusion causes a loss of physiologic functions of the LAA including regulation of fluid and electrolyte homeostasis and functions as a reservoir and booster of left atrial function, though in most patients with AF these might already be dysfunctional.[32]

Factors Favoring Left Atrial Appendage Exclusion Over Anticoagulation

Long-Term Convenience And Dependability: Despite its benefit, a fifth of the AF patients with CHADS2 score ≥2 in the USA are not on anticoagulation.[85] There are many barriers to anticoagulation in high-risk AF patients, foremost being concern for bleeding complications.18 Patients with higher bleeding risk scores are less likely to be anticoagulated.85 Additionally, many patients are non-compliant with anticoagulants due to lack of adequate patient education, no overt clinical benefit, logistical challenges in INR monitoring with warfarin, adverse effects like bruising and other psychosocioeconomic reasons.10, 86 Over long term, adherence to anticoagulation might drop as low as 20% to 30% range.[87] On the other hand, LAA exclusion is a one-time procedure, and although with endovascularly placed devices, anticoagulation or dual antiplatelet therapy might be warranted for up to 6 months, over the long term there is little scope for interruption in benefit due to non-compliance.

Bleeding Complications With Anticoagulants: Risk of bleeding with anticoagulation is the primary reason for development of LAA closure techniques. Warfarin increases intracranial bleeding

by an absolute 0.2% per year compared to aspirin.34 Despite less intracranial bleeding, newer oral anticoagulants still pose a substantial bleeding risk for many patients. Gastrointestinal bleeding occurs in 2.1% to 3.6% per year, and patients with highest bleeding risk were not included in the landmark RCTs.35-40 Some patients might have absolute contraindications to anticoagulation like recurrent falls, history of intracranial hemorrhage, or bleeding diathesis. LAA closure is an attractive alternate to anticoagulation in patients at risk of bleeding. It needs to be noted that for endovascularly implanted devices like Watchman and hybrid procedures like Lariat still require intraprocedural full therapeutic anticoagulation with heparin. Endovascular devices additionally require warfarin or dual antiplatelet therapy at least for 6 weeks post-implantation.

Cost-Effectiveness: A cost-effectiveness analysis on percutaneous LAA occlusion for non-valvular AF as compared to warfarin and dabigatran was performed from the perspective of the Ontario Ministry of Health and Long Term Care, the third-party payer for insured health services in Ontario, Canada. The average discounted lifetime cost was $21,429 for a patient taking warfarin, $25,760 for a patient taking dabigatran, and $27,003 for LAA occlusion. Compared with warfarin, the incremental cost-effectiveness ratio for LAA occlusion was $41,565 per quality-adjusted life year while dabigatran was extendedly dominated.[88]

Combination Of Left Atrial Appendage Exclusion With Antithrombotic Drugs

Certain patients with AF remain at high risk of thromboembolism despite therapeutic anticoagulation. Predictors of cardioembolic strokes despite anticoagulation include dense spontaneous LAA echo contrast, reduced LAA emptying velocities on TEE,89 and systemically elevated levels of D-dimer90 or von Willebrand factor.[91] These predictors need further validation, and whether supplementing anticoagulation with LAA closure in such patients at persistently elevated risk will lead to better outcomes is not known. Such a two-pronged strategy might be considered on an individual case basis, especially in cases of anticoagulation failure with LAA thrombi and embolic events.

Left Atrial Appendage Exclusion Added To Catheter Ablation For Atrial Fibrillation

AFFIRM was the largest RCT evaluating rhythm-control versus rate-control strategy for AF and did not show any benefit in mortality or stroke with rhythm control.[92] However, a subanalysis suggested that mortality was reduced in patients that maintained sinus rhythm and was likely offset by adverse effects of antiarrhythmic drugs.[93] Furthermore, retrospective analyses specifically looking at patients that maintain sinus rhythm following catheter ablation of the left atrium suggest that the risk of thromboembolism is exceedingly small.[17, 94-96]

Electrical isolation of the LAA has been described as an adjunct to pulmonary vein isolation for maintaining sinus rhythm in patients undergoing catheter ablation of atrial fibrillation. Though most of the benefit is reserved for patients with AF triggers emanating from the LAA, some benefit is assumed from alteration in the substrate available to sustain AF.97 However, electrical isolation of the LAA risks loss of mechanical function of the LAA with potential for thromboembolism in the absence of anticoagulation.[98] Epicardial LAA occlusion on the other hand, in addition to excluding the LAA to minimize stoke risk, leads to electrical isolation with subsequent infarction and atrophy.[70, 71] Therefore, the possibility of using epicardial LAA exclusion to complement pulmonary vein isolation in patients with AF needs to be explored. In addition, novel technological developments are underway to use the epicardial access for autonomic modulation by targeting neural ganglia in epicardial fat or for an entirely epicardial ablation procedure to further minimize thromboembolic risks.[99] To this end, minimally invasive thoracoscopic epicardial pulmonary vein isolation with LAA excision and partial cardiac denervation has been developed.100 Sole-Therapy Treatment of Atrial Fibrillation (RESTORE SR II, NCT 00566176) is a prospective feasibility study on 25 patients evaluating minimally invasive epicardial bipolar radiofrequency ablation for pulmonary vein isolation along with LAA exclusion.

As opposed to electrical isolation of the LAA with catheter ablation, epicardial exclusion affords better efficacy and efficiency in electrically isolating the LAA and obviates the thromboembolic risk from electrical standstill in the LAA.[98, 99] However, prior to clinical adoption, the combining epicardial LAA exclusion with ablation for AF needs proof of benefit on both accounts – reduction in AF recurrence and acceptably low stroke risk without long-term anticoagulation. Preliminary observational data suggests that combination of Lariat ligation of LAA in addition to catheter ablation for persistent AF improves reduces AF recurrence and need for repeat catheter ablation.[101]

Current Guideline Recommendations For Stroke Prophylaxis In Atrial Fibrillation

The current AHA/ACC/HRS Guideline for AF focuses on antithrombotic drug therapy for prevention of cardioembolic events. It recommends risk-stratification based on CHA2DS2-VASc score and informed discussion with patients regarding use of anticoagulation for stroke prevention especially in context of bleeding risk. In patients with non-valvular AF and CHA2DS2-VASc score ≥2 oral anticoagulant therapy with warfarin, dabigatran, rivaroxaban or apixaban is recommended (Class I recommendation). For those with CHA2DS2-VASc score 0, omission of antithrombotic therapy is reasonable (Class IIa). In patients with CHA2DS2-VASc score 1, no antithrombotic, aspirin or oral anticoagulation may be considered (Class IIb). For patients undergoing cardiac surgery, they specify that LAA occlusion may be considered (Class IIb). The Guideline makes a note of the percutaneously placed devices, Watchman, Amplatzer Cardiac Plug and Lariat, but do not give any indications for their use.[38] On the other hand, the European (ESC) guideline states that interventional percutaneous LAA closure may be considered in patients at high stroke risk and contraindications to chronic oral anticoagulation (Class IIb).[102]

Future Directions

Several Studies Of Percutaneous Laa Exclusion Are In Progress. The Canadian Left Atrial Appendage Occlusion Study Iii (Laaos Iii, Nct01561651) Is Randomizing 4700 Af Patients With Cha2ds2-Vasc ≥2 Undergoing Cardiac Surgery To Laa Excision Versus No Excision. Eligible (Nct01628068) Is Spanish Multicenter Rct Enrolling 120 Patients To Evaluate Amplatzer Laa Closure With 3-Month Dual Antiplatelet Therapy Versus Standard Anticoagulation For Af Patients With Cha2ds2-Vasc ≥3 And Gastrointestinal Bleeding. Left Atrial Appendage Occlusion Versus Usual Care In Patients With Atrial Fibrillation And Severe Chronic Kidney Disease (Watchafib, Nct02039167) Is Randomizing 300 Patients With Cha2ds2-Vasc ≥2

And Estimated Glomerular Filtration Rate (Egfr) <30 Ml/Min To Warfarin Anticoagulation Versus Watchman Laa Closure With 6 Months Of Dual Antiplatelet Therapy. A Prospective Observational Study Enrolling 150 Patients Is Evaluating Watchman Versus Lariat For Laa Exclusion (Nct01695564). Feasibility Studies Are Evaluating Newer Laa Exclusion Devices Like The Fourth Generation Of Watchman Device (Evolve, Nct01196897), Lambre (Nct02029014), And Open Surgical Tigerpaw System Ii (Nct00962702). There Is A Need For Head-To-Head Comparisons Of Laa Closure Devices With The Newer Oral Anticoagulants And Of Various Techniques For Laa Closure With Each Other. Additionally, Novel Techniques Like Completely Percutaneous Laa Exclusion And Pulmonary Vein Isolation Through Pericardial Access Need To Be Developed And Evaluated.

Conclusions

Stroke is the most dreadful clinical outcome of AF. There have been tremendous scientific and technological advances in mitigating the risk of stroke. Chronic oral anticoagulation remains the backbone for reducing the public health burden of stroke in the general AF population. Newer oral anticoagulants, with simple dosing schemes without need for therapeutic level monitoring and with potentially lower risk of life-threatening bleeding when compared to warfarin, have been a major advance. However, oral anticoagulation has limitations related to non-adherence with treatment and increased risk of bleeding complications. Various validated and emerging techniques to exclude the LAA from the systemic circulation offer an alternate option for stroke prevention, especially appealing for patients at high risk of bleeding complications or absolute contraindications to anticoagulants. In this milieu of increasing options for stroke prevention, in the context of other advances in management of AF like innovations in interventions to maintain sinus rhythm, the physician needs to critically evaluate the scientific evidence to determine pros and cons of various options. Keeping the patients' best interest utmost, the treatment for each patient needs to be individualized and based on the clinical, physiologic, anatomic, and socioeconomic considerations.

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A Review Of The Relevant Embryology, Pathohistology, And Anatomy Of The Left Atrial Appendage For The Invasive Cardiac Electrophysiologist

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Abstract

The three-dimensional morphology of the left atrial appendage provides the substrate for thrombus generation, and is a harbinger for embolic material due to its direct connection to the left-sided circulation. Appreciating the development of the appendage from mesodermal layer to its adult form provides the basis to improve exclusion from the atrial circulation, and thereby can lead to a significant reduction in stroke risk. This process also provides insight into the role of the left atrial appendage as an endocrine organ, its involvement in fluid homeostasis, and its connection to the autonomic nervous system. Knowledge of the surrounding structural arrangement is critical to identify landmarks from both an endocardial and epicardial perspective to improve targeted device placement. Furthermore, correlation of the left atrial appendage body, neck, and ostium to the surrounding anatomy can also improve both procedural efficacy and safety. In addition, a working knowledge of the regional anatomy adds a prudent degree of awareness for procedural complications, and allows for early identification and timely intervention as these situations arise. A detailed understanding of the left atrial appendage embryology, histology, and gross anatomy is imperative to identify the correct device and approach for each individual patient. In addition, this increased awareness can identify areas that are in need of further innovation, and thus provide the ability to adapt and refine existing technologies to overcome pitfalls currently facing catheter-based approaches.

Introduction

The left atrial appendage (LAA) itself is one of the most "lethal" structures that exists in the human body.[1] The anatomical landscape of the pectinate muscles and crevices of the LAA, in the presence of blood stasis when the atrium is in fibrillation, produces an optimal site for the generation of thrombi.[2] The data regarding its pertinence to stroke risk are impressive, where its involvement occurs in approximately 90% of cases with a cardioembolic etiology in non-valvular atrial fibrillation (AF) patients.[3] Thus, this is one of the most critical cardiac structures where it is absolutely essential to have a detailed understanding of the embryology, histopathology, and anatomy for proceduralists of the LAA who wish to improve efficacy while establishing and maintaining safety.[4]

Understanding the left atrial appendage anatomy is becoming of ever increasing importance as the toolkit of LAA exclusion devices continue to grow and more options for targeting this structure are generated.[5] Irrespective of whether a surgical or percutaneous appendage procedure is employed, the goal is to achieve LAA exclusion without damage to the LAA itself or the major structures that lie in its close proximity.[6] Because of its baseline complex structure and the tremendous amount of variation amongst individuals, difficulty still remains when attempting to match the correct approach, device, and patient so that the procedure is both therapeutic and safe.[4] Moreover, the same can be said not only pre-procedurally, but also post-procedurally in order to maintain successful exclusion from the left atrial circulation, as well as to monitor for potential consequences during long term follow-up.[7] Furthermore, this may provide a foundation for solving issues where complete exclusion is difficult, and provide a better understanding of the surrounding landscape, which can make catheter based approaches increasingly complicated.[6]

In this review, we provide the proceduralist with a background of LAA embryology, endocrinology, anatomy, and place the critically

Key Words:
Left Atrial Appendage, Cardiac Embryology, Ostium, Stroke, Embolism, Atrial Fibrillation, Vein Of Marshall, Endocardial Ridge, Mesenchymal, Pulmonary Vein, Phrenic Nerve, Left Circumflex Artery.

Disclosures:
None.

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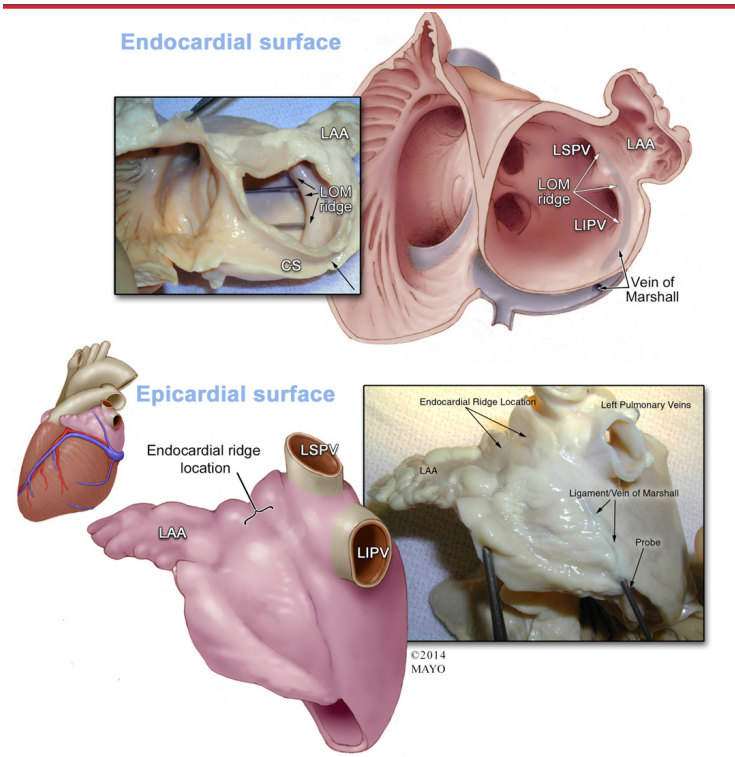

Figure:1 **Complexity of Left Atrial Appendage Morphology**
Shown are endocardial views of the left atrial appendage from post-mortem specimens of human hearts. Left panel: The left atrial appendage ostia have more of an elliptical, rather than round shape. Middle panel: An endocardial view of that shows the relationship of the left atrial appendage ostia, neck, pectinate muscles, and outpouching structure is shown. The smooth left atrium and orifices of pulmonary veins are seen in the figure in relation to the appendage. RA; right atrium. LA; left atrium. White arrows; outpouching structure of the appendage where the neck extends outwards to a 3D body. Right panel: An endocardial view of the left atrial appendage showing the complexity of a multi-lobed structure, 3D shape, and prominent pectinate ridges. LAA; left atrial appendage. White arrows; point towards multiple lobes and pectinate muscles.

related spatio-temporal structures in context, in order to provide a roadmap for safer and more effective exclusion therapies.

Embryologic And Histopathologic Overview Of The Left Atrial Appendage

Development From Mesenchymal Tissue

Cardiac structures are ultimately derived from the mesodermal tissue layer during the third week of embryonal development.[8] The genesis and ultimate location of the left atrial appendage and its surrounding structures begins from a simple connection of paired cardiac mesoderm that fuses to form a two-cell thick tubular heart.[9] The initiation of this anatomical development involves a pro-myocardial plate of cells, which slowly develops into a three-dimensional tubular formation.[8,10] This growth continues on towards a more seasoned cardiac formation via folding in an area that ultimately develops into a heart residing in the eventual pericardial space.[8,10] It is within these early stages of embryonic growth that the left atrial appendage begins to emerge.[11]

It is during the third week of gestation that the left atrial appendage originates and develops from the wall of the left side of the primary left atrium.[12] However, prior to formation of the semblance of a recognizable heart structure, a primary cardiac tube is formed which contains two caudally oriented, asymmetric, inverted "y-shaped" structures which eventually develop into the primary right and left atrial horns; these horns are continuous with the venous system at approximately week four of embryologic development.[8,10] At around week six of embryologic life, further development of the left atrium occurs, but it is dependent on the growth and development of the pulmonary system, which connects to the heart via the pulmonary vein-left sinus horn.[8,10]

The right and left atrial appendages are both formed from the superolateral wall of the primary atrium, with the left appendage specifically arising from the superior and left side of the primary atrial tube.[8] The appendage further matures with the formation of trabeculae, secondary to cellular protrusion into the lumen and surrounding vasculature which engages this substrate from the epicardial aspect, in order to solidify the basal layer.[9] These trabeculations start to form in the atria at around week five in humans.[9] The left atrial appendage is significantly smaller than its counterpart structure on the right side, and is heavily trabeculated, with fibers running in parallel orientation.[12]

Relevant Histology Of The Left Atrial Appendage

The majority of developing thrombi which are ultimately responsible for ischemic events, including those that form during rhythms of af, are generated in the left atrial appendage.[13] In fact, approximately 90% of the thrombi that are found in patients with af are discovered in the laa.[14] A clear reason for this occurrence is due to the loss of the appendages' contractile properties during af, which leads to increased pressure causing expansion and dilation of the laa, as well as a resultant stagnancy of blood in the trabeculated muscle.[14] Indeed, when a slower velocity of blood flow is found in af, patients are more likely to have thrombi in the laa.[15] The issue of stasis can be facilitated by a smaller size of the laa (diameter of the laa being 10-40 mm in some patients), in addition to significantly reduced contractibility, leading to an increasing risk of thrombus formation.[11]

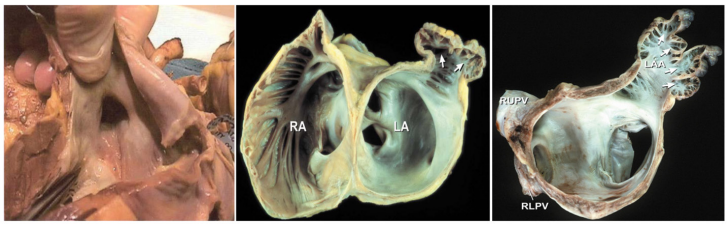

Figure:2 **Morphologic Variation in Left Atrial Appendage Ostia**
Adapted with permission from Cabrera; Heart 2014
Panel A. The ostium of the left atrial appendage with a "chicken wing" morphology is shown. Notice the slightly elliptical morphology of the os. In addition, the proximity to the mitral valve (MV) is seen. Also of note are the crevices/pits surrounding the ostium.
Panel B. Amplatzer Cardiac Plug in situ 10 mm from the ostium to occlude the appendage. Notice that after appendage occlusion, there the divots are "unprotected". Also note the proximity of the device to the circumflex artery (LCx) and mitral valve (MV).
Panels C-D: Variant ostial morphology; these are classified as C) "round" ostial variant, D) "elliptical: variant", E) triangular, F) "water-drop like", G) "foot-like". MV; mitral valve.

Although exclusion of the laa from the atrial circulation can prevent thrombus formation, undesirable changes may occur after disrupting the structure and histology with device therapy.[16]

The underlying histology of the left atrial appendage gives rise to multiple aspects of anatomic and physiologic relevance in the human body.[17] These functions are usually overlooked or poorly

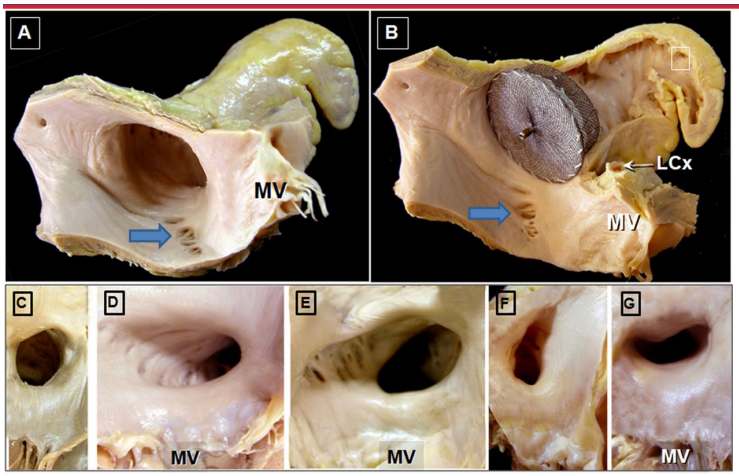

Figure:3 **Morphologic Complexity and Variation in Left Atrial Appendage 3D structure Adapted with permission from Cabrera; Heart 2014**
Panel A: Post-mortem specimens showing a single lobed left atrial appendage (LAA). The closely related pulmonary trunk (PT) and left superior pulmonary vein (LSPV) are also shown.
Panel B: Example of a multi-lobed left atrial appendage (asteric showing distinct lobes). The aorta, as well as the pulmonary trunk and LSPV are seen in this view.
Panels C-F: Examples of variant 3D morphology of left atrial appendage shape; Panel C: "Chicken Wing",
Panel D: "Windsock", Panel E: "Cactus", Panel F: "Cauliflower".

understood, although intervention involving the laa can have multiple downstream effects post-procedurally due to alterations in cellular physiology.[17] Furthermore, the cellular composition of the appendage is quite variable both in composition and compaction. It contains both endocardial and epicardial layers, and these structures are complicated by a disarray of myocyte orientation.[18] Additionally, the myocytes of the laa are more akin to ventricular than atrial cells in physical structure.[17] From an endocardial aspect, the laa has a variable thickness across the area between the muscle bundles.[19]

The characteristic shape of the epicardial aspect of the left appendage is due in part to the intervening conducting bundles of fibers that alter its architecture,[19] and adds to the complexity of its function. In addition to bachman's bundle, the epicardial layer of the laa is comprised of myocytes.[18] Bachman's bundle is a sub-epicardial structure that provides facilitation of conduction through circumferential muscle bundles running from the right atrial appendage and coursing across to feed into the left appendage.[19] These bundles reach the laa from the right atrial appendage after traversing the inter-atrial septum; the course of which requires the bundles themselves to branch both superior and inferiorly to encircle the neck of the laa.[20]

In addition to increased coagulability and stasis in the left appendage, histo-morphologic changes can occur over time especially in patients with chronic af, and these micro-structural changes can further alter the endocardial substrate and may also play a role in thrombus formation.[21] A post-mortem study found that patients with af had appendages that were triple the volume of those without (5.4 ± 3.7 Cc3 vs. 1.7 ± 1.1 Cc3), and had a lower volume of pectinate muscles likely due to increased distension of this structure.[21] Furthermore, thickening of the endocardial surface due to fibrous and elastic changes occurred more often in patients with af, and these changes to the endocardial landscape also included embedding of the pectinate muscles by this infiltration.[21] Another cause of stasis in the laa may be related to its role in atrial amyloidosis and possibly in "atrial myopathy," because amyloid often collects in the laa more than the right.[22] The amyloid deposition in the laa is especially found in patients with chronic af where significant structural remodeling and infiltration occurs over time.[22]

Endocrine Function Of The Left Atrial Appendage

A greatly underappreciated aspect of the appendage is its unique role as an endocrine organ.[17] Interestingly, the laa has been found to contain a variety of cardiac progenitor cells (cpc),[23] and this attribute is fundamental to many of its underlying functions, including its impressive role in endocrine regulation.[23] It is of critical importance to cardiac physiology and homeostasis, as this structure contains almost 30% of the heart's pool of atrial natriuretic factor.[11, 24] The release of this potent endocrine modulator leads to a myriad of effects including change in heart rate, natriuresis, and urination, all underscoring the importance of the laa's role in modulating body volume status.[11] Furthermore, atrial natriuretic factor release is also stimulated by low oxygen, myocyte stretch, and oxytocin, which incrementally improves the tight regulation of pressure overload and volume status sensed via the cells of the appendage.[11, 17]

Distension of the wall of the appendage can occur during procedural interventions as well as certain pathologic states, and the tension on the wall is amplified because of the physical properties of its shape.[17] Increased distention of the laa in an animal study has shown to generate an increase in heart rate, urination, and facilitation of sodium excretion.[25] These data support the potential for the laa

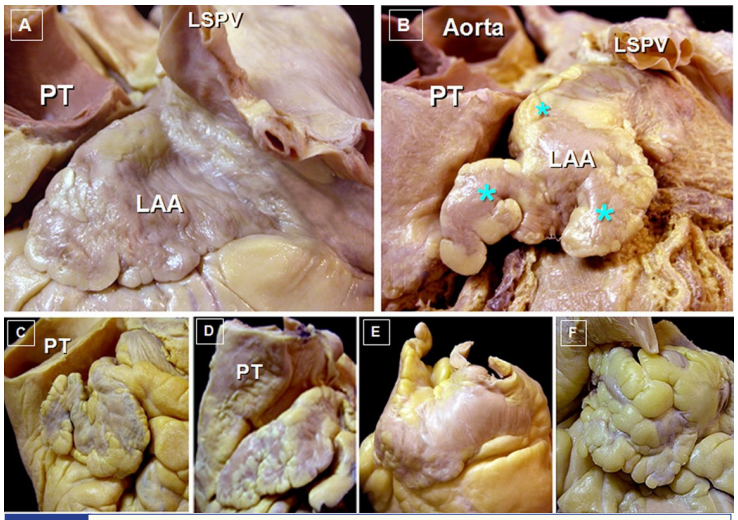

Figure:4 **Diverticular Structures Surrounding the Left Atrial Appendage Ostium**
Left panel: Endocardial view of the atria showing the ostium of the left atrial appendage (LAA) and its surrounding structures. Of special note are the diverticular structures that are proximal to the LAA ostium. The relationship of the left superior and inferior pulmonary veins (LSPV and LIPV) is shown, as well as their separation by the vein/ligament of Marshal (LOM) ridge; which is an endocardial marker for the epicardial vein of Marshall (note that the course of the vein/ligament of Marshall running in between the Left pulmonary veins and the LAA, on its route to empty into the coronary sinus. The relationship of the LAA and the left circumflex artery is also illustrated. Right panel: After the left atrial appendage is occluded with a device (black circle represents the proximal end of the occlusion device), the surrounding pits/divots that are proximal to the ostium remain "unprotected" and in contact with the left atrial circulation. In addition, note the relationship of the proximal end of the occlusion device with the left circumflex artery.

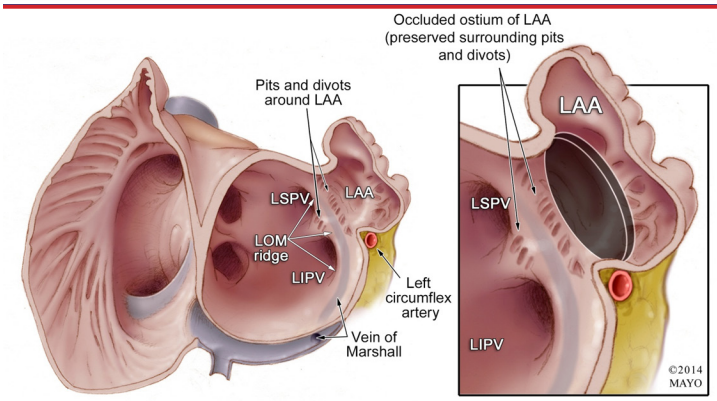

Figure:5 **Relevant Anatomy Surrounding the Left Atrial Appendage**
Illustration of the human heart showing the left atrial appendage (LAA) and its closely related structures. Notice that the tip of the appendage is pointing towards, as well as the body of the LAA, covering the left circumflex artery and great cardiac vein. Also seen is the overlying left phrenic nerve coursing on top of the LAA. The vein of Marshall traverses through the LAA and left superior pulmonary vein. The closely related pulmonary trunk also is shown abutting the LAA.

neuroendocrine response via release of atrial natriuretic factor from stretch receptor activated cells that reside in the laa.[11] Therefore, there was early controversy that the critical role of the laa in normal physiological functioning may be eliminated with laa procedures. For example, one potential concern was in regards to laa exclusion in precluding the ability to maintain this critical pressure-induced, stretch receptor endocrine response.[25] However, the right atrial appendage is likely critical in overcoming this dilemma, as it is able to execute similar endocrine effects as the laa.[11] Although there is the possibility that tight endocrine regulation via both appendage structures are required, and exclusion may eventually lead to long-term adverse results, no studies to date have shown any adverse effects post-exclusion.[17]

In addition to its role in natriuresis and urination, the left appendage has additional capabilities to function in tightly controlling overall volume.[26] For example, it may play a role in facilitating or mediating thirst.[27] An in vivo study in sheep showed results in support of this notion, as the sheep with non-intact versus intact laa had a differential response to water consumption.[22,26,27] The sheep that did not have an intact laa did not increase the amount of water consumption despite dehydration, however the sheep with intact laa did.[22,26] Furthermore, in addition to thirst, the closely connected volume status of an individual may depend on an intact and functioning laa to regulate blood pressure via innervation with both sympathetic and parasympathetic fibers.[11] A study performed in canines found that destroying the base of the laa did in fact decrease the heart rate, which can likely be ascribed to the reflex response from the vagus nerve, and further implicates the role of the autonomic system and its interaction with the laa.[11] Therefore, this structure plays a magnificent role in the physiology of the human body and its appreciation is necessary when choosing which approach is best on a per-patient basis.

Anatomical Variations That Influence Appendage Exclusion Procedures

Pectinate Muscles Of The Left Atrial Appendage

In contrast to the rest of the smooth left atrium, the appendage is comprised of rigid pectinate muscles that are orientated in a "whorl-like" fashion throughout, with thin-walled myocardium interdigitating these raised regions.[28,29] These pectinate structures are almost exclusively found in the appendage, in comparison to the remainder of the left atrium.[20] The majority of hearts have variable appendageal wall thickness, and post-mortem studies have shown that the majority of pectinate muscle thickness to be of at least 1 mm in size.[18,30] Moreover, a retrospective study found a more extensively trabeculated LAA to be a strong independent predictor of thromboembolic risk.[31] In addition to these rigid pectinate muscles, additional complexities associated with the LAA such as the three-dimensional morphology and the shape and size of the appendage ostium can create difficulty when attempting to interface opposing

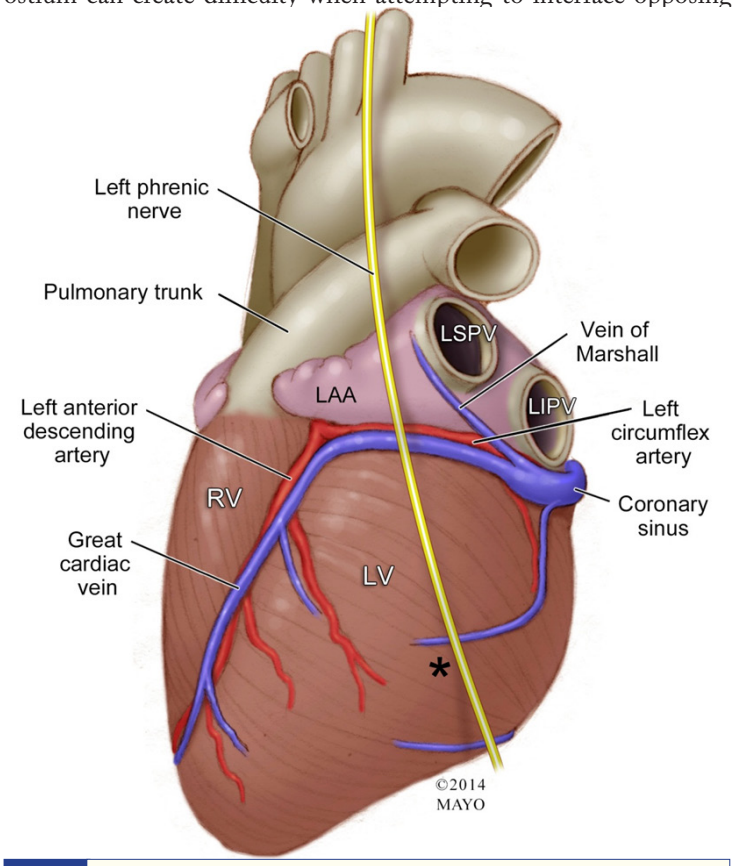

Figure:6 **Endocardial and Epicardial Landmarks of the Left Atrial Appendage Ostium**
Top Panel: The left inset shows a gross anatomical specimen of an endocardial view of the right and left atrium transected at the annulus to show the relationship between the left atrial appendage (LAA), ligament/vein of Marshall (LOM) ridge, and coronary sinus (CS). Two probes are shown marking where the ostia of the left sided pulmonary veins are in relation to this ridge. The accompanying Illustration on the right shows a similar view of the gross anatomy after opening the LAA to provide a view the endocardial surface of the appendage. This image shows the endocardial relationship of the LOM ridge which is a marker for the overlying epicardial ligament of Marshall. This ridge separates the ostia of the left superior and left inferior pulmonary veins (LSPV and LIPV) and the ostium of the LAA. The ligament/vein of Marshall course is shown (blue-grey shadowing), as well as its connection to the CS. Bottom Panel: An illustration of an epicardial view showing the invagination of the epicardial surface which contains the vein/ligament of Marshall is shown in the left inset. The invagination forms a boundary between the LAA and the LSPV/LIPV. The location of the epicardial invagination reflects the location of the endocardial ridge and approximation of the ostium of the LAA. The accompanying right inset shows a gross anatomical specimen depicting this view with a probe inside of the LOM.

surfaces during LAA exclusion procedures (FIGURE 1).[32]

Variable Morphology Of The Left Atrial Appendage Ostium Shape And Dimensions

The three-dimensional shapes of the left atrial appendage are varied and complex.[4] The gross structure of the appendage usually consists of a uni- or multi-lobed, finger or stump-like extension of the left atrium.[28, 29] The distal most lobular structures of the appendage transition towards the left atrium proper by assuming a tubular shape, and further tapers down in size to form a "waist-like" structure.[28] The connecting structure from the base of this outpouching appendage to the opening of the left atrium is via the LAA ostium, which is of particular importance especially with respect to LAA procedures involving endocardially placed occlusion devices. This is because the entry for endocardial delivery of an occlusion device first engages the appendage through accessing this ostial region.[18]

The ostium of the left atrial appendage has great variation in shape and is more elliptical as opposed to the circular structure associated with many appendage exclusion devices.[6] Because the LAA ostium has been noted to have great variation in shape, but falls into certain categories of distinctive morphology, these structures have been given terms for easier classification. Both the nomenclature and the prevalence of these shapes have been displayed in an elegant study to which the ostium was termed to be "oval" (68.9%), "foot-like" (10%), "triangular" (7.7%), "water drop-like", or round (5.7%) [20] (FIGURE 2). This hollowed structure is separated from the left superior pulmonary vein both superiorly and posteriorly by the presence of the left lateral ridge of the atrium; an endocardial invagination of the lateral left atrial wall.[18, 28] The prominent ridge that separates the ostium of the LAA and the left superior pulmonary vein can be seen as a "Q-tip sign" on echocardiographic images, allowing for easier identification of this structure.[29]

A large study performed by Ernst et al was integral in demonstrating an appreciation for the various left atrial appendage morphologies, as well as connection of these shapes to potential underlying pathologic conditions.[33] This study involved 220 hearts and the numerical dimensions of the anatomy was achieved by making resin casts to delicately study this structure.[33] In these hearts, the LAA ostium was found to have an average minimum to maximum diameter of 15-21 mm, an average size from bottom to top of 30 mm, a 31 mm distance at a right angle from the "bottom to top" measurement, and an average appendageal volume of 5220 mm3.[33] Important clinical associations were found between AF and LAA volume, as well as correlation to appendage orifice diameter.[33] In addition, fewer branches of the LAA structure were likely to be found in patients with AF.[33] The authors also found that the larger the volume of both the LAA and ostium were more likely to have thrombus detected.[33] Interestingly, a retrospective study found an independent association with thromboembolic risk in patients who had a smaller sized diameter of LAA os.[31]

Variable Morphology Of The Left Atrial Appendage And Stroke Risk

There are several variations in the left atrial appendage anatomy with respect to shape, volume, length, and width.[33] The variation in LAA morphology has been found to be related to the likelihood of thrombus formation, especially with respect to larger LAA volume, depth, and number of lobes.[34] One study reported the occurrence of the number of lobes in a study of fifty hearts of chronic AF patients; the LAA was comprised of a single lobe in 68%, two lobes in 24%, three lobes in 6%, and four lobes in 2% in their studied cohort.[4] Moreover, there has been a classification of appendageal variation with respect to similarity in three-dimensional shapes of the LAA. One study noted their prevalence in a cohort, and utilized the terms "chicken wing" (48%), "cactus" (30%), "windsock" (19%), and the least common "cauliflower" (3%)[18, 35] (Figure 3).

The left atrial appendage shape may also have prognostic significance in terms of likelihood of stroke. This association was shown in a retrospective study where "chicken wing" was least likely and "cauliflower" morphology was most likely to be associated with a cardioembolic event.[35] Furthermore, in a study with a cohort of low CHADS2 scores and non-valvular AF, the presence of a LAA with a "cauliflower" morphology was found to be a strong independent predictor for stroke risk.[36] However, a separate retrospective study conducted in patients with AF, showed data to support that a smaller LAA ostium and more extensive trabeculations may trump this "cauliflower" morphology in terms of stroke risk.[31]

Critical Problems Associated With Left Atrial Appendage Exclusion Procedures

Although there are multiple devices and approaches, not every patient is able to achieve a complete exclusion of their left atrial appendage. This can be attributed to the wide variation in shape, number of lobes, and ostia for each unique LAA encountered, and is further complicated by potential limitations with certain imaging modalities such as transesophageal echocardiography, which is used during surgical procedures.[15] In addition, a major problem is that the failure to achieve full exclusion may lead to a more dangerous situation because of the potentially increased thrombogenicity with "residual stumps".[23] The incomplete exclusion of the LAA can even occur with external clipping or excision procedures because of residual stump formation, as well as with percutaneous measures; though it seems that the actual type of approach used itself is not the determining factor of this inability for complete exclusion.[37]

The issue of incomplete occlusion of the appendage poses a major threat to the viability of this procedural option, as well as presenting an uncertain and controversial risk of persistent thrombogenesis in these patients.[15] This problem can be borne out during LAA occlusion procedures when proper planning is not carefully performed or is lackluster. For example, it is essential for correct tailoring of the size of the device to match the variant morphology of the LAA in order to ensure a secure fit to prevent collateral blood pooling into unwanted sites that promote thrombi formation.[4] In addition to the variant morphology of the body, the "neck" of the LAA can be variable in patients as well. A retrospective study has shown that the "neck" of the LAA (which connects the body to the left atrium) had an average volume (17.3 ± 6.7 cc3), long axis diameter (20.0 ±5.3 mm), and short axis diameter (14.1 ± 4.7 mm), with associated ranges of volume (5-35.7 cc3), long axis diameter (9.5-29.9), and short axis diameter (3.1 – 24.1 mm).[4]

The finding of "divots" or diverticular pockets surrounding the endocardial surface of the appendage ostia can further complicate the ability to achieve complete exclusion, and these sites may be optimal for thrombus propagation.[6, 29] A post-mortem examination of human hearts showed these "pitted" structures to range from 0.5-10.3 mm in diameter, and found a range of distance from the LAA ostia to vary from 1.4 – 20.9 mm.[6] Because these diverticular-like pouch

structures can vary in size and depth around the appendage ostium,[19] these areas may not be excluded from the left atrial circulation during exclusion procedures regardless of whether the approach is occlusion or ligation, and regardless of whether an endocardial or epicardial approach is employed. The major issue with these pitted areas is that even after LAA device exclusion these divots may remain unprotected and in contact with the left atrial blood (Figure 4). Therefore, these structures can potentially house thrombi that would still pose a thromboembolic risk to the patient. This may indeed prove to be the "Achilles heel" of LAA exclusion in certain patients. Furthermore, if large enough, these pitted regions can pose difficulty during endocardial manipulation and may lead to potential damage of surrounding structures during procedures.[6]

The various morphologies of the left atrial appendage can pose great difficulty for procedural exclusion from the cardiac circulation because of the shape of the device itself.[15] For example, the "chicken-wing" morphology is of particular difficulty for LAA occlusion because of its shape; this is due to the course of this structure taking a very sharp bend (<180 degrees) and having this turn occur extremely close to the ostium (<20 mm).[32] An insightful approach was taken by Freixa et al., and proved to solve the difficultly associated with certain cases with varying morphologies by implanting the Amplatzer Amulet or Plug (St. Jude Medical, MN).[32] The key to the successful procedural outcomes stemmed from the clever use of placing a slightly oversized device (3-6 mm) and deploying the distal end of the device towards the dominant appendage lobe, in order to seal off the ostium with the proximal end of the device.[32] Innovative approaches and studies such as these, as well as their publication will aid in the future application of these ideas and techniques for procedural safety.

Relevant Spatial Relationships For Left Atrial Appendage Procedures

The left atrial appendage is a blind-ended pouch emanating from the left atria and is situated within the pericardium.[28, 29] The anatomical relations of the left appendage are complex and the critical structures surrounding the LAA include: 1) a superiorly directed pulmonary artery, 2) the appendage tip pointing in an inferomedial direction towards the free wall of the left ventricle, 3) the left phrenic nerve coursing overtop of the appendage , 4) fibers of Bachmann's bundle that approach the LAA from the medial aspect of the atrial roof, 5) a posteriorly situated left superior pulmonary vein, and 6) an inferiorly related mitral valve.[6, 12, 18, 28, 38] However, of utmost importance to note when performing any type of appendage procedure is the critical relationship of the LAA covering the area above the left atrioventricular groove, which houses both the left circumflex artery and great cardiac vein (Figure 5).[18, 28]

Relationship of the Left Circumflex Artery to the Left Atrial Appendage Ostium

The proximity of the left circumflex artery is of particular importance when performing either endocardial or epicardial procedures of the left appendage. The left circumflex artery courses along the epicardial surface which overlies the approximate endocardial location of the LAA ostium, and was found to be in close relation to this structure in a study of postmortem hearts.[6] In this study, the authors sought to measure the actual distance of the ostium to the coronary artery.[6] This was performed by measuring the distance from the epicardial location, which correlated to the underlying the location of the endocardial ostium, to the epicardial distance to the coronary artery and on average was separated by a small distance of only 11.3 ± 5.2 mm.[6] The importance of this knowledge becomes readily apparent when taking into context situations where an endocardially placed occlusion device can: 1) be too large for the ostium and pose a risk for compression of the device on the circumflex artery, or 2) cause overdistention of the LAA and poses a risk for perforation[6, 7]

Epicardial/Endocardial Relationship Of The Left Atrial Appendage To The Left Superior Vena Cava And Left Superior Pulmonary Vein

In early embryologic life, the mere presence of blood flowing through the left superior vena cava results in an indentation at a fairly distinct location in between the left atrial appendage and the left superior pulmonary vein.[38] As a result, in adult life, where most patients have a regressed left superior vena cava, an indentation persists between the left atrial appendage and the left superior pulmonary vein which houses the vein/ligament of Marshall.[38] This provides two demarcations that can serve as landmarks from both an epicardial and endocardial perspective (Figure 6). From an epicardial perspective, a persistent indentation remains that courses between the LAA and left superior pulmonary vein.[39] From an endocardial aspect, the left lateral endocardial ridge is present and is consistently located endocardially to the vein of Marshall; this structure separates the appendage ostium from both the left superior and inferior pulmonary vein ostia.[38, 39] Furthermore, potential damage to the left superior pulmonary vein exists with intervention of the LAA during exclusion procedures. This is due to the close proximity of the pulmonary vein to the LAA, which lies directly anterior to this structure.[38] The distance found between the LAA and the left superior pulmonary vein was found in a study of post-mortem human hearts to be 11.1 ± 4.1 mm.[6]

Relationship Of The Left Atrial Appendage Ostium And Mitral Valve

The mitral valve lies inferior to the ostium of the left atrial appendage, along with an interspaced vestibule between these two structures.[28] The mitral valve is therefore at potential risk for damage during any endocardially based procedure as it can be compressed from an oversized device, or simply because of the tight spacing that may exist between these two structures.[6] One study has shown that the average distance between the mitral valve and ostium of the appendage was 10.7 ± 2.4 mm.[6] It is therefore a critical structure for visualization during procedures and should be monitored for dysfunction or device interaction prior to final deployment as well as post-procedurally for surveillance.[40]

Conclusions

In this review we focused on providing the invasive electrophysiologist with an appreciation of the LAA, with special emphasis on its magnificent abilities ranging from its unique cellular properties that are critical in development and endocrine regulation, difficulties that face proceduralists when attempting to match the correct approach and device to highly variable individual patient LAA morphology, and to highlight the extremely important spatial anatomy surrounding the LAA that can be damaged during procedures. Though many advances have been made in this field and innovations continue to abound at a tremendous pace, a well-developed knowledge of the anatomy and physiology of the LAA, including the variations that must be assessed on a case-by-case basis, can increase the safety and efficacy of LAA exclusion procedures.

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Pre-Implant Assessment For Optimal LV Lead Placement In CRT: ECG, ECHO, or MRI?

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Abstract

Cardiac resynchronization therapy (CRT) improves cardiac function in many patients with ventricular dyssynchrony. The optimal use of imaging for pre-implantation assessment remains a subject of debate. Here, we review the literature to date on the utility of echocardiography and cardiac MR, as well as conventional ECG, in choosing the best site for LV lead implantation. Prior to the use of imaging for pre-implantation evaluation, LV leads were placed empirically, based on average responses from population-level studies. Subsequently, patient-specific approaches have been used to maximize response. Both echocardiography and cardiac MR allow determination of areas of latest mechanical activation. Some studies have found improved response when pacing is applied at or near the site of latest mechanical activation. Similarly, both echocardiography and cardiac MR provide information about the location of any myocardial scar, which should be avoided when placing the LV lead due to variable conduction and high capture thresholds. Alternative approaches include targeting the region of latest electrical activation via measurement of the QLV interval and methods based on intraoperative hemodynamic measurements. Each of these modalities offers complementary insights into LV lead placement, so future directions include multimodality pre-implantation evaluation, studies of which are ongoing. Emerging technologies such as leadless implantable pacemakers may free implanting electrophysiologists from the constraints of the coronary sinus, making this information more useful and making non-response to CRT increasingly rare.

Introduction

Ventricular dyssynchrony is a primary electrical disease caused by deficits in infrahisian conduction that results in mechanically inefficient cardiac pump function. Ventricular dyssynchrony, typically manifest in the form of left bundle branch block, affects roughly one-third of patients with symptomatic heart failure.[1] The consequences of such include depressed ejection fraction, decreased exercise tolerance, and increased mortality.[2, 3] In patients with LBBB, activation of the left ventricular lateral wall is delayed. The result is that early in systole, unopposed ventricular septal contraction generates stretch of the still quiescent lateral wall; in late systole, delayed lateral wall contraction occurs against an already pressurized blood pool, resulting in increased wall stress, poor mechanical function, and even aberrant myocardial expression of a variety of proteins including mediators of stress response, calcium handling, and myocyte coupling.[4–6]

Cardiac resynchronization therapy (CRT) is a pacing-based approach to treat patients with ventricular dyssynchrony. Pacing of the late-activated lateral LV to resynchronize ventricular activation has been demonstrated to improve both echocardiographic parameters (LVEF, LVESV, LA volume) and physiologic measurements (max dP/dT) of left ventricular function, as well as clinical outcomes, including NYHA class, six-minute walk time, frequency of arrhythmias, quality of life, hospitalizations for decompensated heart failure, and mortality.[7–13] CRT has proven to reduce morbidity and mortality in patients with severe symptomatic CHF and LBBB, and in patients with more mild CHF symptoms.[8, 14–16]

However, even in trials with appropriate patient selection (LBBB, systolic dysfunction), there continues to be a substantial minority of patients who derive limited benefit from CRT--the so-called non-responders. Depending on the criteria used to determine response, whether echocardiographic, clinical, or biochemical, between 20% and 50% of patients are non-responders.[17] Reasons for non-response may be multifactorial, and likely arise in part from interplay between the site of pacing and the particular substrate (i.e. scar burden, patterns of conduction) being paced.

There are two approaches to CRT lead placement--anatomic and patient-specific. Early studies investigated which anatomic sites produced the best response on a population level. Briefly, they found that basal and lateral sites produced better responses than apical and septal sites.[18] Subsequently, newer studies have incorporated patient-level data, usually imaging, in seeking to find the best sites for the patient at hand. Imaging modalities are used to avoid regions of scar and to target either regions of latest electrical activation or regions of latest mechanical activation. The purpose of this review is to consider different imaging modalities – ECG, echo, and MRI – and their role

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(if any) in the delivery of CRT.

Empiric Lead Placement

Early studies in CRT efficacy as a function of pacing site found that left lateral and posterolateral pacing resulted in greater improvement in pump function than anterior or septal pacing.[10, 18] For years, then, operators implanting LV pacing leads targeted lateral and posterolateral CS tributaries. More recently, a number of studies have suggested that there may be significant patient heterogeneity in optimal pacing sites. Bordachar and colleagues found, in a small series of patients with non-ischemic CMP, that there were frequently patients with optimal LV function attained by pacing non-traditional sites.[19] In a complimentary series of patients with ischemic CMP, Spragg and colleagues found similar results – namely, that there was significant inter-patient heterogeneity in terms of LV pacing sites that yielded optimal LV pump function.[20] Finally, in a larger series of patients receiving CRT for more mild CHF symptoms, Singh and colleagues found that clinical response among patients with anterior, lateral, or posterolateral sites was similar.[21] Apical pacing, though, clearly predicted worse outcomes in this large series of patients.

Based on these trials, many practitioners continue to target lateral and posterolateral pacing sites, delivering therapy that, at the population level, leads to good results in the majority of patients. However, persistent issues with non-response, as well as the desire to maximize response in an individual patient, has led to a broad area of investigation into targeted, patient-specific LV lead placement. Typically that tailored therapy is based on imaging of scar, of mechanical activation timing, and (during implant procedures) of local electrical activation timing as well.

Pre-Implantation Evaluation Modalities

The three main modalities employed in pre-implantation evaluation to guide placement of the coronary sinus lead are ECG (including both twelve-lead and more extensive body-surface mapping), echocardiography, and MRI. In general, the response to CRT is greatest when biventricular pacing serves to make the left ventricular contraction as synchronous as possible. The two criteria for pacing sites that might be predicted to optimize CRT response include (1) pacing at live, non-scarred, myocardium, and (2) pacing at the area of most delayed mechanical contraction or electrical activation. Echocardiography and MRI elucidate both regions of latest mechanical activation and areas of scarred, non-contractile myocardium. In contrast, ECG excels in determining the regions of latest electrical activation; it has some abilities to localize scar, but generally with insufficient spatial resolution to guide lead placement.

Eligibility For CRT And Non-Response

The use of advanced pre-implantation evaluation modalities to optimize LV lead placement assumes appropriate initial patient selection for CRT. While novel screening measures for CRT candidacy have been explored, the simple surface ECG remains the most commonly used and reliable tool for determining likelihood of CRT response. In patients with severe CHF symptoms, LBBB morphology and QRS width > 150ms have been shown to predict greatest likelihood of CRT benefit. Narrower QRS width and/or non-LBBB morphology, while not prohibitive, have been associated with lower response rates. In patients with modest heart failure symptoms, non-LBBB morphology has been shown to predict minimal CRT response, and potentially even harm from LV pacing. Current guidelines emphasize the results of these studies in determining eligibility for CRT (see Figure 1, adopted from 2013 Appropriate Use Criteria).[22]

Avoiding Scar

Patients with ischemic cardiomyopathy, by definition, have fibrosis and scarring of ventricular myocardium. Patients with non-ischemic cardiomyopathy, too, have been shown to have significant burdens of ventricular scarring.[23] In all patients undergoing CRT implant, then, there is the potential for complex patterns of scar generating lines of conduction block, unpredictable patterns of wave front propagation from LV pacing sites, and the possibility of diminished response to CRT. Some studies have shown that global scar burden predicts a worse outcome than that accounted for by the decreased LVEF alone, suggesting the electrical abnormalities in scarred myocardium pose an additional burden.[24,25] In addition, several studies have demonstrated that pacing near scar is associated with worse outcomes[26] presumably secondary to the unpredictable patterns of regional conduction, variable latency, and high thresholds that are characteristic of regions of myocardial scar.

Both echocardiography and MRI help localize regions of scar so that leads can be placed over healthy myocardium. On echocardiography, the ventricular wall must thicken by at least 10% with electrical activation to provide evidence of functioning myocardium. Several studies have found that this degree of thickening on echo is well-correlated with uptake on technetium scan, implying that the tissue at hand is metabolically active and not scar. On MRI, myocardial scar burden can be quantified and compared between potential target regions using late gadolinium enhancement. The fact that echocardiography and MRI are able to localize myocardial scar is an important point that argues for inclusion of at least one of these imaging modalities in preoperative planning, as neither the surface EKG nor intraoperative capture threshold measurements are sufficiently accurate at localizing myocardial scar and avoiding the problems that follow pacing in adjacent regions.

Some studies have shown convincing evidence that avoiding regions of scar is an important component of optimizing CRT response.[27, 28] While the major focus of these trials was to target latest mechanically activated regions of myocardium, as assessed by echocardiography, LV lead placement was also steered away from regions of myocardial scarring. The suggestive results of those trials (described in more detail below) may be in part due to avoidance of pacing in regions of ventricular scar.

Strategies For Pacing At The Site Of Latest Mechanical Activation

Ventricular dyssynchrony represents the variability in time of contraction between the different regions of the ventricle. Intuitively, pacing at the site of latest mechanical activation is appealing as a strategy for optimizing CRT response. There have been a number of efforts to use either echo or MRI-based ventricular imaging protocols to guide CRT therapy, with variable results.

Initially, studies utilizing tissue Doppler echocardiography to guide lead placement were disappointing, including the PROSPECT trial.[29] Although utilizing echocardiography to predict response to CRT is intuitively appealing, since the correction of dyssynchrony is the mechanism by which CRT benefits patients, investigators found that echocardiographic measures of dyssynchrony added little predictive power in patients who met standard indications for CRT. Several prospective, randomized studies have since demonstrated clinical

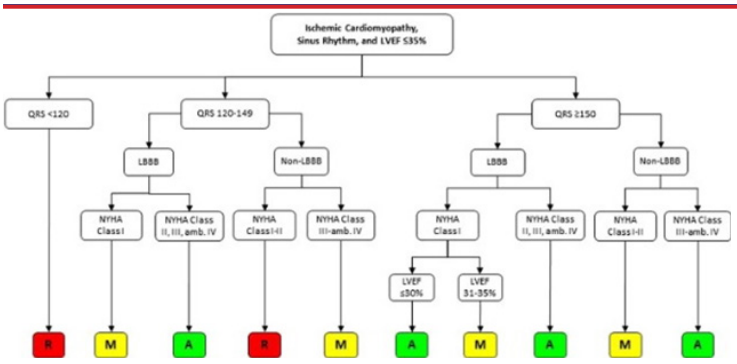

Figure:1 **Appropriate use criteria for CRT in patients with ischemic cardiomyopathy (adopted from Reference 22). A = appropriate; M = may be appropriate; R = rarely appropriate.**

improvement when echocardiographic measures of latest ventricular activation as seen through speckle-tracking are used to guide CS lead placement. The TARGET study randomized patients to either lead placement informed by speckle-tracking echocardiographic measures of latest ventricular activation (latest site of peak contraction with an amplitude of greater than 10%, i.e. latest-contracting myocardium that was not scar) versus routine, non-guided lead placement.[27] The result was clinically significant, with 70% of patients in the echo-guided arm meeting the primary endpoint of at least 15% reduction in left ventricular end-systolic volume (LVESV), in contrast to the 55% of patients achieving this in the control arm. Patients who underwent echo-guided lead placement also had fewer heart failure-related hospitalizations and decreased all-cause mortality. The STARTER trial was similarly designed and yielded concordant results, demonstrating decreased combined all-cause mortality and hospitalizations for heart failure among patients in the echo-guided arm.[28] See Figure 2 for an example of speckle tracking to identify site(s) of latest activation, as performed in the STARTER trial.[28] It should be noted that in both trials, the combined endpoint of death and CHF hospitalization (a secondary endpoint in TARGET and the primary endpoint in STARTER) were reduced, but that the reduction was driven entirely be lowering of CHF events rather than mortality. These studies, while promising, were limited in terms of sample size, number of participating centers, and need to be validated by broader investigations.

MRI has also been used to localize the regions of latest mechanical activation and guide LV lead placement. Compared to echocardiography-based lead placement studies, MRI is not as well-developed, but it remains promising.[30] Feasibility studies have proven that MRI-guided lead placement is possible,[31, 32] but randomized clinical trials demonstrating improved outcomes using this modality in contrast to empiric lead placement or echocardiography-based lead placement are still in progress.[33] MRI has also been used to quantify dyssynchrony and studies have shown that the degree of intraventricular dyssynchrony, as measured by the time-delay between earliest and latest regions of radial mechanical activation, has value as a predictor of morbidity and mortality, even with CRT.[34] One interesting finding of this study is that there appears to be an upper limit of mechanical dyssynchrony that can be corrected by CRT--patients with the highest ventricular dyssynchrony not only fared the worst, but also experienced no increase in LVEF with CRT. Prior investigators have come to similar conclusions.[35] The characteristics of the dyssynchrony, including the regional circumferential strain, can predict improvements in functional class with CRT, so MRI may have some added value in predicting outcomes over and above any utility in guiding lead placement.[36]

It should be noted, however, that although speckle-tracking echocardiography and MRI can be used to determine the site of latest ventricular mechanical contraction, implanting electrophysiologists are constrained by the distribution of the CS tributaries. Consequently, knowing the region of latest mechanical activation is necessary but not sufficient for pacing near sites of greatest mechanical delay. In fact, subsequent analysis of the results of the STARTER trial found a graded clinical response that varied as a function of the distance between the echocardiographically-demonstrated point of latest ventricular mechanical activation and the final location of the CS lead.[37] An alternative approach that may work better within the confines of the CS relies on finding the area of latest electrical activation.

Strategies For Pacing At Sites Of Latest Electrical Activation

The two main modalities available for determining the site of latest electrical activation include intraoperative measurements of the electrical delay with the catheter positioned in the various CS tributaries and inverse electrocardiographic imaging using body-surface mapping electrodes.

The most commonly employed method of finding the area of most delayed ventricular electrical activation involves intraoperative measurements of the QLV interval in each of the CS tributaries. The QLV interval is defined as the time elapsed between the beginning of the QRS complex on surface ECG and the onset of the sensed electrogram at the LV lead as a fraction of the total QRS interval. This approach has been validated and studies have shown that placement of the CS lead at the site of longest QLV interval was correlated with improved hemodynamics, including higher maximum dP/dT.[38] In addition, a substudy of the SMART-AV trial showed that the length of the QLV interval is predictive of response to CRT, in that patients with greater electrical dyssynchrony reflected by a longer QLV interval experience more improvement with CRT.[39] Similar results were observed in the MADIT trial.[21] This method has the benefits of requiring minimal additional intraoperative time and no ancillary studies such as speckle-tracking echo or cardiac MRI. The fact that the QLV interval can only be measured in the tributaries

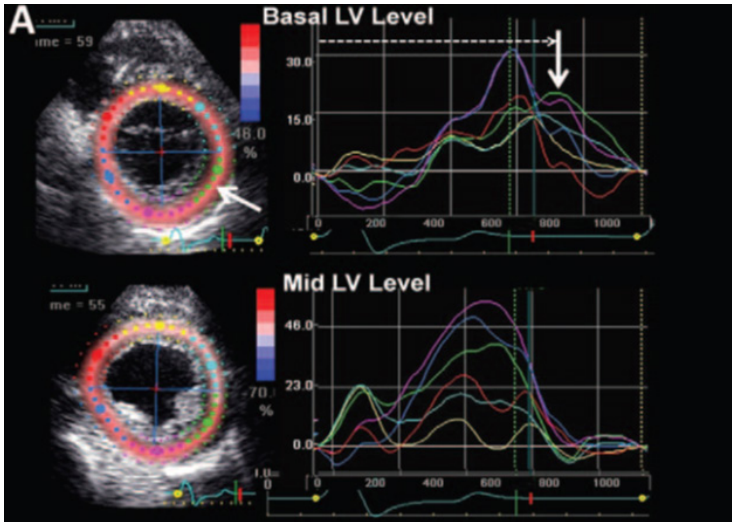

Figure:2 **An example of speckle tracking to assess sites of latest mechanical activation (white arrow), from the STARTER trial (Reference 28).**

of the CS which are catheter-accessible is not a disadvantage of the method because it is only those catheter-accessible regions that are available for placement of the CS lead. Currently, several additional studies are underway correlating QLV interval as measured at the CS lead and clinical and echocardiographic response to CRT.

Inverse electrocardiographic imaging (iECG) serves to non-invasively estimate the electrical potentials along the epicardial surface to determine the patterns of conduction delay, thereby inferring optimal locations for lead placement based on areas of latest electrical activation. Compared to the other modalities discussed above, iECG is earlier in development and in application to patients in clinical studies.

Combined And Alternative Approaches

Since these modalities for pre-implantation assessment have complementary strengths, a multimodality approach is currently being trialed, comparing QLV-guided LV lead placement with image-guided placement using speckle-tracking echo, SPECT, and cardiac CT.[40] Although the imaging will facilitate pacing at sites of latest electromechanical activation and this is preferred to deciding based on population-level data, even better outcomes may be achieved when the entire endocardial surface is surveyed for optimal response via intraventricular roving catheter. In our institutional experience, 8 of 11 patients who underwent intraoperative hemodynamic measurements while being paced at various endocardial surfaces were found to have an optimal pacing site that was not at traditionally used locations for LV pacing.[20] While previous investigations have partially attributed this differential response to endocardial versus epicardial pre-excitation,[41, 42] we found that the improved hemodynamic response was due to more choices in locating the optimal site, rather than endocardial pacing per se; pacing at endocardial sites adjacent to epicardial sites yielded similar hemodynamic results. While promising, the relationship between optimal intraoperative hemodynamic response and long-term clinical outcomes needs further exploration. Notably, determination of optimal pacing site is of limited utility as long as operators are constrained by the distribution of the CS.

Conclusions

In most patients, CRT leads to improved hemodynamics, echocardiograpic parameters, and clinical outcomes. Despite this, a subset of patients are non-responders. Even among those who do derive a benefit, we seek to maximize response. To these ends, there may be a role for patient-tailored therapy via image-guided LV lead placement. While LBBB on surface ECG remains critical for identifying patients most likely to benefit, studies to date have demonstrated the incremental value of echo and cardiac MRI in targeting the latest-activated myocardium and avoiding regions of scar. As developing technologies such as multipolar leads, endocardial leads (among the permanently anticoagulated), and fully intracardiac leadless pacemakers become more readily available, our therapeutic armamentarium grows and we will be able to individualize each patient's treatment based on their cardiac anatomy to optimize outcomes.[43,44] The science of patient-specific lead placement remains in its infancy and much work remains to be done, but perhaps one day the concept of "non-responders to CRT" will be obsolescent.

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Very Long-Term Results Of Atrial Fibrillation Ablation Confirm That This Therapy Is Really Effective

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Abstract

Catheter ablation -in general- is a highly effective and "curative" intervention for a broad spectrum of supraventricular and ventricular arrhythmias. After a successful procedure eliminating a simple arrhythmia substrate, the recurrence rate is low and the short term success correlates well with the long term freedom from the arrhythmia.

Introduction

Since the identification of trigger activity in the pulmonary vein by Haissaguerre et a,[12] catheter ablation of atrial fibrillation (AF) has became an established therapeutic modality for the treatment of patients with AF. Published data in the literature suggest that success rates following ablation of AF are relatively favorable (50-70%)[3,4,5] but most studies have reported limited follow-up of 1 or 2 years after the first ablation and the long-term outcomes have not been fully elucidated.

Why do we need more information regarding the long term follow up data following AF ablation, in contrast with conventional ablation procedures?

First, the clinical significance of an AF recurrence is usually more pronounced than other arrhythmias because of the well known deleterious consequences of this arrhythmia, with special attention to thromboembolic complications.

Furthermore, the pathologic mechanism of AF is complex with a special interplay between the triggering structures and a continuously evolving left atrial substrate. Consequently, it is important to analyze the long term response and define the durability of different ablation techniques to achieve a better clinical outcome.

Pulmonary vein isolation (PVI) is the mainstay therapy of paroxysmal AF, but its success is suboptimal in the persistent population.[5,6] Additional ablation techniques have been introduced during the last decade.[5] The AF population is very heterogeneous, with respect to duration and type of arrhythmia, comorbidities etc. On top of that, ablation results may depend on different definition of success, and follow up methods. Consequently, a comprehensive discussion of long term outcome of catheter ablation should include parameters like type of AF, ablation strategies, the use of antiarrhythmic drugs after ablation, multiple procedures, success definitions, the frequency and intensity of arrhythmia monitoring. The aim of the current study is to review the literature and evaluate the very long term success of catheter ablation of AF.

Definition Of Long Term Follow Up

In the 2012 Expert Consensus on catheter ablation of atrial fibrillation,[7] late recurrence of AF is defined as a recurrence after 12 months or more after AF ablation and the long term success is defined as freedom from AF following the 3 months blanking period through a minimum of 36 months There is also consensus that all patients who undergo catheter ablation of AF should be controlled every six months for at least two years. In our review, we defined very long term follow up to be longer than 3 years after the index procedure

Impact Of Type Of AF

Depending on whether patients have paroxysmal (PAF), persistent, or longstanding persistent AF, the outcome of ablation procedures differs considerably. A systematic review and meta-analysis including,[17] mostly retrospective studies published by Ganesan et a[18] demonstrated that the single procedure success for PAF was 68.6 % at 1 year, 61.1% at 3 years and 62.3% at 5 years. After multiple procedures (average 1.45 procedure per patient) 79% of patients were free from AF at 5 years follow-up. Comparing patients with persistent and long-standing persistent AF after a single procedure the results were less favorable, 50.8% at 1 year, and 41.6% at 3 years. After multiple procedures, the success was definitely more promising in this population, 77.8 % in the long term, but only few studies reported the outcome of AF ablation after more than 3 years suggesting that we need more data to definitively assess the very long term efficacy

Disclosures:
None.

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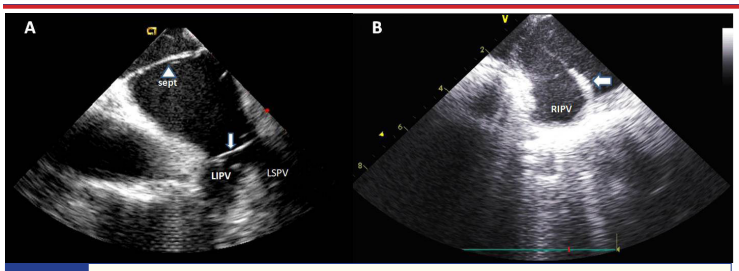

Figure 1: Antral isolation of the left and right pulmonary veins guided by intracardiac echocardiography. Panel A: Lasso catheter was placed in the left common ostium between the left inferior and superior pulmonary vein (white arrow). Panel B: Ablation catheter (white arrow) is touching the right venous carina next to the right inferior pulmonary vein. LSPV: left superior pulmonary vein, LIPV: left inferior pulmonary vein, RIPV: right inferior pulmonary vein, Sept: interatrial septum. Images are originating from the database of Szeged University.

of ablation in persistent atrial fibrillation. The authors concluded that both single and multiple procedure success rates showed adequate stability over 3 years with a significant residual risk for a recurrence and the paroxysmal cohort demonstrated a superior single procedure efficacy. Tzou et al 9 reported an AF freedom, off AAD, of 85% at 3 years and 71% at 5 years, with a 7% per year late recurrence after the first ablation in a mixed paroxysmal and persistent AF population. In a multivariate analysis, persistent AF was an independent predictor for recurrence.

Recently, Steinberg et al.[10] published a large prospective cohort of AF population (72% paroxysmal, 28 % persistent) and followed 445 patients for even a decade after a 1 year complete success following PVI. During a 62 months median follow up, 22 % of patients developed very late arrhythmia recurrence, and the authors demonstrated that the slope of the recurrence curve declined linearly. When they analyzed the differences in outcome on the basis of the arrhythmia pattern before the index ablation procedure, the results were strikingly different. The recurrence rates at 2, 5, an 10 years were 3%, 11%, and 27 % vs 13%, 29%, and 62% for paroxysmal and persistent AF patients, respectively (P< .0001). The authors concluded that the majority of AF patients did quite well over the time, and the ablation results are sustainable even for the long term as well, but using multivariate analysis, persistent AF (hazard ratio 3.08; P< .0001) was an independent risk factor for recurrence of AF.

An interesting question concerning the long term recurrence and efficacy of the ablation procedure whether these interventions can prevent progression of the arrhythmia from paroxysmal to persistent form. In the study of Takigawa et al3 during a median follow up of approximately 48 months, AF progressed from paroxysmal to persistent in 1.2 % of patients in accordance with previous investigations where the AF progression rate was similar (1.5% -3%).11,12 In contrast, the results of pharmacologic therapy are definitely worse, the reported rates vary between 5.5% and 15%/ year.13,14 These observations suggest that the interventional therapy is better than drugs alone for preventing AF progression, which is an important aspect of long term consequences of the arrhythmia.

Impact of Ablation Techniques

Whereas a consensus has been reached on the suitable approach for ablation of patients with paroxysmal AF[7,] no such consensus exists for patients with persistent and long lasting persistent AF regarding the optimal technology of treatment.

Numerous clinical trials demonstrated that the main mechanism of AF recurrence after PVI in the paroxysmal population is the resumption of electrical conduction between the veins and left atrial muscle. This statement is true for either the short or the long term recurrences (see below).[8,15] Based upon these observations we should assume that at least in PAF, the durability of venous isolation and therefore permanent electrical disconnection plays a crucial role in maintaining procedural effectiveness in the long term. Accordingly, any kind of procedural tool or technique which can facilitate the durable isolation of pulmonary veins can be useful.

Segmental PV ablation or wider continuous circumferential antral ablation, two different procedures which have been used most commonly in clinical practice showed different outcomes. Sawhney et al[16] reported that 86% of the patients were free from AF at 1 year follow up after segmental pulmonary vein isolation, with 79%, and 56% free at 2 and 5 years respectively. A meta-analysis done by Proietti at al[17] including[12] studies that compared the effectiveness of wide antral versus segmental pulmonary vein isolation concluded that PVI performed with a wide antral approach is more effective than ostial PVI in achieving freedom from atrial tachyarrhythmia recurrence at long-term follow-up (OR, 0.33; 95% CI, 0.24-0.46; P< .00001). They excluded the studies in which electric isolation was not assessed or if different catheter technologies were used. Ganesan et al[8] also investigated if there is a statistical difference in outcomes of segmental PV isolation compared with wide antral circumferential ablation. The conclusion here was no, but they included also the studies with wide circumferential ablation without assessing the isolation of the pulmonary veins.

An alternative energy source that has been developed to overcome some of the disadvantages of radiofrequency ablation is cryoenergy using a balloon based technology. A comparison (1:1 propensity score match) between cryoballoon and radiofrequency ablation showed similar long term success rates with a recurrence rate of 45 % in both groups after a two-year follow-up 18. Neumann et al[19] reported freedom from AF in 74% of patients with paroxysmal AF and 42% with persistent AF, but the follow up time was shorter. Cryoablation is a new technology and it is under continuous development, but whether it can improve very long term outcomes has to be investigated in the future.

As mentioned earlier, in patients with persistent and longstanding persistent AF the data concerning the outcomes are considerably less favorable than for PAF. The wide contrast in PVI success rates between paroxysmal and persistent AF suggested that the mechanisms can be substantially different, and probably related to electrophysiological and structural remodeling of left atrial substrate. Not surprisingly,

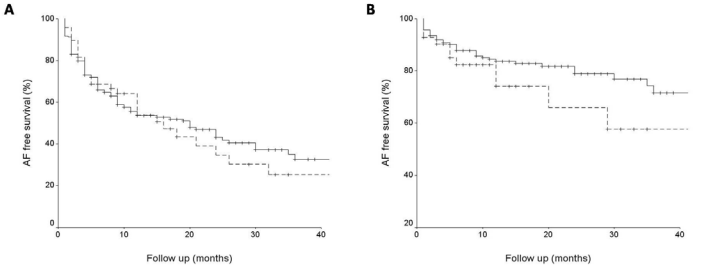

Figure 2: Kaplan-Meier curve representing the arrhythmia free survival after single ablation procedure (Panel A) and following multiple ablation procedures (Panel B) in patients with paroxysmal (solid lines) vs persistent atrial fibrillation (broken lines). Data are originating from the database of Szeged University

current approaches designed to target persistent AF are mainly based on modification of the atrial substrate, but exhibit remarkable differences, and a widely accepted uniform strategy is missing.

Different ablation strategies, including the ablation of complex fractionated atrial electrograms (CFAEs),[20] linear lesions in the left atrium,[21] ablation at the maximal high dominant frequency spots,[22] rotor ablation[23] have been developed as an add-on to pulmonary vein isolation to improve the outcome in this group. PVI alone can be sufficient to maintain sinus rhythm in 21% of patients after a single procedure and in 43.2% after 1-3 procedures in a retrospective analysis6. The same 21-22% success with a single procedure and 37-43% success rate after repeat procedures was published by Brooks at al[5] in a review of 32 studies. They also reported the success rate of other techniques: linear ablation in addition to PVI (11-74%), posterior wall isolation (42-50%) CFAE ablation (36-68%) or "stepwise" ablation approach (38-62%). The integration of repeat procedures and addition of previously ineffective antiarrhythmic drugs further improved clinical success. The variation in the success rate suggests that the best approach in this group is still unclear. However, persistent and long-standing persistent AF can be treated with a relatively high success rate during rather a medium term follow up, since really long term data are still lacking.

Our approach is wide area antral circumferential ablation for paroxysmal and persistent patients as well, with complete isolation of pulmonary veins, without creating additional lesions in the left atrium. During the procedures we use open irrigation radiofrequency catheters and a combination of EAM and intracardiac echocardiography (Figure 1) to enhance the anatomical orientation and the monitoring of catheter-tissue contact. After a mean of 18 months follow up time the recurrence rate after single procedure was 52% and 61%, after multiple procedures was 19% and 29%, in a paroxysmal and persistent cohort respectively (Figure 2).

Impact of Follow up Techniques

Apart from the above mentioned factors, the varying results reported by those studies could be attributed to substantial differences in follow up methods. During the first year, the majority of studies performed clinical examination, electrocardiogram and 24-hour Holter monitoring or event recorders at 3, 6, and 12 months. Beyond the first year, the intensity of follow up is usually reduced to 1 or 2 outpatient visits per year or even based on data from referring clinicians.[24] There is a clear positive correlation between the duration and intensity of the follow-up and the arrhythmia detection rate.[25] For the short term follow up, 7 day Holter and transtelephonic monitoring are proven to be effective to detect asymptomatic AF episodes. Piorkowski et al.[25] showed that using serial 7 day Holter and transtelephonic monitoring, the „real" procedural success rate decreased from 70% to 50% and 45 % respectively.

The definition of long term ablation success remains controversial because current post ablation rhythm monitoring strategies are based on symptom and/or intermittent ECG recordings and thus probably underestimate the real rate of AF recurrences.[26] Continuous monitoring like implantable loop recorders are useful tools[27] but to put these devices into an everyday practice is limited by cost, patients compliance and high burden of false detection.

Predictors And Mechanism Of Recurrence

As we suggested earlier, the success of catheter ablation may depend on technical aspects of the procedure but also on patient

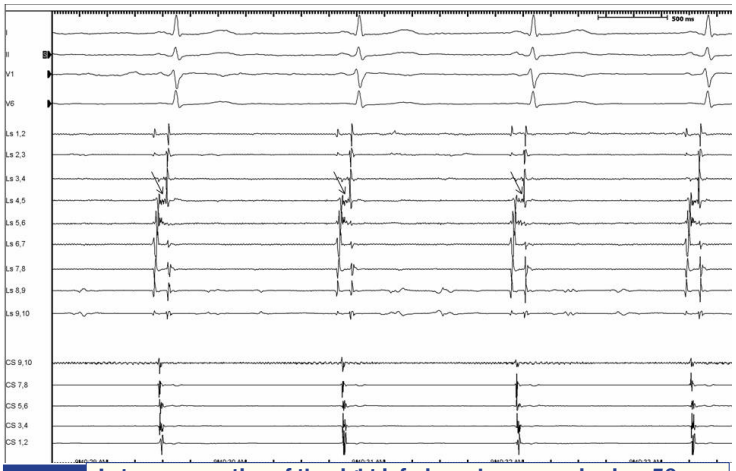

Figure 3: **Late reconnection of the right inferior pulmonary veins in a 56 years old patient with PAF following 32 months the index PVI. Single ablation attempt at the level of earliest PV potentials on Lasso 4-5,bipoles (arrow) resulted immediate isolation of the vein. All of the other pulmonary veins were isolated. Surface ECG leads I, II, V1 and V6, together with intracardiac recordings from the Lasso catheter (Lasso) placed in the right inferior pulmonary vein, and from the proximal to distal coronary sinus bipoles (CS). Tracing is originating from the database of Szeged University.**

related factors. Patients in whom AF recurred, exhibit specific clinical characteristics which can be considered as independent predictors of late AF recurrence. Some studies reported history of persistent AF as a predictor of very late recurrence[8,9,10] while other studies found that there was no significant association between the AF type and risk of recurrence.[15,28] The heterogeneity in results across the studies can be explained by the heterogeneous definition of AF type and the differences in terminology pertaining to "long term" follow up. The duration of AF history is a very important predictor of AF recurrence,[3] but other studies could not find a significant association between AF duration and AF recurrence.[29,30] A possible explanation is that duration of AF does not necessarily correlate with the length of the AF episodes and may not reflect the extent of atrial remodeling.[31] Other commonly identified predictors of AF recurrence are age > 65 years, left atrial diameter >24mm/m^2,31 left ventricular systolic dysfunction, heart failure, structural or valvular heart disease,8 hypertension and hyperlipidemia.[15] These observations indicate the role of enhanced vulnerability of left atrial myocardium induced by these factors beyond the importance of trigger mechanism. Aggressive medical treatment of these conditions and risk factors reduction[32] may improve the efficacy of AF ablation. Pathak et al[32] reported in a recent publication that risk factor management according to American Heart Association/American College of Cardiology guidelines significantly improved the outcome of AF ablation in terms of AF burden and also generated favorable changes in cardiac remodeling.

The main mechanism of the early recurrence following atrial fibrillation ablation is the reconnection of previously isolated pulmonary veins. In contrast, in patients with very late recurrence the mechanism is not completely elucidated. Lin et al[33] found that the majority of patients with recurrent AF undergoing a 3rd or more procedure after a mean follow up of 36±22 months (range 12 to 119 months) had reconnected pulmonary veins with triggers originating from the culprit PVs. (Figure 3). However, in 20% of patients, new non-PV triggers were identified at the time of 3rd or 4th procedure

and the majority of non-PV triggers were mapped in the right atrium or coronary sinus. Steinberg at al[10] also found that in patients undergoing reablation for very late AF recurrence, just 4% of PVs were completely isolated. Conversely, Sotomi at al[34] found that the prevalence of PV reconnections and trigger PV reconnection were significantly lower in the very late recurrence group (>12 months, 69%) than in the late recurrence group (3-12 months, 90%) and also more patients required non-PV trigger ablation. In accordance with this observation, Kurotobi at al[35] demonstrated that the presence of residual arrhytmogenic non-PV foci are associated with an increased long term recurrence rate after successful isolation of PVs and left atrial linear lesions in a long-standing persistent AF population.

Conclusions

During the last decade, numerous data became available regarding the long term efficacy of the interventional treatment of atrial fibrillation. These data can be especially important for estimating prognosis, evaluation of currently available ablation techniques, and last but not least for the reimbursement policy of procedures. If we summarize the results of mostly retrospective analyses, we can conclude that long term freedom from AF is achievable and maintainable over 2-3 years or even more with mild increases in arrhythmia recurrence over the time. This statement is especially true for the paroxysmal AF population, following initial PVI procedures. Single procedure success rate is definitely lower in the long term, so for achieving a durable result, multiple procedures have to be taken into account. The success of an ablation procedure is less encouraging in the persistent population, moreover there is no real consensus regarding the best ablation strategy beyond PVI, to improve the long term efficacy rate.

It is likely that the main mechanism behind very late recurrences of AF is the PV reconduction and recurrent pulmonary vein triggers, but progressive remodeling of left atrial substrate as well as non-PV triggers can play an important role over time, especially in the persistent AF population.

It should be noted that strict AF free success rates in both groups probably underestimate the real long term clinical benefit of the procedures if we focus on symptomatic improvement or fewer hospitalizations. Furthermore, it can not be overemphasized that studies demonstrating very different results regarding the outcome of procedures are showing significant heterogeneity in terms of the definition of success, methodology of follow up, and the applied ablation technologies.

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