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Happy Holidays !!

Dear Colleagues

We thank you for your continued interest and patronage of the Journal of Atrial Fibrillation. We appreciate your patience in enduring some of the hiccups we had in the submission and review process. Starting January 1st, we will be upgrading our site to ensure easier submission, navigation and communication. We also had some technical glitches in the PUBMED uploading software. These issues have been addressed and you should see significant changes on these fronts.

Hope you had a great Thanksgiving weekend. With the Holidays, close by we are sure the clinical activity is in high gear. December is probably going to be relatively quiet from the stand point of academic activity. We will probably see some of you at the AF, VT and VF Symposium in Chicago this weekend.

In this issue of the Journal, we have several exciting articles ranging from atrial fibrosis and left atrial appendage leak closure. As always, we strive to bring high quality educational material to you. We encourage you to consider JAFIB to publish your work. If you are interested in contributing some high value review articles we will be happy to feature them in the upcoming issues of the journal.

We wish you a Merry Christmas and Happy Holidays.

Have a great summer.
Best wishes

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Arrhythmia-Induced Cardiomyopathy: Prevalent, Under-Recognized, Reversible

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Abstract

Arrhythmia-induced cardiomyopathy (AIC) is a clinical condition in which a persistent tachyarrhythmia or frequent ectopy contribute to ventricular dysfunction leading to systolic heart failure. AIC can be partially or completely corrected with adequate treatment of the culprit arrhythmia. Several molecular and cellular alterations by which tachyarrhythmias lead to cardiomyopathy have been identified. AIC can affect children and adults, can be clinically silent in the form of asymptomatic tachycardia with cardiomyopathy, or can present with manifest heart failure. A high index of suspicion for AIC and aggressive treatment of the culprit arrhythmia can result in resolution of heart failure symptoms and improvement in cardiac function. Recurrent arrhythmia, following recovery from the index episode, can hasten the left ventricular dysfunction and result in HF, suggesting persistent adverse remodeling despite recovery of left ventricular function. Several aspects of AIC, such as predisposing factors, early diagnosis, preventive measures to avoid adverse remodeling, and long-term prognosis, remain unclear, and need further research.

Clinical Vignette 1:

Especially, A 53-year-old man with history of severe mitral regurgitation and paroxysmal atrial fibrillation (AF) with preserved left ventricular ejection fraction (LVEF) undergoes mitral valve repair and MAZE procedure and presents a year later with a 2-month history of progressive fatigue, exertional dyspnea, and dry cough. His blood pressure was 116/74 mm Hg and, heart rate (HR) was 95 beats per minute (bpm). Physical exam revealed an irregular rhythm, bibasilar lung crackles and peripheral edema. Echocardiogram showed normal mitral valve function left ventricular (LV) end-diastolic dimension of 6.3 cm with severe LV dysfunction (LVEF 20-25%) and global hypokinesis. Coronary angiogram showed no obstructive disease. A 12-lead electrocardiogram (ECG) is shown [Figure 1].

What is the optimal management strategy for this patient?

Introduction

Heart failure (HF) is increasing worldwide and identifying a potentially reversible cause for HF and cardiomyopathy (CMP) can lead to appropriate management with improvement in symptoms and LVEF.[1] Arrhythmia-induced cardiomyopathy (AIC) is an important, potentially reversible cause of HF. The first description of AIC dates back to 1949 when Philips and Levine recognized that rapid AF can lead to HF in patients with otherwise normal hearts.[2] Despite the awareness in medical literature for many years, AIC still remains under-recognized.

AIC can be defined as a clinical entity in which a pathologic tachyarrhythmia or frequent ectopy ultimately leads to LV dysfunction and systolic HF.[3] Cardiomyopathy from arrhythmias can happen de novo in a structurally normal heart (arrhythmia-induced) or can be superimposed on pre-existing structural heart disease (arrhythmia-mediated).[1] The characteristic feature of AIC is recovery of LV function, either complete or in part, following elimination or adequate suppression of the arrhythmia.

Causes of AIC:

Several arrhythmias can result in AIC and are listed in [Table 1].[3] A clear threshold HR for development of AIC does not exist; however, several arrhythmia-related factors contribute to AIC.[1] A study in patients with focal atrial tachycardia (AT) showed that those with slower, unremitting tachycardia had a higher risk for developing AIC.[4] In terms of premature ventricular contractions (PVCs), a high daily burden of PVCs appears to be a major predictor for AIC.[5], [6]

Epidemiology

Age is not a barrier for AIC development as it can affect patients in intrauterine life, infancy, childhood and adulthood.[1], [7] The common types of arrhythmias resulting in AIC do differ in adults and children. AIC is most commonly secondary to AF in adults.[8] Atrial ectopic tachycardia (59%) and permanent junctional reciprocating tachycardia (23%) are common causes of AIC in children.[1] AIC can occur in patients with structural heart diseas.[1] as well as in transplanted hearts.[9] Some role for genetic predisposition in development of AIC has been found but literature on this is limited.[1] It is anticipated that several other factors might also be playing a role in patient's

Key Words

Arrhythmia, cardiomyopathy, heart failure, arrhythmia-induced cardiomyopathy, left ventricular dysfunction, recovery.

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predisposition to develop AIC, but are not well understood. It is likely the interplay of arrhythmias and patient characteristics that determine the transition from arrhythmia to cardiomyopathy. In children, about 28% of patients with AET develop AIC.[1] Among the adult population, about 10% of those with focal AT[4], and about 9-34% of those with PVCs or non-sustained ventricular contractions have been shown to develop AIC.[1] There are inherent selection biases in these data. The accurate incidence and prevalence of AIC remains to be defined.

Mechanisms:

Diligent investigations on carefully constructed animal models have helped further the mechanistic relationship between arrhythmia and CMP. Much of the seminal work in this arena was conducted by Dr. Francis Spinale and colleagues[10]-[12], who used a model of rapid-pacing induced CMP. A full discussion of the pathogenetic mechanisms underlying AIC is beyond the scope of this review but a brief overview of the cellular, extracellular, biochemical and contractile changes in response to tachycardia is provided in [Figure 2]. Data from animal models, however, are not easily translated to clinical practice as several gaps in our knowledge exist regarding arrhythmia-specific pathophysiological mechanisms.

Clinical Features:

AIC can have varied presentations. In utero, AIC can present as hydrops fetalis.[7] In children and adults, the presentation of AIC can vary from asymptomatic arrhythmia with cardiomyopathy to end-stage HF. As the name suggests, there are 2 components of AIC- arrhythmias and an unexplained CMP. Arrhythmias may be apparent if the patient has symptoms or already have a pre-existing diagnosis. However, many patients might be asymptomatic from arrhythmias making early diagnosis difficult. Furthermore, expression of symptoms by children might be a challenge in this sub-group of patients. In these patients, AIC may not be detected till manifest HF develops.[1]

The relationship between arrhythmias and CMP can oftentimes create confusion as to whether the arrhythmia is the cause or culprit of CMP. Frequently, arrhythmias are not aggressively treated, resulting in worsening of CMP and HF. The following clinical scenarios should raise suspicion for either arrhythmia-induced or arrhythmia-mediated CMP.

a. Simultaneous presentation of a tachyarrhythmia/frequent ectopy and systolic HF from LV dysfunction in a patient with no prior cardiac disease.

b. Asymptomatic CMP in the setting of a persistent arrhythmia or frequent ectopy.

c. A patient with known structural heart disease or CMP now with worsening LV dysfunction and HF secondary to an arrhythmia.

The above-mentioned case scenarios are not diagnostic for AIC, as all of them could have other causes for HF and/or CMP. But it is crucial that AIC is considered high up in the differential diagnosis list and the arrhythmia managed aggressively given the potential for partial or complete reversibility of HF and LV dysfunction in AIC, irrespective of underlying structural heart disease. In summary, whenever arrhythmias and HF co-exist, one should have a high index of suspicion for AIC and aggressive treatment of both becomes necessary.

The following clinical scenario illustrates the challenges of the above-mentioned possibilities, and the significance of a correct diagnosis.

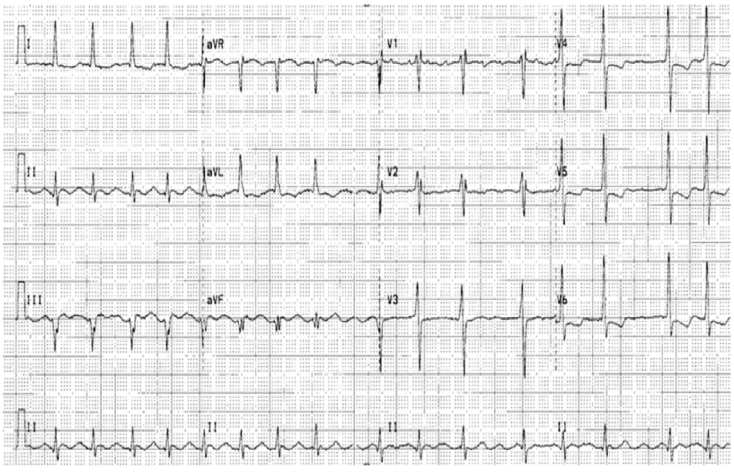

Figure 1: 12-lead ECG showing atrial flutter with variable AV block suggestive of left atrial origin. Ventricular rate is about 95 beats per minute

Table 1: Reproduced with permission from Gopinathannair R et al, JACC 2015 (reference # 1).

Causes of Arrhythmia-Induced Cardiomyopathy
Superventricular
Atrial fibrillation
Atrial flutter
Atrial tachycardia
AV nodal re-entrant tachycardia
AV re-entrant tachycardia
Permanent junctional reciprocating tachycardia
Junctional ectopic tachycardia
Ventricular
Idopathic ventricular tachycardia
Fascicular tachycardia
Ectopy
Frequent premature ventricular contractions
Frequent premature atrial contractions
Pacing
Persistent rapid atrial abd/or ventricular pacing

AV=atrioventricular

Clinical Vignette 2:

A 70-year-old female with history of dilated nonischemic CMP, ventricular tachycardia (VT) by records and status post implantable cardioverter defibrillator (ICD) implantation at an outside hospital 5 years ago, was evaluated for ICD repositioning for radiation therapy for breast cancer. Patient was on digoxin, beta-blocker and amiodarone. Clinical exam was unremarkable. 12-lead ECG showed HR of 64 bpm and no other abnormalities. Echocardiogram showed an LVEF of 60%. (LV end diastolic diameter of 5.1 cm). No arrhythmias were seen on device interrogation. Her ICD generator was removed, amiodarone and digoxin were stopped and lisinopril was added. The patient completed her radiation therapy for breast cancer but few months later, complained of palpitations and fatigue but no HF symptoms. 12-lead ECG [Figure 3] showed sinus rhythm with ventricular bigeminy of a left bundle branch block, inferior axis morphology. A 24-hour Holter monitor showed a PVC burden of 36%. Repeat echocardiogram showed an LVEF of 30% and global hypokinesis.

PVC-mediated AIC was suspected and patient underwent EP

study where PVCs were mapped to the posterior right ventricular outflow tract and was successful ablated [Figure 4]. Her functional capacity significantly improved within a few weeks and TTE 8 months after ablation showed LVEF of 41%. Another TTE performed 28 months after ablation showed complete recovery of LVEF (56%) and right ventricular function. Beta-blockers and angiotensin-converting enzyme inhibitors (ACEI) were continued during this period.

Looking at this case retrospectively, it is likely that her initial diagnosis of dilated CMP and VT was PVC-induced. Amiodarone use might have resulted in decline of her PVC/VT burden leading to improvement of LVEF. The patient developed high PVC burden several months after amiodarone was stopped, resulting in CMP. The longer recovery time for LVEF could suggest persistent ultrastructural changes from her initial diagnosis of CMP.

Diagnosis:

Diagnosis of AIC can be challenging at times. Physical exam findings can often be non-specific and standard imaging may not be able to differentiate AIC from dilated CMP and consequent arrhythmia.

Several studies have reported findings that might help in early

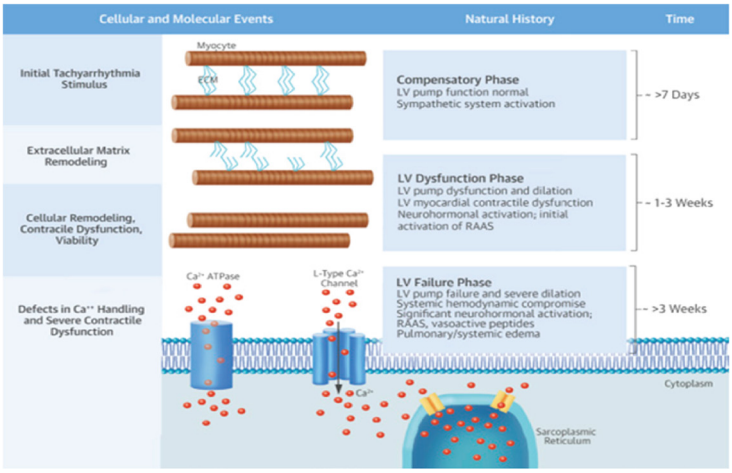

Figure 2: **Figure explaining pathophysiology of arrhythmia-induced cardiomyopathy (AIC).It shows the time course of events that happen in response to rapid pacing in animals. Defects at level of ECM and cellular remodeling, along with defects in handling of calcium by cells and neurohormonal activation ultimately leads to left ventricular dysfunction and heart failure. Reproduced with permission from Gopinathannair R et al, JACC 2015 (reference # 1)**

diagnosis. Absence of late gadolinium enhancement on cardiac magnetic resonance imaging might rule out underlying structural heart disease.[13] LVEDD has been noted to be lower in AIC patients, when compared to patients of dilated CMP.[14] Unipolar electroanatomic mapping can be helpful in differentiating AIC from irreversible CMP patients.[14] It was shown in a study that rapid decline of NT-pro B-type natriuretic peptide levels at one week following arrhythmia suppression favors the diagnosis of AIC.[15] Ultimately, recovery of LV function following successful treatment of the arrhythmias helps confirm the diagnosis of AIC.[1]

Management Strategies:

Management of AIC should involve the following:-

(1) Aggressive treatment of culprit arrhythmia with a goal for cure, (2) Acute treatment for HF, (3) Close surveillance and continuation of standard neurohormonal antagonists as patient's LV function improves over time.

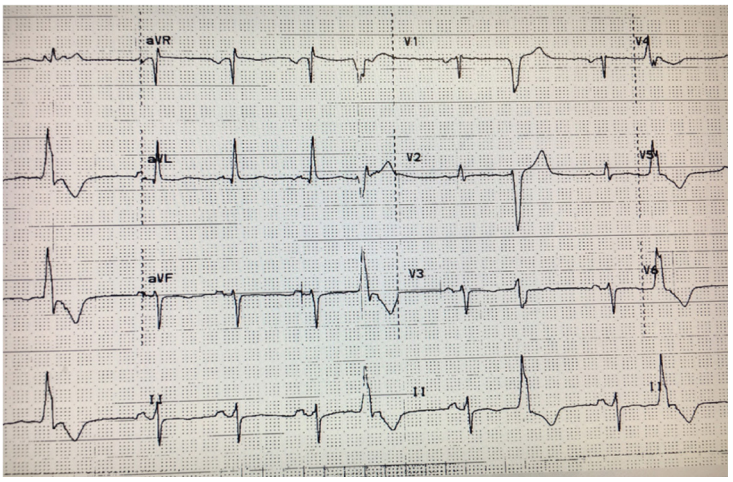

Figure 3: **12-lead ECG showing sinus rhythm with frequent premature ventricular contractions (PVCs) having a left bundle branch block, inferior axis morphology**

Interventions to Control Arrhythmias

This is critical for ensuring recovery and should be done as early as possible in these patients.

Rate Control Therapy

Different agents alone or in combination can be used to achieve rate control in AF. Although lenient rate control (<110 bpm at rest) [16] is comparable to strict rate control, there has been debate over target HR in AIC patients. However, in certain AF patients[17], irregular rhythm by itself can lead to LV impairment despite adequate rate control therapy. Thus, a rhythm control strategy may be needed in a large portion of AF patients.[1]

Rhythm Control Therapy

Rhythm control strategies include electrical cardioversion, anti-arrhythmic drugs (AAD), and catheter ablation. AADs are often used for pharmacologic cardioversion and for maintenance of sinus rhythm. They are also useful for PVC-mediated and other supraventricular arrhythmia mediated AIC if catheter ablation is not feasible, not desired, or was unsuccessful.[1]

A study of 58 patients with AF and HF [18] showed that pulmonary vein isolation improved LVEF and functional status regardless of underlying heart disease and adequacy of rate control prior to ablation. In patients with AF and HF, catheter ablation has also been shown to be more effective than atrioventricular (AV) node ablation and biventricular pacing.[19] A study on 203 patients with persistent AF and HF showed that catheter ablation is better than amiodarone in terms of long-term efficacy and LVEF improvement.[20] Catheter ablation should be considered the treatment of choice for atrial flutter, focal AT and other supraventricular arrhythmia-induced CMP.[1] A meta-analysis of 158 studies [21] showed that catheter ablation has approximately 91% success rate for atrial flutter and a low risk of complications. However, one should follow these patients closely given the risk for development of AF with time. Medi et al has shown excellent results with catheter ablation for focal-AT mediated AIC.[4]

For PVCs, catheter ablation has higher success rates than AADs in reducing frequency of PVCs and in improving cardiac function.[22] PVCs have been associated with poor response to cardiac resynchronization therapy (CRT) in some HF patients. Radiofrequency ablation of PVCs in these patients improves LV function and can enhance efficacy of CRT.[23]

Conflicting evidence exists as to the efficacy of rate versus rhythm

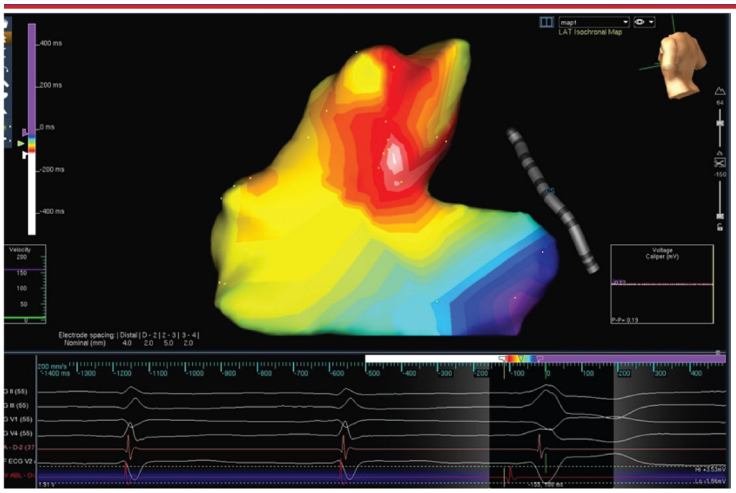

Figure 4: 3D electroanatomic activation map of the right ventricular outflow tract showing the site of earliest activation and successful site of ablation (white colored area) in the posteroseptal right ventricular outflow tract

control for patients with AF and CMP. The AF-CHF trial showed no difference[24] but had several shortcomings when it comes to AIC patients. The CAFÉ-II trial[25] showed that cardioversion and AAD therapy, when compared to rate control therapy, significantly improved LVEF and quality of life in patients with persistent AF and HF. Cardioversion with antiarrhythmic therapy should only be used in atrial flutter patients as an option if catheter ablation is not possible.[1]

Management Strategy for the patient in Clinical Vignette # 1:

The 12-lead ECG [Figure 1] shows atrial flutter with variable AV block and an average ventricular rate of 95 bpm. Flutter wave morphology is positive in V1 and inferior leads and negative in aVL and is strongly suggestive of a left atrial origin, especially given history of prior MAZE procedure. 24-hour Holter monitoring showed average ventricular rate of 114 bpm (range: 91-138 bpm). The patient was already on digoxin and beta-blockers for rate control. In this patient, who now has both atrial flutter and HF, further rate control and titration of HF medications, although needed, may not be enough to improve his symptoms and LV function. Moreover, in atrial flutter, it is difficult to achieve and maintain adequate rate control. Available data would support rhythm control in this situation.

Treatment options including antiarrhythmic therapy with cardioversion as well as catheter ablation were discussed with the patient and patient chose to undergo catheter ablation. Electrophysiology study showed a macro-reentrant left atrial flutter with a critical isthmus localized to the anterior aspect of the left atrial roof [Figure 5]. Catheter ablation at this location terminated the flutter and made it non-inducible. Reconnected pulmonary veins were isolated again. There was complete resolution of HF symptoms following restoration of sinus rhythm. Echocardiogram performed at 3 months post-ablation showed normal LV size and function and with an LVEF of 50-55% Diagnosis of atrial flutter-induced AIC was made. Patient has not had any recurrent atrial arrhythmias over a follow-up period of 3 years.

Therapy for HF

Appropriate therapy for HF is essential in these patients. ACEI and beta-blockers can aid in favorable LV remodeling but the duration of therapy is not well understood.

Continuation of HF therapy as patient's LV function improves over time

Following arrhythmia control, LV function generally improves over time in these patients. Beta-blockers and ACEI have role in favorable remodeling, and it is not very clear as to when they should be stopped after initial LV improvement in AIC patients.[26]

Recovery and Prognosis:

Different studies point to different timelines for recovery of LV function following treatment of the culprit arrhythmia. A study on 24 patients with predominantly AF-mediated AIC showed that LV function improved in a mean of 5.8 months.[8] In a study of PVC-mediated AIC[27], in whom PVCs were adequately treated, 2/3rd of patients recovered LV function by 4 months. For the rest of the group, the time to recovery ranged from 5-45 months. Overall, all patients in the group had LV function improvement. It was noted that late responders of LVEF improvement usually had source of PVCs in the epicardial region.

It has been noted on cardiac imaging that despite improvement in LVEF, LV dimensions remain elevated when compared to age, gender and LVEF matched control group.[28] Moreover, one study reported cases of sudden cardiac death in AIC patients who had already recovered in regards to their LVEF.[8] It was noted that those patients had lower LVEF at presentation as compared to other patients in the study. This raises concern as to whether some degree of negative remodeling persists despite arrhythmia suppression and LV function recovery. This is also illustrated by the evidence that recurrent tachyarrhythmias following initial recovery can result in rapid decline in LVEF.[8] Thus, AIC takes months to years to develop, months to resolve, and recurrent arrhythmias can be calamitous.

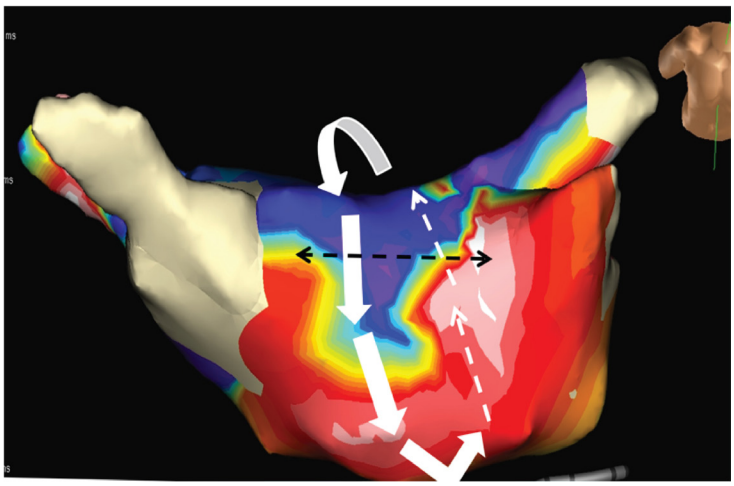

Figure 5: 3D electroanatomic activation map showing a macro-reentrant left atrial flutter with a critical isthmus localized to the anterior aspect of the left atrial roof. Interrupted black lines show ablation line across the roof

Summary

The concept of AIC has been reported several decades ago, but has been more and more recognized recently. The trademark of AIC is the reversal of CMP following suppression or elimination of the culprit arrhythmia, and therein lies the significance of this fascinating disease entity for the practicing clinician. In a world where HF incidence keeps increasing, identifying and treating a reversible cause for HF and CMP is critical and AIC really exemplifies that old adage of "a stitch in time". AIC remains under-recognized, probably diagnosed as idiopathic CMP in many cases with no focused monitoring for

any culprit arrhythmias. In others, arrhythmias are often attributed to structural heart disease and/or HF. It is not to be forgotten that even in patients with a known structural heart disease, like ischemic disease, arrhythmias can worsen CMP and result in HF. A high index of suspicion and appropriate management of these patients can change their lives, as highlighted in the clinical vignettes in this article. However, negative remodeling may persist following initial LV function recovery in AIC patients and recurrent arrhythmias can hasten development of CMP. Close surveillance is thus needed in these patients.

Although significant progress has been made in understanding different aspects of pathogenesis, diagnosis and treatment of AIC, further studies are warranted to thoroughly fill in the gaps in knowledge of this disease entity, mainly with respect to arrhythmia-specific mechanisms, predisposing factors and long-term outcomes.

Disclosures

None.

References

1. Gopinathannair Rakesh, EtheridgeSusan P, MarchlinskiFrancis E, SpinaleFrancis G, LakkireddyDhanunjaya, OlshanskyBrian. Arrhythmia-Induced Cardiomyopathies: Mechanisms, Recognition, and Management. J. Am. Coll. Cardiol. 2015;66 (15):1714–28
2. PHILLIPS E, LEVINES A. Auricular fibrillation without other evidence of heart disease; a cause of reversible heart failure. Am. J. Med. 1949;7 (4):478–89
3. Gopinathannair Rakesh, SullivanRenee, OlshanskyBrian. Tachycardia-mediated cardiomyopathy: recognition and management. Curr Heart Fail Rep. 2009;6 (4):257–64
4. Medi Caroline, KalmanJonathan M, HaqqaniHaris, VohraJitendra K, MortonJoseph B, SparksPaul B, KistlerPeter M. Tachycardia-mediated cardiomyopathy secondary to focal atrial tachycardia: long-term outcome after catheter ablation. J. Am. Coll. Cardiol. 2009;53 (19):1791–7
5. Baman Timir S, LangeDave C, IlgKarl J, GuptaSanjaya K, LiuTzu-Yu, AlguireCraig, ArmstrongWilliam, GoodEric, ChughAman, JongnarangsinKrit, PelosiFrank, CrawfordThomas, EbingerMatthew, OralHakan, MoradyFred, BogunFrank. Relationship between burden of premature ventricular complexes and left ventricular function. Heart Rhythm. 2010;7 (7):865–9
6. Kanei Yumiko, FriedmanMeir, OgawaNaomi, HanonSam, LamPatrick, SchweitzerPaul. Frequent premature ventricular complexes originating from the right ventricular outflow tract are associated with left ventricular dysfunction. Ann Noninvasive Electrocardiol. 2008;13 (1):81–5
7. Krapp M, GembruchU, BaumannP. Venous blood flow pattern suggesting tachycardia-induced 'cardiomyopathy' in the fetus. Ultrasound Obstet Gynecol. 1997;10 (1):32–40
8. Nerheim Pamela, Birger-BotkinSally, PirachaLubna, OlshanskyBrian. Heart failure and sudden death in patients with tachycardia-induced cardiomyopathy and recurrent tachycardia. Circulation. 2004;110 (3):247–52
9. Zwicker C, BeckerM, LepperW, KochK C, WestenfeldR. Cardiogenic shock due to tachycardiomyopathy after heart transplantation: successful treatment with ivabradine. Cardiology. 2010;116 (3):174–7
10. Spinale F G, CokerM L, ThomasC V, WalkerJ D, MukherjeeR, HebbarL. Time-dependent changes in matrix metalloproteinase activity and expression during the progression of congestive heart failure: relation to ventricular and myocyte function. Circ. Res. 1998;82 (4):482–95
11. Spinale F G, de GasparoM, WhitebreadS, HebbarL, ClairM J, MeltonD M, KrombachR S, MukherjeeR, IanniniJ P, OS J. Modulation of the renin-angiotensin pathway through enzyme inhibition and specific receptor blockade in pacing-induced heart failure: I. Effects on left ventricular performance and neurohormonal systems. Circulation. 1997;96 (7):2385–96
12. Spinale F G, ZellnerJ L, JohnsonW S, EbleD M, MunyerP D. Cellular and extracellular remodeling with the development and recovery from tachycardia-induced cardiomyopathy: changes in fibrillar collagen, myocyte adhesion capacity and proteoglycans. J. Mol. Cell. Cardiol. 1996;28 (8):1591–608
13. Hasdemir Can, YukselAlper, CamliDilsat, KartalYildirim, SimsekEvrim, MusayevOktay, IsayevElnur, AydinMehmet, CanLevent H. Late gadolinium enhancement CMR in patients with tachycardia-induced cardiomyopathy caused by idiopathic ventricular arrhythmias. Pacing Clin Electrophysiol. 2012;35 (4):465–70
14. Campos Bieito, JaureguiMiguel E, ParkKyoung-Min, MountantonakisStavros E, GerstenfeldEdward P, HaqqaniHaris, GarciaFermin C, HutchinsonMathew D, CallansDavid J, DixitSanjay, LinDavid, RileyMichael P, TzouWendy, CooperJoshua M, BalaRupa, ZadoErica S, MarchlinskiFrancis E. New unipolar electrogram criteria to identify irreversibility of nonischemic left ventricular cardiomyopathy. J. Am. Coll. Cardiol. 2012;60 (21):2194–204
15. Nia Amir M, GassanovNatig, DahlemKristina M, CaglayanEvren, HellmichMartin, ErdmannErland, ErFikret. Diagnostic accuracy of NT-proBNP ratio (BNP-R) for early diagnosis of tachycardia-mediated cardiomyopathy: a pilot study. Clin Res Cardiol. 2011;100 (10):887–96
16. Van Gelder Isabelle C, GroenveldHessel F, CrijnsHarry J G M, TuiningaYpe S, TijssenJan G P, AlingsA Marco, HillegeHans L, Bergsma-KadijkJohanna A, CornelJan H, KampOtto, TukkieRaymond, BoskerHans A, Van VeldhuisenDirk J, Van den BergMaarten P. Lenient versus strict rate control in patients with atrial fibrillation. N. Engl. J. Med. 2010;362 (15):1363–73
17. Nedios Sotirios, SommerPhilipp, DagresNikolaos, KosiukJedrzej, AryaArash, RichterSergio, GasparThomas, KanagkinisNikolaos, DinovBorislav, PiorkowskiChristopher, BollmannAndreas, HindricksGerhard, RolfSascha. Long-term follow-up after atrial fibrillation ablation in patients with impaired left ventricular systolic function: the importance of rhythm and rate control. Heart Rhythm. 2014;11 (3):344–51
18. Patel Dimpi, KhanMohammed. The Role of Atrial Fibrillation Catheter Ablation in Patients with Congestive Heart Failure: "Burning"for a Cure. J Atr Fibrillation. 2011;4 (4)
19. Khan Mohammed N, JaïsPierre, CummingsJennifer, Di BiaseLuigi, SandersPrashanthan, MartinDavid O, KautznerJosef, HaoSteven, ThemistoclakisSakis, FanelliRaffaele, PotenzaDomenico, MassaroRaimondo, WazniOussama, SchweikertRobert, SalibaWalid, WangPaul, Al-AhmadAmin, BeheirySalwa, SantarelliPietro, StarlingRandall C, Dello RussoAntonio, PelargonioGemma, BrachmannJohannes, SchibgillaVolker, BonsoAldo, CasellaMichela, RavieleAntonio, HaïssaguerreMichel, NataleAndrea. Pulmonary-vein isolation for atrial fibrillation in patients with heart failure. N. Engl. J. Med. 2008;359 (17):1778–85
20. Di Biase Luigi, MohantyPrasant, MohantySanghamitra, SantangeliPasquale, TrivediChintan, LakkireddyDhanunjaya, ReddyMadhu, JaisPierre, ThemistoclakisSakis, Dello RussoAntonio, CasellaMichela, PelargonioGemma, NarducciMaria Lucia, SchweikertRobert, NeuzilPetr, SanchezJavier, HortonRodney, BeheirySalwa, HongoRichard, HaoSteven, RossilloAntonio, ForleoGiovanni, TondoClaudio, BurkhardtJ David, HaissaguerreMichel, NataleAndrea. Ablation Versus Amiodarone for Treatment of Persistent Atrial Fibrillation in Patients With Congestive Heart Failure and an Implanted Device: Results From the AATAC Multicenter Randomized Trial. Circulation. 2016;133 (17):1637–44
21. Pérez Francisco J, SchubertChristine M, ParvezBabar, PathakVishesh, EllenbogenKenneth A, WoodMark A. Long-term outcomes after catheter ablation of cavo-tricuspid isthmus dependent atrial flutter: a meta-analysis. Circ Arrhythm Electrophysiol. 2009;2 (4):393–401
22. Zhong Li, LeeYing-Hsiang, HuangXin-Miao, AsirvathamSamuel J, ShenWin-

Kuang, FriedmanPaul A, HodgeDavid O, SlusserJoshua P, SongZhi-Yuan, PackerDouglas L, ChaYong-Mei. Relative efficacy of catheter ablation vs antiarrhythmic drugs in treating premature ventricular contractions: a single-center retrospective study. Heart Rhythm. 2014;11 (2):187–93

23. Lakkireddy Dhanunjaya, Di BiaseLuigi, RyschonKay, BiriaMazda, SwarupVijay, ReddyYeruva Madhu, VermaAtul, BommanaSudharani, BurkhardtDavid, DendiRaghuveer, Dello RussoAntonio, CasellaMichela, CarbucicchioCorrado, TondoClaudio, DawnBuddhadeb, NataleAndrea. Radiofrequency ablation of premature ventricular ectopy improves the efficacy of cardiac resynchronization therapy in nonresponders. J. Am. Coll. Cardiol. 2012;60 (16):1531–9
24. Perez Alexandra, TouchetteDaniel R, DiDomenicoRobert J, StamosThomas D, WaltonSurrey M. Comparison of rate control versus rhythm control for management of atrial fibrillation in patients with coexisting heart failure: a cost-effectiveness analysis. Pharmacotherapy. 2011;31 (6):552–65
25. Shelton R J, ClarkA L, GoodeK, RigbyA S, HoughtonT, KayeG C, ClelandJ G F. A randomised, controlled study of rate versus rhythm control in patients with chronic atrial fibrillation and heart failure: (CAFE-II Study). Heart. 2009;95 (11):924–30
26. Ilkhanoff Leonard, GerstenfeldEdward P, ZadoErica S, MarchlinskiFrancis E. Changes in ventricular dimensions and function during recovery of atrial tachycardia-induced cardiomyopathy treated with catheter ablation. J. Cardiovasc. Electrophysiol. 2007;18 (10):1104–6
27. Yokokawa Miki, GoodEric, CrawfordThomas, ChughAman, PelosiFrank, LatchamsettyRakesh, JongnarangsinKrit, ArmstrongWilliam, GhanbariHamid, OralHakan, MoradyFred, BogunFrank. Recovery from left ventricular dysfunction after ablation of frequent premature ventricular complexes. Heart Rhythm. 2013;10 (2):172–5
28. Dandamudi Gopi, RampurwalaAbbas Y, MahenthiranJothiharan, MillerJohn M, DasMithilesh K. Persistent left ventricular dilatation in tachycardia-induced cardiomyopathy patients after appropriate treatment and normalization of ejection fraction. Heart Rhythm. 2008;5 (8):1111–4

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Leaks After Left Atrial Appendage Lligation with Lariat Device: Incidence, Pathophysiology, Clinical Implications and Methods of Closure- A Case Based Discussion

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Abstract

Catheter based left atrial appendage (LAA) closure techniques are emerging as a promising alternative for stroke prevention in patients who cannot tolerate oral anticoagulation. Lariat procedure involves percutaneous catheter based epicardial ligation of the LAA with a suture via an endo-epicardial hybrid approach. It offers the advantage of not leaving behind a focus for thrombus formation or embolization. Similar to surgical ligation of the left atrial appendage, Lariat ligation is limited by leaks in a small percentage of patients. The incidence of leaks is variable and can be seen in the immediate post procedure period or during follow up. The electrical and mechanical implications of leaks are still under debate. In this review, we discuss the incidence, pathophysiology, clinical implications and methods of closure of leaks after Lariat. In the end, we present a case of a Lariat leak closed with an Amplatzer septal occluder.

Background

Atrial fibrillation (AF) remains the most common sustained arrhythmia in the United States affecting more than 6.1 million adults [1]. It is associated with significant morbidity and mortality as it is an independent risk factor for stroke[2]. Thrombus in the left atrial appendage (LAA) contributes to 90% of AF related strokes[3]. Oral anticoagulation(OAC) can reduce the risk of stroke by up to 64%[4]. However, their use is contra-indicated in some patients because of significant risk of bleeding[5]. Procedural exclusion of the LAA is an alternative in patients with high risk of bleeding. Recent studies also suggest LAA as a non-pulmonary vein focus of origin of AF [6]. Epicardial based exclusion procedures can electrically isolate the LAA and there might be a benefit of reducing AF burden in addition to stroke prevention. Surgical separation of the LAA during coronary artery bypass grafting or valve replacements has been around for a long time [3]. Minimally invasive surgical techniques like AtriClip (AtriCure Inc. Cincinnati, Ohio) are also available [7], [8]. Historically, surgical techniques including off pump suturing, endocardial suturing and stapling have been associated with significant incomplete closure, stumps and increased risk of systemic thromboembolism [9].

Several nonsurgical percutaneous LAAC techniques were developed recently. The Watchman device (Boston Scientific Corp, Minneapolis, MN) which is deployed after trans-septal puncture via percutaneous catheter-based delivery system is one of them. The PROTECT-AF trial showed non inferiority of the Watchman device in preventing strokes when compared to warfarin in AF patients who cannot tolerate anticoagulation[10]. Lariat suture ligation (SentreHEART Inc, Redwood, CA) is another LAAC technique. It allows for percutaneous catheter based epicardial ligation of the LAA with a suture via an endo-epicardial hybrid approach[11].

Similar to surgical closure techniques (between 10 and 80%) [12], percutaneous LAAC techniques are limited by leaks in a small percentage of patients. Leaks can develop at the time of implant due to incomplete closure or de-Novo during follow up due to tissue remodeling. Their clinical implications are still under debate. With some reports suggesting an association of leaks with thromboembolism, it's an area of growing interest. In this manuscript we describe the incidence, pathophysiology, clinical implications and methods of closure for post Lariat leaks.

Incidence and types of leaks

Several studies have shown that leaks are a complication of percutaneous LAAC devices [10], [13], [14]. The incidence and characteristics of leaks vary based on the procedure. With endocardial plug type devices a circular devices attempts to occlude a non-circular orifice with variable dimensions thereby producing the "Edge effect" [13][Figure 2].Depending on the compliance and remodeling capability of the LAA whether the tissue around the device remains snug fit or not is variable. In the case of epicardial systems there are

Key Words

Atrial fibrillation (AF), Left atrial appendage (LAA), Left atrial appendage closure (LAAC), LAA ligation, Lariat, Leaks after Lariat procedure.

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two types of issues – 1. Central leaks due to suture not ligating the entire neck of the LAA and 2. Stump – long piece of the LAA neck or base left behind. We have previously described the leaks after Lariat procedure as concentric and central owing to the "Gunny sack effect" caused by suture ligation around the LAA [13][Figure 1].

The incidence of leaks after Lariat procedure range from 0% to 24% [13], [15]-[19][Table 1]. The large variation in the incidence rates are likely due to an evolving technique, site of suture application and lack of standardized imaging for identifying leaks. The leak size is determined by the final diameter of the suture loop used and whether

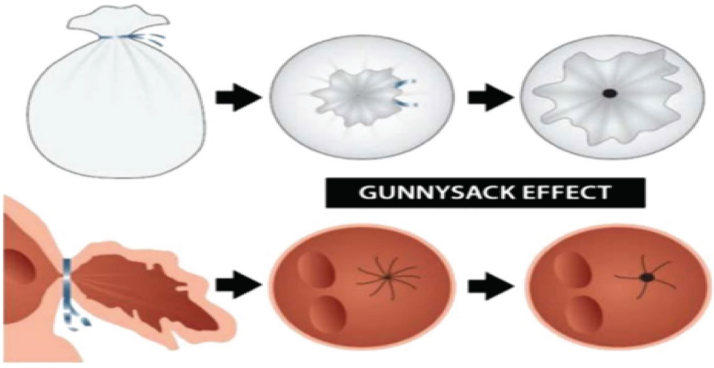

Figure 1: Shows the "Gunny sack effect" describing a concentric leak after Lariat procedure. Image adapted from the study by Pillarisetti et al

repeated tensuring was done after the initial suture deployment or not. If the suture is deployed too close to the atrium, it can result in a larger suture loop with a significant amount of bunched up tissue that may subsequently unfurl opening up the central portion of the suture loop. In a recent study, one of the factors which led to higher reporting of leaks was the use of 3D TEE[14]. In this study 3 additional patients were found to have leaks which were missed on traditional 2D TEE.

Leaks were reported as major (≥5mm) or minor (≤5mm) based on the size for the endocardial closure devices. Majority of leaks after the Lariat procedure were ≤2mm and rarely >5mm [13]. The definition of an acceptable versus unacceptable leak is still up for debate. Leaks can occur in the immediate post procedure period or can be observed during follow up. [Figure 3] and [Figure 4] show acute and long term closure rates in various studies. In a prospective study by Pillarisetti at al which included 259 patients, 5 patients (2%) had small leaks at the time of implantation, 33 patients (13%) had leaks at 1-3 months

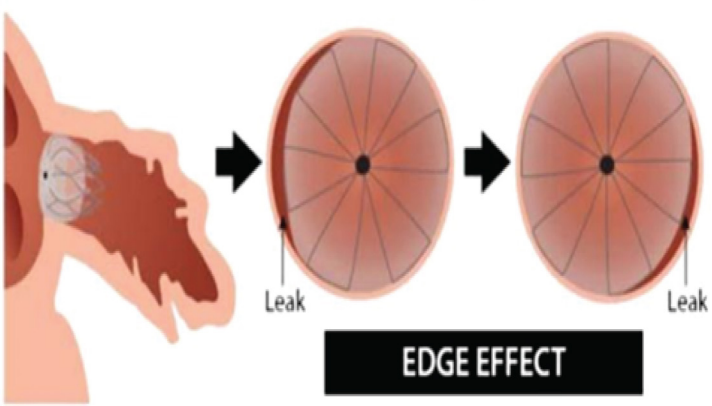

Figure 2: Shows the "Edge effect" describing a peri-device leak after Watchman device. Image adapted from the study by Pillarisetti et al

and 9 months follow ups. In a retrospective study by Gianni et al, 98 patients underwent Lariat suture ligation and followed with 3D TEE immediately post procedure, at 6 months and at 12 months. Acute leaks (at the time of the procedure) were seen in 5 patients (5%). Of these 5 patients, only 2 persisted at 6 months follow up. Among patients with no acute leaks, early leaks (evident at or before 6 months follow up) were identified in 12(13%) patients and late leaks (diagnosed after the 6 months follow up) were identified in 2 patients (5%). In this study, a total of 14(15%) and 19(20%) patients had leaks at 6 months and 12 months follow up respectively [14]. In a recent large multicenter evaluation of 682 patients reported by our group, acute leaks less than 2mm were seen in 13 patients (1.8%). Follow up TEE was available in 480 patients, which showed leaks between 2-5mm in 31 patients (6.5%)[20]. Acute leaks are likely because of suboptimal tightening of the suture. They might spontaneously close due to endothelialization or fibrosis, especially if size is <3mm. Early or late leaks maybe due to knot loosening due to tissue unfurling or tissue necrosis at the site of suture as observed with surgical ligation [21]. They are less likely to close spontaneously in our experience.

Pathophysiology of leaks in Lariat system

The following factors play a very important role in the presence or absence of leaks.

Size of the LAA at the site of closure – large necks often result in incomplete closure as there is too much tissue to approximate

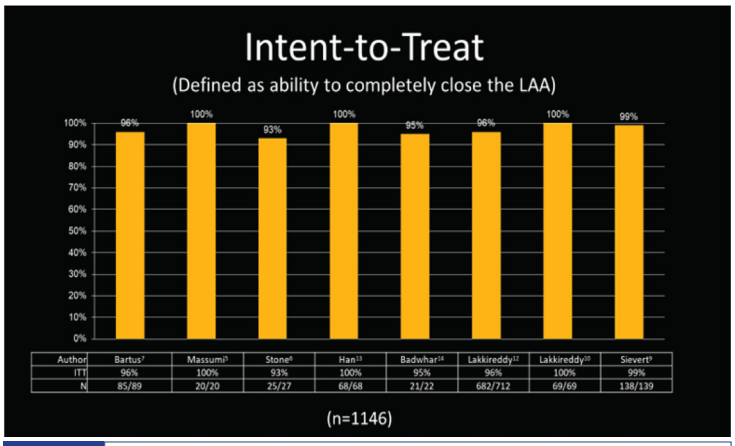

Figure 3: Shows the acute closure rates with Lariat device in various reported studies

Proximity to the atrial wall - The closer one gets to the atrial wall at the base more tissue gets bunched up into the suture and often prevents it from tensuring right. Over a period of time the tissue inside the loop remodels and unfurls to open a communication proximal and distal to the ligature.

Appropriate deployment and tensuring of the suture - If the device is not lined up properly and the tissue is not tensured the chances of leaks is high.

. False closure due to the pressure from the device - Occasionally, the magnets might not align and are attached outside the LAA. If the operator doesn't realize the issue and moves the delivery device forwards deploying the suture and falsely compressing the LAA resulting in pseudo closure. An atrial angiogram should always be performed once the nitinol loop comes off of the LAA prior to withdrawing the sheath to the right side.

Incomplete closure due to basal lobes - In a small percentage of patients the proximal portion of the LAA may have separate lobes

Table 1: Incidence rates of leaks after Lariat suture ligation of the LAA

Author (year) [reference #]	N	Acute	Early(<6m)	Late(6-12m)
Bartus et al (2013)[15]	85, 81, 65	3(4%)	4(5%)	1(2%)
Massumi et al (2013)[16]	20, 17, 17	0(0%)	1(6%)	1(6%)
Miller et al (2013)[18]	41, 41	3(7%)	10(24%)	-
Price et al (2013) [19]	145, 63	5(8%)	13(20%)	-
Pillarisetti et al (2015)[13]	259, 259, 259	5(2%)	33(13%)	33(13%)
Gianni et al (2016)[14]	98, 96, 96	5(5%)	14(15%)	19(20%)
Lakkireddy et al(2016)	682, 480, 480	13(1.8%)	31(6.5%)	31(6.5%)

*N=Number of patients in each study at the time of procedure, 6months and 12months.

and the suture may simply ligate one of the lobes leaving behind the others untreated.

Why does a Lariat close the LAA better than a surgical hand knot?

In vast majority of hand knots that were done during open heart procedures, the heart was on a heart-lung pump with LAA being flaccid. It is very hard to tie a suture around flaccid piece of tissue. The analogy one can try here is that of a deflated vs inflated balloon and applying a knot around it. It's a lot easier to tie a self-retaining knot around the neck of an inflated balloon and subsequent tensuring will result in making it tighter. The Lariat suture delivery follows this very principle and has shown that the closure rates are dramatically higher than what has been described in surgical literature [Figure 5]. Once the self-retaining suture is deployed, subsequent tensuring of the suture helps to tighten the suture around the tissue, desiccating it further and allowing for the lowest possible suture diameter to close off the neck. So in larger necks it may be necessary to tensure the suture more than once. And confirming closure after the Lariat loop comes off of the LAA is critical to ensure acute closure.

Clinical Implications of leaks

Successful LAAC with Lariat suture ligation system results in electrical and mechanical isolation of the LAA reducing the risk of stroke and recurrence of AF. There is limited data on the electrical and mechanical implications in patients with leaks following Lariat procedure. This was studied in a recent prospective multicenter study by our group. A total of 91 patients with AF who underwent Lariat suture ligation followed by catheter ablation were studied. Of these, 7 patients had leaks ranging from 1-3mm and 4 patients had leaks between 4-5mm. Morphological characteristics of the LAA remnant (LAAR) were assessed with CT scans obtained pre procedure and at 1 month. Electrical activity of the LAAR was assessed during CA performed within a month from the Lariat procedure. We reported significant reduction in the LAA volumes (66%) and size (67%) however larger leaks had slightly larger LAAR. Of the 4 patients with leaks between 4-5mm, 3 demonstrated electrical activity during CA and were successfully isolated. There was lack of statistically significant correlation between leaks and recurrence of AF at 1 year follow up.

Leaks following surgical exclusion of the LAA have been reported to be associated with thromboembolism. Continued anti-coagulation is recommended in these patients because of this risk. This association with thromboembolism is poorly understood with leaks following percutaneous LAAC techniques. Theoretically, in patients with Watchman device the implant can act as a nidus for thrombus formation and stroke in the absence of anti-coagulation or antiplatelet therapy. In PROTECT-AF study, albeit leaks with associated thrombi, there was no association between stroke and the presence or size of the leaks[10]. Similar findings were observed in the subgroup of patients with Watchman device in the study by Pillarisetti et al [13]

There is no randomized controlled data for Lariat looking at the impact of leak on the overall risk of stroke. It is clear while the presence of a leak may not increase the stroke risk but complete closure doesn't assure the elimination of stroke risk. Even though epicardial exclusion of the LAA with Lariat suture does not leave a nidus for thrombus formation there still is a risk in the immediate post procedural period. Thrombus at the closure site has been reported in 2.5% Lariat cases irrespective of the closure. This is thought to be secondary to local inflammatory changes caused by tissue infarction due to application of the suture [13]. In a recent retrospective study with 98 patients, 5 developed thromboembolisms. Three of the 5 were found to have leaks on 3D TEE, 2 patients in which the TEE was not available presented with thromboembolic events. None of the patients without leaks developed thromboembolic events [14]. In 2 of 3 patients with leaks on 3D TEE they were not detected on 2D TEE. This observation questions the role of various imaging modalities in identifying leaks.

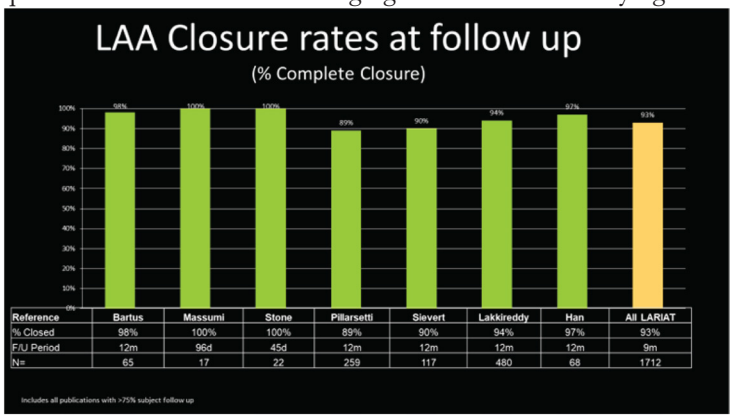

Figure 4: Shows the longterm closure rates during follow up. > 75% of patients had follow up TEEs in these studies

This association with thromboembolism was not reproducible in a recent multicenter prospective study which followed 259 consecutive patients with 2D TEE who underwent LAAC with Lariat suture [13]. There is a significant uncertainty regarding the association between leaks and thromboembolism.

Methods of closing leaks

Most operators choose to resume anticoagulation/antiplatelet agents in patients with leaks after percutaneous LAAC in the absence of contraindications. This might not be the case for most patients who undergo Lariat procedure because of their high bleeding risk. The other alternative is to pursue repeat exclusion of the LAA. Before consideration for exclusion procedures it's important to keep in mind that leaks ≤2 mm might spontaneously close [15], [20] and can be observed, while leaks ≥3mm are less likely to close.

Several endocardial occlusion devices are being used for closure of leaks after surgical or non-surgical LAA exclusion [21]-[23]. The concentric and central location of leaks seen after Lariat suture ligation makes it feasible for septal closure devices. Because of the narrow neck of the LAA conventional closure devices like

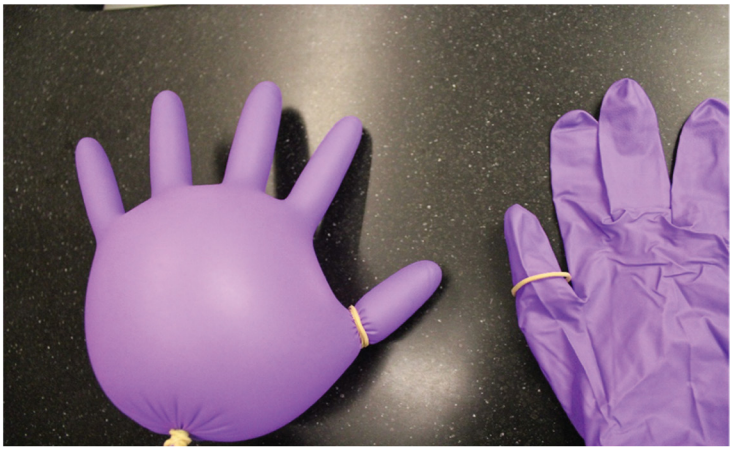

Figure 5: Shows the difference in suture deployment when the target is inflated vs deflated

Watchmen device cannot be used [21]. Amplatzer septal occluder (ASO), originally designed for the closure of atrial septal defects, is now being used off label for closing LAA leaks. In a recent case series, we reported 5 patients with leaks ranging from 3.5 mm - 5 mm after Lariat procedure successfully closed with ASO device [21]. All patients were on anti-platelet agents (clopidogrel 75mg qday) for 6 weeks until endothelialization of the device as per standard practice. There was no residual leak noted at 3 months follow up. ASO is a self-expandable device made of nitinol mesh and fabric patches delivered through a transseptal sheath positioned in the LAA. Mosley et al reported successful closure of 3 late Lariat leaks using Amplatzer vascular plug 4(AVP-4). AVP-4, approved to close AV fistulas, is a double lobed retractable nitinol based device which is deployed through a 4-5 French diagnostic catheter [22]. There was another case of incomplete LAA closure that was closed with an Atriclip using a minimally invasive technique. In this case, only the distal lobe of the bilobed LAA was closed with the Lariat leaving behind a large proximal lobe [24]. Alternative approaches like coils or other septal occluders (e.g., GORE Helex septal occluder[GORE medical, Flagstaff, AZ]) can also be used[25]. Several exclusion techniques were described anecdotally. A repeat Lariat suture was used to close a leak in one recent case report [21]. This can be difficult because of potential adhesions from pericardial inflammation caused by the initial pericardial access and suture.

How to close a leak using ASO: A stepwise descriptive Case study

A 75 year old female patient with permanent AF status post multiple left antral ablations who suffered an embolic CVA (CHADSVASC of 5) while on Coumadin underwent Lariat suture ligation. She had a large LAA with a neck diameter of 4cm. There was significant difficulty encircling the whole appendage and required multiple attempts during the procedure. She had a 1mm residual leak at the end of the procedure on TEE. She was subsequently found to have a 4 mm leak at her 3 month follow up. Because of her high stroke risk it was decided to pursue closure of the leak with ASO. After correct patient identification, an informed consent was obtained after discussing the risks and benefits of the procedure. The procedure was performed in a hybrid catheterization lab under general anesthesia. A TEE was performed prior to gaining access to exclude LAA thrombus and to assess the dimension of the neck of the leak between the LAA and the LA. After obtaining femoral vein access, transseptal access was obtained by using a Brockenbrough needle and an 8.5Fr SL1 sheath (St.Jude Medical, St Paul, MN) under TEE and fluoroscopic guidance. A left atrial appendogram was obtained in the right anterior oblique and left anterior oblique views to assess the dimensions and characteristic of the leak between the LAA and LA.

Complete opacification of the LAA was obtained with the appendogram with neck diameter measuring 4 mm. The SL1 sheath was exchanged for an 8.5 Fr Mullins sheath. A soft-tipped 0.035-inch wire was passed across the neck into the LAA under fluoroscopic and TEE guidance. The distal tip of the Mullins sheath was positioned just beyond the neck.

A 5 mm ASO was chosen based on the patients LAA leak. The ASO device was advanced through the sheath beyond the neck. It was unsheathed such that the outer disk was deployed inside the LAA and the inner disk on the LA aspect of the neck with the waist of the device exactly aligned with the neck. A "tug test" was performed to ensure the stability of the device. Angiography and TEE were used to confirm the absence of any residual leak across the device [Figure 6]. The patient was started on clopidogrel 75mg qday for 6 weeks until endothelialization of the device as per standard practice. There was no residual leak noted at 3 months follow up on TEE.

Post procedural anticoagulant or antiplatelet regimen after device closure of a leak

If the patient is able to take oral anticoagulation at least in the short term, should be treated with one for at least 6 weeks to allow for endothelialization followed by dual antiplatet therapy (DAPT).

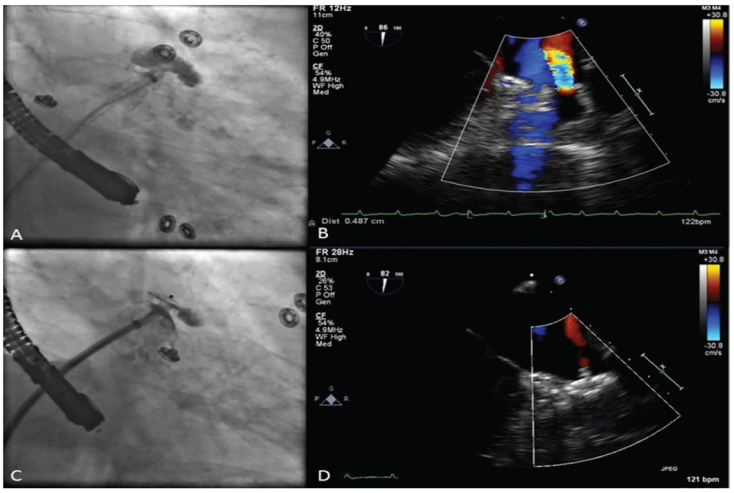

Figure 6: Panel A shows remnant connection between left atrium and LAA after contrast injection. Panel B shows the same leak on TEE. Panel C shows ASO device obliterating the remnant connection between the LA and the appendage after contrast. Panel D shows TEE images of the ASO device in situ. LAA= Left atrial appendage, ASO = Amplatzer septal occluder, TEE = Transesophageal echocardiogram

If OAC is not an option DAPT for at least 6 months is important. After 6 months ASA 81 mg may suffice. Periodic TEE monitoring may be important to understand the long term implications of device related thrombus in these cases is still not well understood.

Conclusions

Leaks are a known complication after Lariat suture ligation. They can be detected at the time of procedure or during follow up. There is no correlation between leaks and recurrence of AF. There is limited data on the relationship between leaks and thromboembolism. Because of the possible association with thromboembolism patients should be followed up long term with serial TEE imaging. Anticoagulation

should be resumed if feasible or repeat percutaneous closure with endovascular or epicardial techniques should be pursued if there is a high risk of stroke. The concentric and central nature of the leak after Lariat makes it feasible to use septal closure devices to close a leak.

Disclosures

None.

References

1. Go Alan S, MozaffarianDariush, RogerVéronique L, BenjaminEmelia J, BerryJarett D, BlahaMichael J, DaiShifan, FordEarl S, FoxCaroline S, FrancoSheila, FullertonHeather J, GillespieCathleen, HailpernSusan M, HeitJohn A, HowardVirginia J, HuffmanMark D, JuddSuzanne E, KisselaBrett M, KittnerSteven J, LacklandDaniel T, LichtmanJudith H, LisabethLynda D, MackeyRachel H, MagidDavid J, MarcusGregory M, MarelliAriane, MatcharDavid B, McGuireDarren K, MohlerEmile R, MoyClaudia S, MussolinoMichael E, NeumarRobert W, NicholGraham, PandeyDilip K, PaynterNina P, ReevesMatthew J, SorliePaul D, SteinJoel, TowfighiAmytis, TuranTanya N, ViraniSalim S, WongNathan D, WooDaniel, TurnerMelanie B. Executive summary: heart disease and stroke statistics--2014 update: a report from the American Heart Association. Circulation. 2014;129 (3):399–410
2. Wolf P A, AbbottR D, KannelW B. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. Stroke. 1991;22 (8):983–8
3. Blackshear J L, OdellJ A. Appendage obliteration to reduce stroke in cardiac surgical patients with atrial fibrillation. Ann. Thorac. Surg. 1996;61 (2):755–9
4. Hart Robert G, PearceLesly A, AguilarMaria I. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. Ann. Intern. Med. 2007;146 (12):857–67
5. Hughes M, LipG Y H. Risk factors for anticoagulation-related bleeding complications in patients with atrial fibrillation: a systematic review. QJM. 2007;100 (10):599–607
6. Di Biase Luigi, BurkhardtJ David, MohantyPrasant, SanchezJavier, MohantySanghamitra, HortonRodney, GallinghouseG Joseph, BaileyShane M, ZagrodzkyJason D, SantangeliPasquale, HaoSteven, HongoRichard, BeheirySalwa, ThemistoclakisSakis, BonsoAldo, RossilloAntonio, CorradoAndrea, RavieleAntonio, Al-AhmadAmin, WangPaul, CummingsJennifer E, SchweikertRobert A, PelargonioGemma, Dello RussoAntonio, CasellaMichela, SantarelliPietro, LewisWilliam R, NataleAndrea. Left atrial appendage: an underrecognized trigger site of atrial fibrillation. Circulation. 2010;122 (2):109–18
7. Blackshear Joseph L, JohnsonW Dudley, OdellJohn A, BakerVickie S, HowardMary, PearceLesly, StoneChristopher, PackerDouglas L, SchaffHartzell V. Thoracoscopic extracardiac obliteration of the left atrial appendage for stroke risk reduction in atrial fibrillation. J. Am. Coll. Cardiol. 2003;42 (7):1249–52
8. Salzberg Sacha P, PlassAndre, EmmertMaximillian Y, DesbiollesLotus, AlkadhiHatem, GrünenfelderJurg, GenoniMichele. Left atrial appendage clip occlusion: early clinical results. J. Thorac. Cardiovasc. Surg. 2010;139 (5):1269–74
9. Katz E S, TsiamtsiourisT, ApplebaumR M, SchwartzbardA, TunickP A, KronzonI. Surgical left atrial appendage ligation is frequently incomplete: a transesophageal echocardiograhic study. J. Am. Coll. Cardiol. 2000;36 (2):468–71
10. Fountain Rebecca Brown, HolmesDavid R, ChandrasekaranKrishnaswamy, PackerDouglas, AsirvathamSamuel, Van TasselRobert, TuriZoltan. The PROTECT AF (WATCHMAN Left Atrial Appendage System for Embolic PROTECTion in Patients with Atrial Fibrillation) trial. Am. Heart J. 2006;151 (5):956–61
11. Lee Randall J, BartusKrzysztof, YakubovSteven J. Catheter-based left atrial appendage (LAA) ligation for the prevention of embolic events arising from the LAA: initial experience in a canine model. Circ Cardiovasc Interv. 2010;3 (3):224–9
12. Dawson Alan G, AsopaSanjay, DunningJoel. Should patients undergoing cardiac surgery with atrial fibrillation have left atrial appendage exclusion?. Interact Cardiovasc Thorac Surg. 2010;10 (2):306–11
13. Pillarisetti Jayasree, ReddyYeruva Madhu, GundaSampath, SwarupVijay, LeeRandall, RasekhAbdi, HortonRodney, MassumiAli, ChengJie, BartusKrzystzof, BadhwarNitish, HanFrederick, AtkinsDonita, BommanaSudharani, EarnestMatthew, NathJayant, FerrellRyan, BormannSteven, DawnBuddhadeb, Di BiaseLuigi, MansourMoussa, NataleAndrea, LakkireddyDhanunjaya. Endocardial (Watchman) vs epicardial (Lariat) left atrial appendage exclusion devices: Understanding the differences in the location and type of leaks and their clinical implications. Heart Rhythm. 2015;12 (7):1501–7
14. Gianni Carola, Di BiaseLuigi, TrivediChintan, MohantySanghamitra, GökoğlanYalçın, GüneşMahmut F, BaiRong, Al-AhmadAmin, BurkhardtJ David, HortonRodney P, KrumermanAndrew K, PalmaEugen C, ValderrábanoMiguel, GibsonDouglas, PriceMatthew J, NataleAndrea. Clinical Implications of Leaks Following Left Atrial Appendage Ligation With the LARIAT Device. JACC Cardiovasc Interv. 2016;9 (10):1051–7
15. Bartus Krzysztof, HanFrederick T, BednarekJacek, MycJacek, KapelakBoguslaw, SadowskiJerzy, LelakowskiJacek, BartusStanislaw, YakubovSteven J, LeeRandall J. Percutaneous left atrial appendage suture ligation using the LARIAT device in patients with atrial fibrillation: initial clinical experience. J. Am. Coll. Cardiol. 2013;62 (2):108–118
16. Massumi Ali, CheluMihail Gabriel, NazeriAlireza, MayStephen Allen, Afshar-KharaghanHamid, SaeedMohammad, RazaviMehdi, RasekhAbdi. Initial experience with a novel percutaneous left atrial appendage exclusion device in patients with atrial fibrillation, increased stroke risk, and contraindications to anticoagulation. Am. J. Cardiol. 2013;111 (6):869–73
17. Stone Diana, ByrneTimothy, PershadAshish. Early results with the LARIAT device for left atrial appendage exclusion in patients with atrial fibrillation at high risk for stroke and anticoagulation. Catheter Cardiovasc Interv. 2015;86 (1):121–7
18. Miller Marc A, GangireddySandeep R, DoshiShephal K, AryanaArash, KoruthJacob S, SennhauserSusie, d'AvilaAndre, DukkipatiSrinivas R, NeuzilPetr, ReddyVivek Y. Multicenter study on acute and long-term safety and efficacy of percutaneous left atrial appendage closure using an epicardial suture snaring device. Heart Rhythm. 2014;11 (11):1853–9
19. Price Matthew J, GibsonDouglas N, YakubovSteven J, SchultzJason C, Di BiaseLuigi, NataleAndrea, BurkhardtJ David, PershadAshish, ByrneTimothy J, GidneyBrett, AragonJoseph R, GoldsteinJeffrey, MoultonKriegh, PatelTaral, KnightBradley, LinAlbert C, ValderrábanoMiguel. Early safety and efficacy of percutaneous left atrial appendage suture ligation: results from the U.S. transcatheter LAA ligation consortium. J. Am. Coll. Cardiol. 2014;64 (6):565–72
20. Lakkireddy Dhanunjaya, AfzalMuhammad R, LeeRandall J, NagarajHosakote, TschoppDavid, GidneyBrett, EllisChristopher, AltmanEric, LeeBrian, KarSaibal, BhadwarNitish, SanchezMauricio, GadiyaramVaruna, EvonichRudolph, RasekhAbdi, ChengJie, CuocoFrank, ChandhokSheetal, GundaSampath, ReddyMadhu, AtkinsDonita, BommanaSudharani, CuculichPhillip, GibsonDouglas, NathJayant, FerrellRyan, MatthewEarnest, WilberDavid. Short and long-term outcomes of percutaneous left atrial appendage suture ligation: Results from a US multicenter evaluation. Heart Rhythm. 2016;13 (5):1030–6
21. Pillai Anand M, KanmanthareddyArun, EarnestMatthew, ReddyMadhu, FerrellRyan, NathJayanth, PillarisettiJayasree, VallakatiAjay, LakkireddyDhanunjaya. Initial experience with post Lariat left atrial appendage leak closure with Amplatzer septal occluder device and repeat Lariat application. Heart Rhythm. 2014;11 (11):1877–83
22. Mosley William J, SmithMichael R, PriceMatthew J. Percutaneous management of late leak after lariat transcatheter ligation of the left atrial appendage in patients with atrial fibrillation at high risk for stroke. Catheter Cardiovasc Interv. 2014;83 (4):664–9
23. Aryana Arash, CavacoDiogo, ArthurArvin, O'NeillPadraig Gearoid,

AdragãoPedro, D'AvilaAndré. Percutaneous endocardial occlusion of incompletely surgically ligated left atrial appendage. J. Cardiovasc. Electrophysiol. 2013;24 (9):968–74

24. Aznaurov Sam G, BallStephen K, EllisChristopher R. Thoracoscopic Atriclip Closure of Left Atrial Appendage After Failed Ligation via LARIAT. JACC Cardiovasc Interv. 2015;8 (15):e265–e267
25. Yeow Wen-Loong, MatsumotoTakashi, KarSaibal. Successful closure of residual leak following LARIAT procedure in a patient with high risk of stroke and hemorrhage. Catheter Cardiovasc Interv. 2014;83 (4):661–3

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Atrioesophageal Fistula After Atrial Fibrillation Ablation: A Single Center Series

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Abstract

Background: RecentlyThe incidence of atrioesophageal fistula (AEF) after atrial fibrillation catheter ablation is reported to be 0.015%-0.04%, though it is likely underreported due to a number of factors including misdiagnosis. We report our institutional experience with AEF.

Methods: Patients with confirmed diagnosis of AEF between 2004 and 2016 at our institution were identified (n=5) and their clinical characteristics and outcome were analyzed.

Results: AEF occurred in 5 patients who underwent AF catheter ablation (3 ablated at our institution; 2 transferred from outside hospitals after diagnosis of AEF). Symptoms were chest pain (n=3), fever (n=3), TIA/stroke (n=3), dysphagia (n=1), and headache (n=1). Chest pain was the earliest symptom and occurred 21-24 days post-RFA. One patient had sudden death without preceding symptoms. Findings included leukocytosis (WBC count range of 17200-19,000) and sepsis. Chest CT was obtained in 3 patients and showed air in the left atrium or mediastinum. Three patients had evidence of multifocal stroke on MRI. Three patients died before surgery could be performed. Two patients (40%) underwent emergent surgery which included partial excision of atrial wall, closure with bovine pericardial patch and closure of esophageal lesion. Surgical outcomes were favorable (100% survival).

Conclusion: Chest pain and fever were the early symptoms of AEF and occurred before the neurologic complications. Chest CT was an excellent tool for detection of AEF. All patients who were diagnosed correctly and underwent surgery survived. Early detection is imperative as prompt surgery may improve survival. Health-care community education is the key to ensure early detection and transfer to a qualified surgical center.

Introduction

Atrioesophageal fistula (AEF) is a rare but serious complication of atrial fibrillation (AF) catheter ablation with associated high mortality rates. The incidence of confirmed AEF after AF catheter ablation is 0.015%-0.04% based on surveys, but this figure is likely underreported due to a number of factors including misdiagnosis and low response rate.[1]–[3] AEF was the second most common cause of mortality after cardiac tamponade, accounting for 16% of fatality related to complications of AF catheter ablation in a large retrospective study. [4] AEF mortality rate has been reported to be 40-100%.[3],[5]–[7]

The high mortality rate related to this complication is likely in part due to lack of clinical awareness leading to delayed diagnosis in addition to the complex nature of surgical repair required for treatment.[1],[2],[8] In this study, we report our institutional experience with AEF.

Key Words

atrial fibrillation, atrioesophageal fistula, radiofrequency catheter ablation, complications.

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Methods

Between 2004 and 2016, all adult patients with confirmed diagnosis of AEF at our institution were identified based on chart review. This included patients who were referred from, diagnosed or initially treated at outside hospitals prior to transfer to our institution. Records of patients were reviewed for demographic and clinical data. Clinical data included index catheter ablation, presenting symptoms and timing, laboratory values, radiographic and pathology results, type of surgical repair, post-operative course and outcomes.

Statistical Analysis

Continuous data are presented as medians and ranges and categorical data are presented by absolute numbers and percentages.

Results

Demographics, Ablation Technique and Clinical Presentation

Five confirmed cases of AEF after catheter ablation were identified between 2004 and 2016. Of these, 3 cases occurred at our institution and the remaining 2 were referred to our center for management of AEF. A total of 1212 AF procedures were done at our institution in that time period. Median age was 61 years (range 54-71). Three were male, 3 had paroxysmal AF and 2 had persistent AF.

Four underwent radiofrequency ablation and 1 had high intensity focus ultrasound (HIFU) ablation (patient 2). All patient had

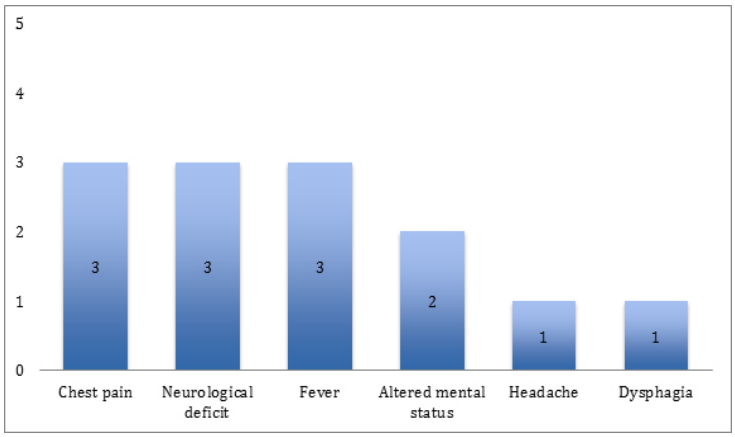

Figure 1: Frequency of Clinical Findings in Five Patients presenting with AEF to our institution

pulmonary vein isolation (PVI). Procedural details for 3 patients with index ablation done at our institution were available (patients 3-5). All procedures were done under general anesthesia. Of these, 2 had ostial PVI (patients 3 and 5) and patient 4 underwent wide area circumferential catheter ablation (WACA). In addition to PVI, patient 4 had Focal Impulse and Rotor Modulation (FIRM) ablation in the left atrial roof, patient 5 had additional posterior roof and lateral mitral isthmus line, and patient 3 underwent ablation of complex fractionated atrial electrograms (CFAEs) in the mid anterior wall, roof, posterior wall inferior to the RIPV and mitral annular region. CFAEs noted adjacent to the esophagus were not ablated. EZ Steer Thermocool irrigated catheter (BioSense Webster Diamond Bar, CA) was used in 2 patients (patient 3 and 4) and an 8 mm Navistar DS non-irrigated catheter ((BioSense Webster Diamond Bar, CA) was used in 1 patient for ablation (patient 5). Power range of 25-40 watts with temperature cut-off of 42˚C were employed for irrigated catheters and a power of 50 watts with temperature cut-off of 50˚C was used with the non-irrigated catheter. All reported lesions were 30-60 seconds long with loss of local electrogram used as an endpoint. RF applications on the posterior left atrium were limited to 25 watts for patients 3 and 4. Using a single-thermocouple esophageal temperature probe, esophageal luminal temperature (LET) was monitored during ablation in the 3 patients whose index procedure done at our institution. RF applications were stopped when LET reached 38.5˚C or there was an increase in LET by >1˚C. Maximum reported esophageal temperature did not exceed 39.0 ˚C. Information on esophageal protective measures were not available for 2 patients who were transferred for management of AEF from outside institutions. 2 out of 5 patients (patients 3 and 4) received prophylactic proton pump inhibitor (PPI) peri-operatively. Devices to displace esophagus were not used for any of the patients.

Patients developed symptoms related to AEF between 21 and 27 days after index ablation procedure (median 24 days). Symptoms included chest pain (n=3), fever (n=3), TIA/stroke symptoms (n=3), dysphagia (n=1), and headache (n=1). Chest pain was the earliest symptom and occurred 21-24 days post-RFA [Figure 1]. When neurologic symptoms were present they included visual disturbance (n=2), hemiparesis (n=2), and hemi-neglect (n=1).

Laboratory and clinical findings included leukocytosis in all of the patients (range 17200-19,000) and sepsis (n=3). Blood cultures were obtained from 3 patients which grew Strep anginosus (patient 1), Strep constellatus (patient 2) and Strep viridans (patient 3).

Intra-operative pathologic specimen cultures were obtained from patients 1 and 2. It revealed Strep anginosus, Lactobacillus, and Candida albicans in one patient (patient 1) and no growth in the other.

Diagnostic Procedures

Brain magnetic resonance imaging was performed in 3 patients all of whom had evidence of multifocal embolic stroke (patients 1, 2 and 5). Contrast-enhanced CT scan of chest using intravenous contrast was obtained in 3 patients and showed air in the left atrium or mediastinum (patients 1,2 and 3). The initial chest CT was done on the day of admission for patients 1 and 2 and on the 2nd day for patient 3. CT imaging was repeated on the 2nd day of admission for patient 2 due to an initial non-diagnostic result and a high index of suspicion. Pathology specimens obtained during surgery or autopsy confirmed the diagnosis of AEF in all patients. The level of AEF was noted for 4 of the patients; it was near the RIPV for patient 1, adjacent to LSPV for patient 2, and involving the LIPV for patients 3 and 4. Images of pathologic specimens for 2 of the patients with AEF are shown in [Figure 2]. [Table 1] summarizes the clinical data for each patient.

Surgical Repair of Atrioesophageal Fistula

Two patients underwent emergent surgical repair of the AEF (patient 1 and 2). Both patients presented with chest pain and TIA/stroke symptoms. Chest CT using IV contrast confirmed the diagnosis in both patients.

Surgical repair was performed by a team with a cardiac and a thoracic surgeon. Following median sternotomy and cardiopulmonary bypass,

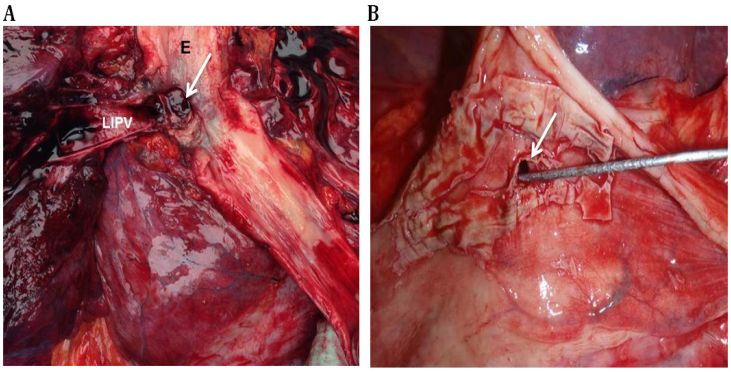

Figure 2: Pathologic specimens of atrioesophageal fistula (AEF) A: Esophageal (E)-left inferior pulmonary vein (LIPV) fistula (arrow) in patient 4 B: AEF (arrow) near the LIPV with transmural necrosis of LIPV in Patient 3

left atriotomy was performed, extending the incision underneath the superior and inferior vena cava. Extensive debridement along the pulmonary veins was done with removal of the left atrial posterior wall and necrotic debris and visualization of the atrioesophageal fistula. A bovine pericardial patch was then sewn to reconstruct the entire posterior wall of the left atrium followed by closure of the atriotomy. Upon discontinuation of cardiopulmonary bypass and closure of median sternotomy, surgical repair of the esophagus was undertaken. Following Esophagogastroduodenoscopy (EGD), the right latissimus dorsi and right 5th intercostal muscles were harvested via a right thoracotomy approach. The distal esophagus was then dissected off the left atrium entirely and the fistula was

Table 1: Patients and Procedure Characteristics

TABLE 1
Patients and Procedure Characteristics

Pt #	Age (years)	Gender	AF Type	Procedure	Time from Procedure to Presentation (days)	Clinical Presentation	Diagnosis Modality (pre-emptive/definitive)	Treatment	Outcome
1	54	Male	PAF	PVI RFA	24	Chest pain, unilateral weakness, fever, sepsis	Chest CT/ surgery	Surgery	Survived
2	70	Male	PAF	PVI HIFU	21	Chest pain, fever, hemiparesis, sepsis	Chest CT/ surgery	Surgery	Survived
3	71	Female	PerAF	PVI+CFAE RFA	27	Chest pain, headache, near-syncope, fever	Chest CT/autopsy	Non-surgical	Deceased (2 days after diagnosis)
4	55	Male	PerAF	PVI +FIRM RFA	21	Sudden death	Autopsy	N/A	Deceased
5	61	Female	PAF	PVI RFA	26	Visual changes, altered mental status, stroke	Chest CT/ autopsy	Non-surgical	Deceased (5 days after diagnosis)

AF: atrial fibrillation; CFAE: complex fractionated atrial electograms; FIRM: focal impulse and rotor modulation; HIFU: high-intensity focused ultrasound; PAF: paroxysmal atrial fibrillation; PerAF: persistent atrial fibrillation; PVI: pulmonary vein isolation; RFA: radiofrequency ablation

taken down from the left atrial posterior wall and the descending thoracic aorta. The fistula opening on the esophagus side was closed. A myotomy was performed centered around the esophageal fistula and the right intercostal muscle flap was used to cover the esophageal myotomy. The latissimus dorsi muscle flap was then sutured to the left atrial repair site to ensure complete separation of the posterior left atrial wall from the esophagus.

Clinical Outcomes

Three patients died before surgery could be performed. In 2 of the 3 patients, death occurred from complications of cerebral embolic events (patients 3 and 5); one died 2 days (patient 3) and the other 5 days (patient 5) after the initial diagnosis of AEF. Non-surgical treatment included broad spectrum antimicrobials and respiratory support with mechanical ventilation. Antimicrobial therapy (for surgical and non-surgical patients) included vancomycin (n=4), piperacillin-tazobactam (n=3), meropenem (n=1) and fluconazole (n=3). One patient had sudden death without preceding symptoms and AEF was diagnosed on autopsy with air embolism as the presumptive cause of death based on autopsy findings. Two patients (40%) underwent successful emergent surgery and survived (100% survival). At one-year follow-up, both patients were alive and free of residual neurologic deficits.

Discussion

Atrioesophageal fistula is a rare but potentially fatal complication of AF catheter ablation. Symptoms usually develop 3-6 weeks after the index ablation and may be vague, leading to lack of recognition and delayed diagnosis, explaining the high mortality rate.

Pathogenesis

The pathogenesis of AEF formation is not fully understood. The close anatomic relationship between the esophagus and the left atrial posterior wall likely plays a key role. The esophagus is located in a groove posterior to the left atrium bounded by the thoracic vertebral column and the aorta posteriorly. Thermal injury during ablation is thought to affect the esophageal microvasculature leading to ischemic necrosis and ulceration. Progression from ulceration to AEF formation may be facilitated by esophagitis, adjacent fatty necrosis, gastric hypomotility, and periesophageal vagal plexus injury resulting in lower esophageal sphincter relaxation and acid reflux.[9]–[13] The need for these sub-acute changes to occur could explain the delayed presentation of AEF after ablation.

Risk Reduction

Several strategies may decrease the risk of AEF formation after catheter ablation. These include use of an esophageal temperature probe for continuous monitoring of esophageal luminal temperature during ablation, real-time visualization of esophagus with barium paste or intracardiac echocardiography (ICE) during the procedure, reduction of power applied to the posterior left atrial wall in the vicinity of the esophagus, prophylactic administration of proton pump inhibitors, mechanical displacement of esophagus or intrapericardial balloon retraction of left atrium, and use of cryoenergy.[14]–[17] Despite these protective measures, risk of AEF is not completely eliminated.[18]–[20]

Clinical presentation and Diagnostic Tools

Patients included in our study presented with a constellation of thoracic, infectious and neurologic findings including chest pain, fever, leukocytosis, sepsis, TIA and stroke between 3-4 weeks after ablation. Chest pain and fever were the leading symptoms of AEF and occurred days to hours before the neurologic complications.

CT scan of chest with intravenous contrast was diagnostic in all the patients who were imaged. The most common findings were air in the left atrium and pneumomediastinum. One patient required a second chest CT one day after the initial imaging due to non-diagnostic initial findings and a high index of suspicion. This imaging modality has been shown to be the most useful tool in multiple prior studies.[7],[21],[22] A high index of suspicion should be guiding image interpretation and in cases of equivocal or non-diagnostic scans, repeat CT imaging may have diagnostic value specially if pre-test probability remains high. Brain MRI was an excellent tool for identifying neurologic sequelae of AEF and when performed, showed multifocal embolic lesions. Diagnostic EGD should not be performed prior to surgical repair due to the inherent risk of worsening air emboli from endoscopic air insufflation required during examination. In the surgical patients, EGD was only performed intraoperatively after the left atrial side of the fistula was repaired in order to identify the site of fistula on the esophageal side to guide operative repair.

Treatment and Outcome

There is limited data regarding the prognosis of those patients who survive to undergo surgical repair due to the small number of reported cases, but it appears to be favorable.[8],[18] Based on the data

available, the type of repair seems to affect prognosis, with those receiving esophageal stenting having the worst outcome and those undergoing surgery with combined left atrial and esophageal repair having the best result.[18],[21],[23]

In this series, AEF was promptly diagnosed and treated with surgical repair in 2 patients. Both patients survived without any perioperative complications. The surgical technique used was a combined left atrial and esophageal repair. The importance of primary esophageal repair in addition to left atrial repair to minimize postoperative morbidity has been emphasized previously.[21] Interposition of a muscle flap (in our series, intercostal and latissimus dorsi muscle flaps were used) appears beneficial by providing physical separation between the left atrium and esophagus and by allowing the pedicled muscle flap to bring blood supply into a contaminated area.[24]–[26]

Although mixed results have been reported in the literature for the surgical repair of AEF, so far this is the only strategy associated with survival in patients with AEF.[21],[26]–[29] Fatal outcomes after surgical repair may be related to late presentation or delay in diagnosis and intervention. Primary esophageal stenting, while may be successful in treatment of esophageal perforation[30] and even esophagopericardial fistulas[31], has been associated with uniform fatal outcomes for the treatment of confirmed AEF and is therefore not recommended.[18],[21],[32],[33]

Management suggestions

Despite preventative measures implemented during AF catheter ablation, esophageal thermal injury may occur for various reasons leading to AEF formation.[18],[34]–[36] Awareness of this complication among the medical community including emergency and primary care physicians is crucial. High index of suspicion is required for prompt diagnosis and treatment. A triad of chest pain, fever, and neurologic symptoms 3-4 weeks after AF ablation is highly concerning for AEF. However, given the low incidence of this complication and an overall lack of familiarity with AF catheter ablation techniques in the ER and primary care community, these symptoms may be attributed to other causes.

All patients with suspected diagnosis of AEF should undergo immediate contrast-enhanced chest CT and be transferred to a hospital equipped with a cardiothoracic surgery facility. Immediate combined left atrial and esophageal repair is the best option based on our experience. Perioperative care in the ICU should include broad-spectrum antimicrobials, early initiation of feeding via jejunostomy tube and ongoing neurologic evaluation and rehabilitation.

Limitations

Our study has a number of limitations. (1) As expected by the very low prevalence of AEF, our cohort size was small. (2) Complete diagnostic data was lacking on one patient who presented with AEF to an outside facility. (3) Details of procedural techniques and esophageal protective measures during ablation were not available for 2 patients who were transferred to our facility for management of AEF.

Conclusions

Atrioesophageal fistula remains a serious complication of AF catheter ablation despite frequently used esophageal protection strategies. When untreated, the outcome is near-universally fatal. Prompt diagnosis of AEF and urgent referral for surgical repair is imperative as outcomes of early surgical repair are favorable. Health-care community education is the key to ensure early detection and transfer to a qualified surgical center.

Disclosures

None.

References

1. Cappato Riccardo, CalkinsHugh, ChenShih-Ann, DaviesWyn, IesakaYoshito, KalmanJonathan, KimYou-Ho, KleinGeorge, PackerDouglas, SkanesAllan. Worldwide survey on the methods, efficacy, and safety of catheter ablation for human atrial fibrillation. Circulation. 2005;111 (9):1100–5
2. Cappato Riccardo, CalkinsHugh, ChenShih-Ann, DaviesWyn, IesakaYoshito, KalmanJonathan, KimYou-Ho, KleinGeorge, NataleAndrea, PackerDouglas, SkanesAllan, AmbrogiFederico, BiganzoliElia. Updated worldwide survey on the methods, efficacy, and safety of catheter ablation for human atrial fibrillation. Circ Arrhythm Electrophysiol. 2010;3 (1):32–8
3. Ghia Kasturi K, ChughAman, GoodEric, PelosiFrank, JongnarangsinKrit, BogunFrank, MoradyFred, OralHakan. A nationwide survey on the prevalence of atrioesophageal fistula after left atrial radiofrequency catheter ablation. J Interv Card Electrophysiol. 2009;24 (1):33–6
4. Cappato Riccardo, CalkinsHugh, ChenShih-Ann, DaviesWyn, IesakaYoshito, KalmanJonathan, KimYou-Ho, KleinGeorge, NataleAndrea, PackerDouglas, SkanesAllan. Prevalence and causes of fatal outcome in catheter ablation of atrial fibrillation. J. Am. Coll. Cardiol. 2009;53 (19):1798–803
5. Dagres Nikolaos, KottkampHans, PiorkowskiChristopher, DollNicolas, MohrFriedrich, HorlitzMarc, KremastinosDimitrios Th, HindricksGerhard. Rapid detection and successful treatment of esophageal perforation after radiofrequency ablation of atrial fibrillation: lessons from five cases. J. Cardiovasc. Electrophysiol. 2006;17 (11):1213–5
6. Cummings Jennifer E, SchweikertRobert A, SalibaWalid I, BurkhardtJ David, KilikaslanFethi, SaadEduardo, NataleAndrea. Brief communication: atrial-esophageal fistulas after radiofrequency ablation. Ann. Intern. Med. 2006;144 (8):572–4
7. Siegel Marc O, ParentiDavid M, SimonGary L. Atrial-esophageal fistula after atrial radiofrequency catheter ablation. Clin. Infect. Dis. 2010;51 (1):73–6
8. Chavez Patricia, MesserliFranz H, Casso DominguezAbel, AzizEmad F, SichrovskyTina, GarciaDaniel, BarrettConnor D, DanikStephan. Atrioesophageal fistula following ablation procedures for atrial fibrillation: systematic review of case reports. Open Heart. 2015;2 (1)
9. Nair Girish M, NeryPablo B, RedpathCalum J, LamBuu-Khanh, BirnieDavid H. Atrioesophageal fistula in the era of atrial fibrillation ablation: a review. Can J Cardiol. 2014;30 (4):388–95
10. Zellerhoff Stephan, UllerichHansjörg, LenzeFrank, MeisterTobias, WasmerKristina, MönnigGerold, KöbeJulia, MilbergPeter, BittnerAlex, DomschkeWolfram, BreithardtGünter, EckardtLars. Damage to the esophagus after atrial fibrillation ablation: Just the tip of the iceberg? High prevalence of mediastinal changes diagnosed by endosonography. Circ Arrhythm Electrophysiol. 2010;3 (2):155–9
11. Zellerhoff Stephan, LenzeFrank, EckardtLars. Prophylactic proton pump inhibition after atrial fibrillation ablation: is there any evidence?. Europace. 2011;13 (9):1219–21
12. Shah Dipen, DumonceauJean-Marc, BurriHaran, SunthornHenri, SchroftAndreas, Gentil-BaronPascale, YokoyamaYasuhiro, TakahashiAtsushi. Acute pyloric spasm and gastric hypomotility: an extracardiac adverse effect of percutaneous radiofrequency ablation for atrial fibrillation. J. Am. Coll. Cardiol. 2005;46 (2):327–30
13. Pisani Cristiano F, HachulDenise, SosaEduardo, ScanavaccaMauricio. Gastric hypomotility following epicardial vagal denervation ablation to treat atrial fibrillation. J. Cardiovasc. Electrophysiol. 2008;19 (2):211–3
14. Redfearn Damian P, TrimGeoffrey M, SkanesAllan C, PetrellisBasilios,

KrahnAndrew D, YeeRaymond, KleinGeorge J. Esophageal temperature monitoring during radiofrequency ablation of atrial fibrillation. J. Cardiovasc. Electrophysiol. 2005;16 (6):589–93

15. Liu Enzhao, ShehataMichael, LiuTong, AmornAllen, CingolaniEugenio, KannarkatVinod, ChughSumeet S, WangXunzhang. Prevention of esophageal thermal injury during radiofrequency ablation for atrial fibrillation. J Interv Card Electrophysiol. 2012;35 (1):35–44
16. Buch Eric, NakaharaShiro, ShivkumarKalyanam. Intra-pericardial balloon retraction of the left atrium: a novel method to prevent esophageal injury during catheter ablation. Heart Rhythm. 2008;5 (10):1473–5
17. Contreras-Valdes Fernando M, HeistE Kevin, DanikStephan B, BarrettConor D, BlendeaDan, BruggeWilliam R, PtaszekLeon, RuskinJeremy N, MansourMoussa. Severity of esophageal injury predicts time to healing after radiofrequency catheter ablation for atrial fibrillation. Heart Rhythm. 2011;8 (12):1862–8
18. Mohanty Sanghamitra, SantangeliPasquale, MohantyPrasant, Di BiaseLuigi, TrivediChintan, BaiRong, HortonRodney, BurkhardtJ David, SanchezJavier E, ZagrodzkyJason, BaileyShane, GallinghouseJoseph G, HranitzkyPatrick M, SunAlbert Y, HongoRichard, BeheirySalwa, NataleAndrea. Outcomes of atrioesophageal fistula following catheter ablation of atrial fibrillation treated with surgical repair versus esophageal stenting. J. Cardiovasc. Electrophysiol. 2014;25 (6):579–84
19. Guhl Emily N, SiddowayDonald, AdelsteinEvan, BazazRaveen, MendenhallGeorge S, NemecJan, SabaSamir, SchwartzmanDavid, VoigtAndrew, WangNorman C, JainSandeep K. Incidence and Predictors of Complications During Cryoballoon Pulmonary Vein Isolation for Atrial Fibrillation. J Am Heart Assoc. 2016;5 (7)
20. John Roy M, KapurSunil, EllenbogenKenneth A, KoneruJayanthi N. Atrioesophageal fistula formation with cryoballoon ablation is most commonly related to the left inferior pulmonary vein. Heart Rhythm. 2017;14 (2):184–189
21. Singh Sheldon M, d'AvilaAndre, SinghSteve K, StelzerPaul, SaadEduardo B, SkanesAllan, AryanaArash, ChinitzJason S, KulinaRobert, MillerMarc A, ReddyVivek Y. Clinical outcomes after repair of left atrial esophageal fistulas occurring after atrial fibrillation ablation procedures. Heart Rhythm. 2013;10 (11):1591–7
22. Khandhar Sandeep, NitzschkeStephanie, AdNiv. Left atrioesophageal fistula following catheter ablation for atrial fibrillation: off-bypass, primary repair using an extrapericardial approach. J. Thorac. Cardiovasc. Surg. 2010;139 (2):507–9
23. Hartman Alan R, GlassmanLawrence, KatzStanley, ChinitzLarry, RossWilliam. Surgical repair of a left atrial-esophageal fistula after radiofrequency catheter ablation for atrial fibrillation. Ann. Thorac. Surg. 2012;94 (4):e91–3
24. D'Avila Andre, PtaszekLeon M, YuPaul B, WalkerJennifer D, WrightCameron, NoseworthyPeter A, MyersAndrea, RefaatMarwan, RuskinJeremy N. Images in cardiovascular medicine. Left atrial-esophageal fistula after pulmonary vein isolation: a cautionary tale. Circulation. 2007;115 (17):e432–3
25. Vassileva Christina M, ShawgoTilitha, ShaboskyJohn, SolimanSoliman, HazelriggStephen. Repair of left atrial-esophageal fistula following percutaneous radiofrequency ablation for atrial fibrillation. J Card Surg. 2011;26 (5):556–8
26. Haggerty Kara A, GeorgeTimothy J, ArnaoutakisGeorge J, BarreiroChristopher J, ShahAshish S, SussmanMarc S. Successful repair of an atrioesophageal fistula after catheter ablation for atrial fibrillation. Ann. Thorac. Surg. 2012;93 (1):313–5
27. Rivera Giovanni A, DavidIrving B, AnandRishi G. Successful atrioesophageal fistula repair after atrial fibrillation ablation. J. Am. Coll. Cardiol. 2013;61 (11)
28. Shim Hun Bo, KimChilsung, KimHong-Kwan, SungKiick. Successful management of atrio-esophageal fistula after cardiac radiofrequency catheter ablation. Korean J Thorac Cardiovasc Surg. 2013;46 (2):142–5
29. Sonmez Bingur, DemirsoyErgun, YaganNaci, UnalMehmet, ArbatliHarun, SenerDeniz, BaranTurker, IlkovaFeryal. A fatal complication due to radiofrequency ablation for atrial fibrillation: atrio-esophageal fistula. Ann. Thorac. Surg. 2003;76 (1):281–3
30. Sepesi Boris, RaymondDaniel P, PetersJeffrey H. Esophageal perforation: surgical, endoscopic and medical management strategies. Curr. Opin. Gastroenterol. 2010;26 (4):379–83
31. Eitel Charlotte, RolfSascha, ZachäusMarkus, JohnSilke, SommerPhilipp, BollmannAndreas, AryaArash, PiorkowskiChristopher, HindricksGerhard, HalmUlrich. Successful nonsurgical treatment of esophagopericardial fistulas after atrial fibrillation catheter ablation: a case series. Circ Arrhythm Electrophysiol. 2013;6 (4):675–81
32. Zellerhoff Stephan, LenzeFrank, SchulzRonald, EckardtLars. Fatal course of esophageal stenting of an atrioesophageal fistula after atrial fibrillation ablation. Heart Rhythm. 2011;8 (4):624–6
33. Hazell Wayne, HeavenDavid, KazemiAlex, FourieDean. Atrio-oesophageal fistula: an emergent complication of radiofrequency ablation. Emerg Med Australas. 2009;21 (4):329–32
34. Bruce G Keith, BunchT Jared, MiltonMark A, SarabandaAlvaro, JohnsonSusan B, PackerDouglas L. Discrepancies between catheter tip and tissue temperature in cooled-tip ablation: relevance to guiding left atrial ablation. Circulation. 2005;112 (7):954–60
35. Bunch T Jared, NelsonJennifer, FoleyTom, AllisonScott, CrandallBrian G, OsbornJeffrey S, WeissJ Peter, AndersonJeffrey L, NielsenPeter, AndersonLars, LappeDonald L, DayJohn D. Temporary esophageal stenting allows healing of esophageal perforations following atrial fibrillation ablation procedures. J. Cardiovasc. Electrophysiol. 2006;17 (4):435–9
36. Di Biase Luigi, SaenzLuis Carlos, BurkhardtDavid J, VaccaMiguel, ElayiClaude S, BarrettConor D, HortonRodney, BaiRong, SiuAlan, FahmyTamer S, PatelDimpi, ArmaganijanLuciana, WuChia Tung, KaiSonne, ChingChing Keong, PhillipsKaren, SchweikertRobert A, CummingsJennifer E, ArrudaMauricio, SalibaWalid I, DodigMilan, NataleAndrea. Esophageal capsule endoscopy after radiofrequency catheter ablation for atrial fibrillation: documented higher risk of luminal esophageal damage with general anesthesia as compared with conscious sedation. Circ Arrhythm Electrophysiol. 2009;2 (2):108–12

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Efficacy of Catheter Ablation and Concomitant Antiarrhythmic Drugs on the Reduction of the Arrhythmia Burden in Patients with Long-Standing Persistent Atrial Fibrillation

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Abstract

Background: Little is known about the long-term outcome and recurrent form recurrence after catheter ablation of atrial fibrillation (AF) in patients with long-standing persistent AF.

Methods: Two hundred thirty-six patients with persistent AF (193 men; age, 61.5±10.7 years) were enrolled, and were classified according to the duration of AF: AF duration of <1 year (group A, n=99), between 1 to 5 years (group B, n=101), and ≥5 years (group C, n=36). The long-term recurrence rate and recurrent form were compared among the groups.

Results: During a median follow-up of 3.7 years, the recurrence rate was significantly worse in group C after the index and multiple procedures (Log-Rank, both for a P<0.001 in comparison to group A). In the multivariate analysis, the duration was an independent predictor of an arrhythmia recurrence (HR, 1.206; 95%CI, 1.053 to 1.381; P=0.007). Recurrent AF became permanent in 8 patients (3.4%), which was not associated with a difference in the groups (Log-rank, P=0.055), while antiarrhythmic drugs (AADs) were continued in 70% of the recurrent patients.

Conclusions: Despite a high AF recurrence rate in the patients with an AF duration of ≥5 years, the majority of the patients with recurrence who continued on AADs had a paroxysmal form of AF. Catheter ablation and concomitant AADs may be effective in reducing the AF burden in such patients with an advanced AF disease stage.

Introduction

Catheter ablation is an established therapy for atrial fibrillation (AF). Pulmonary vein isolation (PVI) is the cornerstone of the procedure, particularly in patients with paroxysmal PAF (PAF) [1]. However, the efficacy of PVI alone for the treatment of persistent AF is limited, which has resulted in an increasing demand for additional modification of the atrial substrate, such as targeting complex fractionated atrial electrograms (CFAEs) [2], linear lesions [3], [4], and their combinations. Despite these continued efforts to identify additive strategies, the recurrence rate after catheter ablation in patients with persistent AF has been high compared to that with PAF, and particularly in patients with an AF duration of >2 years [5]. Although it is suggested that the increase in the AF duration is associated with a higher risk of recurrence after ablation, little is known about the recurrence of AF in long standing AF patients post ablation treated with concomitant antiarrhythmic medications. In this study, we sought to determine the long-term recurrence rate in long-standing persistent patients with an AF duration of ≥5 years.

Key Words

Persistent atrial fibrillation, Catheter ablation, Antiarrhythmic drugs.

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Materials and Methods

Study subjects

The study was comprised of 236 consecutive patients undergoing catheter ablation of persistent AF at Musashino Red Cross Hospital, Tokyo. There were 193 men, with 137 having long-standing AF, and their mean age was 62±11 years (range 25-82, [Table 1]). This study was approved by the Institutional Review Board, and written informed consent was obtained before the procedure.

Definition

Persistent AF was defined as continuous AF that was sustained beyond seven days [1], and longstanding persistent AF as continuous AF of greater than a 12 month duration. The duration of persistent AF was determined from the last time when sinus rhythm (SR) was recorded on the electrocardiogram (ECG) to the time during the index procedure. If the AF was found incidentally through a routine health check, the onset was retraced when SR was lastly confirmed on the ECG. Patients were classified by the duration of the AF into three groups: those with an AF duration of less than 1 year (group A, n= 99), those with an AF duration between 1 to 5 years (group B, n=101), and those with an AF duration of more than 5 years (group C, n=36). The long-term outcome after the index and

multiple procedures was compared between the three groups. We also investigated the mode of recurrent arrhythmias, namely, whether the recurrent AF became permanent or paroxysmal on antiarrhythmic drugs (AADs). Recurrent AF was defined as permanent if the AF persisted despite multiple procedures and AADs.

Procedure

All AADs were discontinued for at least 5 half-lives before the ablation. All patients were anticoagulated with warfarin for at least a month before the procedure (target INR 2–3), and the therapeutic anticoagulation was maintained with intravenous heparin after discontinuing warfarin one day before the procedure. Transesophageal echocardiography was performed within 24 hours prior to the procedure. The electrophysiological study was performed under mild sedation with dexmedetomidine hydrochloride. Four vascular sheaths (i.e., one 5-F, and three 8-F) were inserted into the right femoral vein under lidocaine local anesthesia. A 7-F, 20-pole or 14-pole two-site mapping catheter (Irvine Biomedical Inc, Irvin, CA) was inserted through the right jugular vein and positioned in the coronary sinus (CS) for pacing, recording, and internal cardioversion. A 50 IU/kg body weight of heparin was administered after the insertion of the vascular sheaths. A transseptal puncture was performed using a standard needle (Adult BRK 71 cm, St. Jude Medical, Minneapolis, Minnesota). A 50 IU/kg body weight of heparin was re-administered after the transseptal puncture, and heparinized saline was additionally infused to maintain the activated clotting time at 300–350 seconds. After the transseptal puncture, two long sheaths (SL0, SJM, Minneapolis, MN) were introduced into both superior PVs. The pulmonary vein (PV) electrograms were monitored with a decapolar circumferential mapping catheter (Lasso, Biosense Webster, Diamond Bar, CA, USA). A 3.5-mm irrigation catheter (ThermoCool, Biosense Webster, Diamond Bar, CA, USA) was used, under the guidance of a 3-dimensional (3D) mapping system (CARTO3, Biosense Webster). An esophageal temperature probe was advanced into the esophagus, and later adjusted to its closest proximity to the ablation sites along the left atrial (LA) posterior wall. The power was limited to 20-25W on the LA posterior wall, and the RF application was truncated when the esophageal temperature rose up to 41 degrees Celsius. Before the initiation of the PV isolation (PVI), up to three internal cardioversions (10J, 20J, and 30J) were administered. If AF persisted after the cardioversion, a PVI was performed during AF. A decapolar, circular catheter (Lasso, Biosense Webster) was used for the bipolar EGM recording at the PV antrum filtered at 30 to 500 Hz and displayed on a commercially available electrophysiological recording system (GE, Houston, TX), and to confirm the PVI, which was defined as PV bi-directional conduction block. After the PVI, internal cardioversion was re-administered when the AF continued. After restoring SR, if the AF was reinitiated, non-PV foci were pursued. Once AF converted into an organized AT, activation mapping on the 3D mapping system, entrainment, and ablation were performed. Roof and floor lines connecting the bottom floor region of the bilateral lower PVs were added in the presence of an LA posterior wall trigger or roof dependent macro-reentrant AT, and a mitral isthmus line was created in the case of macroreentrant perimitral flutter. Cavo-tricuspid isthmus (CTI) ablation was performed with an endpoint of bidirectional conduction block in all patients. Isolation of the superior vena cava (SVC) was only performed when SVC triggered AF was present or the sleeve length of the superior vena cava was ≥ 30 mm [6].

In the repeat procedure, after the isolation of the reconnected PVs, AF or AT was induced by atrial burst pacing in case of SR, using 10-second burst pacing intervals at an output of 10 V starting at a cycle length of 250 ms decreasing down to refractoriness from the right appendage. During native or induced AT, activation mapping on the 3D mapping system, entrainment mapping, and ablation were performed. During native or induced AF, substrate modification with a linear defragmentation method was performed sequentially in a predetermined order [7]. Linear point-by-point lesions guided by the 3D mapping system in the regions were performed in the following order: LA roof, floor lines connecting both PVs, LA septum from the high septum to fossa ovalis, inferior LA along the CS, base of the LA appendage, LA anterior wall, right atrial (RA) septum from the SVC-RA junction to the inferior vena cava (intercaval line), crista terminalis, and base of the RA appendage. The endpoint of the substrate ablation was AF termination. If the AF continued after all the steps, internal cardioversion was performed. If the AF was converted to AT, it was mapped and ablated. If the AF was not induced after the isolation of the reconnected PV, a substrate modification was not performed. An SVC isolation was performed in the patients who underwent it during the index procedure or SVC triggered AF was found during the repeat procedures.

Follow-up after the catheter ablation

The oral anticoagulants were resumed immediately after the procedure, targeting an international normalized ratio of 2 to 3. Patients underwent continuous ECG monitoring as inpatients for two days after the procedure. The first outpatient clinic visit was 3

Table 1: Clinical characteristics

	Group A: AF duration < 1 year (n=99)	Group B: AF duration 1-5years (n=101)	Group C: AF duration ≥ 5 years (n=36)	P Value
Male (%)	78 (78.8)	87 (86.1)	28 (77.8)	0.321
Age	63.7 ± 9.7	58.8 ± 11.7	62.6 ± 9.2	0.016
AF history (years)	2.8 ± 4.4	3.0 ± 2.1	8.1 ± 2.8	<0.001
Duration of persistence (years)	0.5 ± 0.2	2.2 ± 1.1	7.8 ± 2.7	<0.001
Hypertension (%)	27 (27.3)	23 (22.8)	10 (27.8)	0.720
Diabetes (%)	3 (3.0)	4 (4.0)	4 (11.1)	0.130
Prior stroke (%)	7 (7.1)	4(4.0)	4 (11.1)	0.297
Congestive heart failure (%)	5 (5.1)	15 (14.9)	2 (5.6)	0.041
CHADS2-Score	0.5 ± 0.7	0.5 ± 0.8	0.7 ± 1.0	0.503
Cardiomyopathy				
Ischemic (%)	4 (4.0)	3 (3.0)	1 (2.8)	0.894
Dilated (%)	0 (0)	4 (4.0)	0 (0)	0.066
Hypertrophic (%)	3 (3.0)	1 (1.0)	2 (5.6)	0.302
Valvular (%)	3 (3.0)	3 (3.0)	2 (5.6)	0.738
eGFR	65.5 ± 17.1	70.1 ± 14.5	65.0 ± 17.9	0.134
BNP (pg/ml)	121.4 ± 123.8	110.1 ± 132.9	120.5 ± 200.9	0.610
LVEF (%)	64.1 ± 9.2	62.8 ± 13.0	68.0 ± 7.8	0.121
LVDd (mm)	47 ± 7	49 ± 7	48 ± 5	0.109
Left Atrial Diameter (mm)	40 ± 7	41 ± 5	44 ± 6	0.024

AF, atrial fibrillation; eGFR, estimated glomerular filtration rate; BNP, brain natriuric peptide; LVEF, left ventricular ejection fraction; LVDd, left ventricular diastolic diameter. Values are given as the mean ± SD.

weeks after the procedure. In all patients, the AADs were continued for at least the first 3 months of the blanking period. An attempt was made to discontinue the AADs 3-6 months following the ablation, except for in the patients with AF or AT recurrences, defined by an episode lasting ≥30 seconds. A repeat procedure was offered if recurrences occurred 3 months following the index procedure. The AADs were continued or resumed in recurrent patients who refused a repeat procedure or recurred after multiple procedures. Oral anticoagulants were essentially discontinued based on the patient's $CHADS_2$ score [1]. The follow-up visits consisted of a clinical interview, ECG, and 24-hour Holter monitoring every 3, 6, and 12 months. After 12 months, the patients were seen thereafter every 6-12 months at our center. Either the last follow-up entry data set based on the last office visit or a telephone questionnaire were used to assess the long-term freedom from recurrence.

Statistical analysis

The categorical variables are expressed as absolute and relative frequencies. Continuous variables are expressed as the mean ± SD or median and interquartile range (IQR) (25th, 75th percentile) as appropriate. A comparison between the groups was performed with a Student's t-test or Wilcoxon rank-sum test, as appropriate. For categorical data, a Chi-squared or Fisher's exact test was applied, as appropriate. The estimated freedom from arrhythmia recurrence after catheter ablation was calculated using a Kaplan-Meier analysis, and long-lank statistics were used for the overall comparisons among the three groups. In addition, a post hoc pairwise analysis was performed with the use of the Bonferroni method. To clarify the clinical predictors of the outcomes, a univariate Cox proportional analysis was first performed. Sequentially, all variables significant in the univariate analysis were included in the multivariate analysis, and the hazard ratios (HRs) and 95% confidence intervals (CI) were calculated. A 2-tailed p value of <0.05 was considered to indicate statistical significance. All statistical analyses were performed with SPSS statistics software (IBM Corp, Armonk, NY).

Results

The baseline demographics, clinical characteristics, echocardiographic variables, and biomarkers are shown in Table 1. The age was the highest in the group A and lowest in the group B patients. The duration of AF in the three groups was 2.8±4.4 years, 3.0±2.1, and 8.1±2.8, respectively (P < 0.001). The duration of the persistence was 0.5±0.2 years, 2.2±1.1, and 7.8±2.7, respectively (P < 0.001). Three hundred seventy-eight procedures, that is 1.6 procedures per patient, were performed: 119 had 1, 96 had 2, 17 had 3, and 4 had 4 procedures. Figure 1 provides an overview of the procedures. After the index procedure, SR was maintained in 107 of 236 (45%) patients. A roof and bottom floor line, mitral isthmus line, and SVC isolation were performed in 38 (16%), 6 (3%), and 22 patients (9%), respectively. Among the 129 patients with a recurrence, 2nd procedures were performed in 117 patients, including 12 (5%) who had only an AT recurrence. During the 2nd procedure, after isolating the reconnected PV, no further AF or AT was induced in 34 patients (29% of the 117 patients), and only AT was induced in four patients (3%). Substrate modification during AF was performed in the remaining 83 patients, and in 11 of whom AF was terminated by ablation (13%). After the 2nd procedures, 59 of 117 patients (50%) presented with recurrences, 16 (14%) of whom had AT. Of the 59 patients, 19 underwent 3rd procedures, and 10 had recurrences, including three with AT recurrences. Among the 10 patients, four patients underwent a 4th procedure, and one patient had an AF recurrence. During a median follow-up of 3.3 (IQR: 1.9, 5.3) years, 177 of 236 (75%) patients remained in SR. AADs were continued in 112 of 236 patients: 72 of 177 patients (41%) without recurrences, and 40 of 59 (70%) with recurrences. Bepridil was used in 77 (mean dose 99 ± 39mg), amiodarone in 11 (mean dose 113 ± 39mg), and class I AADs in 24. Oral anticoagulants were discontinued in 85 patients (48%) without recurrences, and in 19 (32%) with recurrences. Of the 19 patients with recurrences, 18 discontinued their oral anticoagulants due to a $CHADS_2$ score of less than 1. The remaining patient with a $CHADS_2$ score of 2 preferred to discontinue oral anticoagulants.

Clinical outcome after the index procedure

In the Kaplan-Meier analysis, the estimated probability of an atrial arrhythmia-free survival without AADs at 1, 2 and 5 years was 49%, 38%, and 26%, respectively (Figure 2). With AADs, the estimated probability of an atrial arrhythmia-free survival at 1, 2 and 5 years was 64% (group A 73%, group B 63%, and group C 32%), 51% (group A 58%, group B 50%, and group C 29%), and 37% (group A 46%, group B 37%, and group C 15%), respectively (Figure 2). There was a significant difference between the groups in terms of the recurrence rate after the index procedure (P<0.001, Figure 2). In the three subgroups, there was no difference between Group A and Group B (P=0.182), whereas Group C had a significantly higher recurrence rate than Group A (P<0.001).

Clinical outcome after multiple procedures

In the Kaplan-Meier analysis, the estimated probability of an atrial arrhythmia-free survival without AADs at 1, 2 and 5 years was 64%, 60%, and 41%, respectively (Figure 2). With AADs, the estimated probability of an atrial arrhythmia-free survival at 1, 2 and 5 years was 95% (group A 99%, group B 94%, and group C 86%), 90% (group A 98%, group B 86%, and group C 80%), and 69% (group A 84%, group B 65%, and group C 55%), respectively (Figure 2). There was a significant difference between the groups in terms of the recurrence rate after multiple procedures (P=0.001: P=0.024 for Group A vs. B, P<0.001 for Group A vs. C, and P=0.047 for Group B vs. C).

Factors for arrhythmia recurrence

[Table 2] summarizes the clinical factors associated with the recurrence after multiple procedures. In the univariate analysis, the duration from the time when the patient was initially diagnosed with paroxysmal or persistent AF to the time during the index procedure (HR 1.112; CI, 1.033 to 1.197; P = 0.005), and the duration of persistent AF (HR 1.246; CI, 1.120-1.385; P < 0.005) were predictors of arrhythmia recurrence. In the multivariate analysis, the duration of persistent AF was an independent predictor of arrhythmia recurrence (HR, 1.206; 95% CI, 1.053 to 1.381; P = 0.007).

Incidence of permanent AF after multiple procedures

A permanent form of AF recurrence occurred in eight of the 236 patients (3%), and the incidence rate was 9.29 cases per 1000 person-years. No patients with AF recurrence in group A had permanent AF. Five of the eight patients were from group B (5% of 101 patients), whereas the remaining three patients were from group C (8% of 36 patients). In the Kaplan-Meier analysis, there was no significant difference between the three groups in terms of the number of patients with permanent AF (P=0.055, Figure 2). There was also no significant difference in the incidence of permanent AF between each group (P=0.157 for Group A vs. B, P=0.053 for Group A vs. C, and P=0.997 for Group B vs. C).

Table 2: Factors for arrhythmia recurrence after multiple procedures

	Univariable			Multivariable		
	HR	P	95% CI	HR	P	95% CI
Male gender	0.983	0.207	0.956-1.010			
Age	1.251	0.586	0.560-2.794			
Duration of AF	1.112	0.005	1.033-1.197	1.054	0.299	0.954-1.164
Duration of AF persistence	1.246	<0.001	1.120-1.385	1.206	0.007	1.053-1.381
Hypertension	0.83	0.603	0.411-1.675			
Diabetes	0.302	0.258	0.038-2.410			
Prior stroke	0.21	0.136	0.27-1.637			
Congestive heart failure	0.675	0.494	0.219-2.083			
Ischemic cardiomyopathy	0.439	0.446	0.053-3.644			
Dilated cardiomyopathy	3.218	0.248	0.44-23.383			
Hypertrophic cardiomyopathy	3.259	0.155	0.639-16.620			
Valvular cardiomyopathy	3.302	0.099	0.798-13.654			
eGFR	1.006	0.546	0.987-1.025			
BNP	0.999	0.668	0.997-1.002			
LVEF	0.983	0.223	0.957-1.010			
LVDd	1.044	0.058	0.999-1.090			
Left Atrial Diameter	1.038	0.143	0.987-1.091			

AF, atrial fibrillation; eGFR, estimated glomerular filtration rate; BNP, brain natriuric peptide; LVEF, left ventricular ejection fraction; LVDd, left ventricular diastolic diameter. Values are given as the mean ± SD.

Procedural adverse events

Among 378 procedures, there were four major complications (1%) in this study. Transient ischemic attacks occurred in two patients. One patient experienced one shortly after the catheter ablation, and the other experienced one 10 days after the catheter ablation. One patient developed pulmonary edema requiring mechanical ventilation, resulting in a prolonged hospitalization. Cardiac tamponade occurred in one patient. During the follow-up period, two patient died from non-cardiac causes (one patient died from pharyngeal cancer, and the other from pancreatic cancer), while no patients died from cardiac disease. No late thromboembolic events occurred more than one month after the catheter ablation, and no PV stenosis or atrioesophageal fistula occurred.

Discussion

In this single center study, we found that the AF duration was significantly associated with arrhythmia recurrence after the catheter ablation. However, in conjunction with AADs, the incidence of permanent AF in patients with long-standing persistent AF was similarly low compared to that with an AF duration of <1 year.

Impact of catheter ablation and concomitant AADs on the downgrade of persistent AF

The impact of the AF duration on the arrhythmia recurrence, shown in this study, was in agreement with the previous study. Tilz et al. demonstrated that the arrhythmia-free survival was significantly higher among patients with an AF duration of <2 years than among those with an AF duration of >2 years [5]. In our study, patients with an AF duration of ≥5 years had the highest arrhythmia recurrence rate. However, the number of such patients with a persistent form of AF was fairly low (8%) after multiple procedures, while AADs were continued in 70% of the recurrent patients. In our study, the majority of the recurrent patients having been continued on bepridil, class IV AADs with a multiple ion-channel blocker, was highly effective for the maintenance of SR in patients with persistent AF, compared with amiodarone [8]-[10]. Kondo et al. demonstrated that bepridil reduced the recurrence of AF compared to amiodarone and class I AADs in patients who underwent catheter ablation of persistent AF [11], and a Japanese nationwide survey of catheter ablation of AF revealed that bepridil was most frequently prescribed (17.4%), specifically in patients with persistent AF [12], both of which were in agreement with our results. The annual incidence of permanent AF was 0.929% in this study, which was lower than that for PAF in those treated with bepridil (4%) alone [13], suggesting the additional effect of catheter ablation on bepridil. Importantly, the relatively low dose of bepridil (99±39mg) for AF recurrence was effective for avoiding a permanent form of AF recurrence, while minimizing the risk of QT prolongation associated with high doses of 200mg [14], [15]. Due to the concern over the impairment of the long-term atrial function after extensive substrate modification [16], extensive substrate modification was selectively performed in 35% of the patients (83 of 236 patients) . Considering the limited number of recurrent patients with permanent AF, our stratified approach for catheter ablation of persistent AF, in conjunction with low dose AADs, contributed to the downgrade of persistent AF, likely associated with the reduction in the AF burden.

In this study, the LA diameter differed among the groups, suggesting the correlation between the duration of AF and degree of atrial structural remodeling. The LA diameter has been shown to be a predictor of recurrence after catheter ablation [1], but it was not a predictor of recurrence in the univariate analysis in this study, possibly due to our limited sample size and patient selection bias that patients with severely dilated LA may have been excluded.

AF burden, thromboembolic events, and mortality

The AF burden is highly associated with the incidence of thromboembolic events, which are one of major adverse events associated with AF. Recent studies with a large number of AF patients has shown an increased risk of thromboembolic events in patients with persistent AF as compared to PAF [17]-[20]. Takabayashi et al. reported that the annual incidence of thromboembolic events was 1.4 and 3.0 per 100 person-years in patients without a progression from PAF to persistent AF, and those who progressed to persistent AF, respectively [19]. In the study of the ENGAGE AF-TIMI 48 trial, strokes/systemic embolic events were lower in those patients with PAF (1.49%/year), compared to that in persistent (1.83%/year) and permanent AF (1.95%/year). Furthermore, the all-cause mortality was lower in those with paroxysmal (3.0%/year) than in those with persistent (4.4%/year) and permanent AF (4.4%/year) [20]. Other reports also demonstrated a higher risk for all-cause mortality in patients with persistent AF than in those with PAF [17], [18]. Interestingly, the majority of deaths in a large anticoagulated AF population were not related to strokes [21]. Marijon et al. reported that cardiac deaths accounted for 37.4% of all deaths (persistent AF was 67.2% of 18113 patients), whereas stroke and hemorrhage related deaths represented 9.8%. Those results suggest that the increased mortality may not only be related to an increased risk of thromboembolic events, but to an impairment of the cardiac function associated with AF persistence in patients with a high AF burden. There have been previous studies demonstrating a low incidence of

thromboembolic events after a successful catheter ablation of AF [22]-[24]. More recently, a propensity score-matched analysis revealed that the adjusted HRs for strokes and mortality were lower in patients undergoing catheter ablation than in those who did not [25]. Therefore, catheter ablation of AF may have an impact on the decreased risk of thromboembolic events and mortality, possibly due to the beneficial effect of the reduction in the AF burden.

Limitations

First, our single center study had no control group without catheter ablation to compare the incidence of thromboembolic events and the cardiovascular mortality. Furthermore, there was a lack of evidence to support the favorable effect of downgrading AF on the clinical outcomes due to the relatively small number of patients. To address that issue, lager and randomized trials are required. Second, almost half of the patients continued on AADs after the procedures. Although there were no patients with adverse events from the AADs in this study, the long-term safety of AADs should be cautiously monitored in our patients. Third, in the absence of the continuous monitoring devices, it was likely that some of the patients we regarded as being free from AF had undetected arrhythmia recurrences. These false negatives, if detected, should have been included in the patients without arrhythmia recurrences. Nevertheless, the undetected PAF would not have affected the clinical relevance of our study. Fourth, the symptomatic severity was not systematically assessed during the enrollment of the patients. The efficacy of catheter ablation in patients with symptomatic persistent AF has been widely recognized, while it has not fully investigated in asymptomatic patients. Recently, we conducted a study to determine the efficacy of catheter ablation in patients with asymptomatic persistent AF, and found that maintenance of SR after catheter ablation was associated with an improvement in quality of life, exercise performance, and plasma B-type natriuretic peptide level [26]. Interestingly, there was a significant linear correlation of an increased duration of exercise and plasma BNP decrease. It is suggested that catheter ablation is effective for the maintenance of SR irrespective of symptoms in patients with persistent AF'.

Conclusions

The risk of AF recurrence increases as the duration of persistent AF increases. However, the majority of recurrent patients with long-standing persistent AF continued on AADs and continued to have a paroxysmal form of AF. In conjunction with AADs, catheter ablation may have an impact on the reduction in the AF burden in such patients with an advanced AF disease stage.

Disclosures

None.

References

1. Calkins Hugh, KuckKarl Heinz, CappatoRiccardo, BrugadaJosep, CammA John, ChenShih-Ann, CrijnsHarry J G, DamianoRalph J, DaviesD Wyn, DiMarcoJohn, EdgertonJames, EllenbogenKenneth, EzekowitzMichael D, HainesDavid E, HaissaguerreMichel, HindricksGerhard, IesakaYoshito, JackmanWarren, JalifeJose, JaisPierre, KalmanJonathan, KeaneDavid, KimYoung-Hoon, KirchhofPaulus, KleinGeorge, KottkampHans, KumagaiKoichiro, LindsayBruce D, MansourMoussa, MarchlinskiFrancis E, McCarthyPatrick M, MontJ Lluis, MoradyFred, NademaneeKoonlawee, NakagawaHiroshi, NataleAndrea, NattelStanley, PackerDouglas L, PapponeCarlo, PrystowskyEric, RavieleAntonio, ReddyVivek, RuskinJeremy N, SheminRichard J, TsaoHsuan-Ming, WilberDavid. 2012 HRS/EHRA/ECAS expert consensus statement on catheter and surgical ablation of atrial fibrillation: recommendations for patient selection, procedural techniques, patient management and follow-up, definitions, endpoints, and research trial design. J Interv Card Electrophysiol. 2012;33 (2):171–257
2. Nademanee Koonlawee, McKenzieJohn, KosarErol, SchwabMark, SunsaneewitayakulBuncha, VasavakulThaveekiat, KhunnawatChotikorn, NgarmukosTachapong. A new approach for catheter ablation of atrial fibrillation: mapping of the electrophysiologic substrate. J. Am. Coll. Cardiol. 2004;43 (11):2044–53
3. Haïssaguerre Michel, SandersPrashanthan, HociniMélèze, TakahashiYoshihide, RotterMartin, SacherFrederic, RostockThomas, HsuLi-Fern, BordacharPierre, ReuterSylvain, RoudautRaymond, ClémentyJacques, JaïsPierre. Catheter ablation of long-lasting persistent atrial fibrillation: critical structures for termination. J. Cardiovasc. Electrophysiol. 2005;16 (11):1125–37
4. Jaïs Pierre, HociniMélèze, HsuLi-Fern, SandersPrashanthan, ScaveeChristophe, WeerasooriyaRukshen, MacleLaurent, RaybaudFlorence, GarrigueStéphane, ShahDipen C, Le MetayerPhilippe, ClémentyJacques, HaïssaguerreMichel. Technique and results of linear ablation at the mitral isthmus. Circulation. 2004;110 (19):2996–3002
5. Tilz Roland Richard, RilligAndreas, ThumAnna-Maria, AryaAnita, WohlmuthPeter, MetznerAndreas, MathewShibu, YoshigaYasuhiro, WissnerErik, KuckKarl-Heinz, OuyangFeifan. Catheter ablation of long-standing persistent atrial fibrillation: 5-year outcomes of the Hamburg Sequential Ablation Strategy. J. Am. Coll. Cardiol. 2012;60 (19):1921–9
6. Higuchi Koji, YamauchiYasuteru, HiraoKenzo, SasakiTakeshi, HachiyaHitoshi, SekiguchiYukio, NittaJunichi, IsobeMitsuaki. Superior vena cava as initiator of atrial fibrillation: factors related to its arrhythmogenicity. Heart Rhythm. 2010;7 (9):1186–91
7. Miyazaki Shinsuke, TaniguchiHiroshi, KomatsuYuki, UchiyamaTakashi, KusaShigeki, NakamuraHiroaki, HachiyaHitoshi, IsobeMitsuaki, HiraoKenzo, IesakaYoshito. Sequential biatrial linear defragmentation approach for persistent atrial fibrillation. Heart Rhythm. 2013;10 (3):338–46
8. Nakazato Yuji, YasudaMasayuki, SasakiAkitoshi, IidaYouji, KawanoYasunobu, NakazatoKaoru, TokanoTakashi, MinedaYoriaki, SumiyoshiMasataka, NakataYasuro, DaidaHiroyuki. Conversion and maintenance of sinus rhythm by bepridil in patients with persistent atrial fibrillation. Circ. J. 2005;69 (1):44–8
9. Fujiki Akira, TsunedaTakayuki, SakabeMasao, NakagawaKeiko, MizumakiKoichi, HiraiTadakazu, InoueHiroshi. Maintenance of sinus rhythm and recovery of atrial mechanical function after cardioversion with bepridil or in combination with aprindine in long-lasting persistent atrial fibrillation. Circ. J. 2004;68 (9):834–9
10. Yamase Miki, NakazatoYuji, DaidaHiroyuki. Effectiveness of amiodarone versus bepridil in achieving conversion to sinus rhythm in patients with persistent atrial fibrillation: a randomised trial. Heart. 2012;98 (14):1067–71
11. Kondo Takehito, MiakeJunichiro, KatoMasaru, OguraKazuyoshi, IitsukaKazuhiko, YamamotoKazuhiro. Impact of postprocedural antiarrhythmic drug therapy with bepridil on maintaining sinus rhythm after catheter ablation for persistent atrial fibrillation. J Cardiol. 2016;68 (3):229–35
12. Murakawa Yuji, NogamiAkihiko, ShodaMorio, InoueKoichi, NaitoShigeto, KumagaiKoichiro, MiyauchiYasushi, YamaneTeiichi, MoritaNorishige, MitamuraHideo, OkumuraKen. Nationwide survey of catheter ablation for atrial fibrillation: The Japanese catheter ablation registry of atrial fibrillation (J-CARAF)-A report on periprocedural oral anticoagulants. J Arrhythm. 2015;31 (1):29–32
13. Shimizu A. Prognosis of paroxysmal atrial fibrillation (PAF) in patients treated with rhythm control and predictors of the transition from PAF to chronic AF. Jpn J Electrocardiol. 2010;30:171–173
14. Yamashita Takeshi, OgawaSatoshi, SatoToshiaki, AizawaYoshifusa, AtarashiHirotsugu, FujikiAkira, InoueHiroshi, ItoMakoto, KatohTakao,

KobayashiYouichi, KoretsuneYukihiro, KumagaiKoichiro, NiwanoShinichi, OkazakiOsamu, OkumuraKen, SakuKeijiro, TanabeTeruhisa, OrigasaHideki. Dose-response effects of bepridil in patients with persistent atrial fibrillation monitored with transtelephonic electrocardiograms: a multicenter, randomized, placebo-controlled,double-blind study (J-BAF Study). Circ. J. 2009;73 (6):1020–7

15. Shiga Tsuyoshi, SuzukiAtsushi, NaganumaMiyoko, HosakaFumitaka, ShodaMorio, HagiwaraNobuhisa. Clinical outcome in patients with paroxysmal or persistent atrial fibrillation receiving bepridil. Circ. J. 2011;75 (6):1334–42
16. Cochet Hubert, ScherrDaniel, ZellerhoffStephan, SacherFrederic, DervalNicolas, DenisArnaud, KnechtSebastien, KomatsuYuki, MontaudonMichel, LaurentFrançois, PieskeBurkert M, HociniMélèze, HaïssaguerreMichel, JaïsPierre. Atrial structure and function 5 years after successful ablation for persistent atrial fibrillation: an MRI study. J. Cardiovasc. Electrophysiol. 2014;25 (7):671–9
17. Al-Khatib Sana M, ThomasLaine, WallentinLars, LopesRenato D, GershBernard, GarciaDavid, EzekowitzJustin, AlingsMarco, YangHongqui, AlexanderJohn H, FlakerGregory, HannaMichael, GrangerChristopher B. Outcomes of apixaban vs. warfarin by type and duration of atrial fibrillation: results from the ARISTOTLE trial. Eur. Heart J. 2013;34 (31):2464–71
18. Steinberg Benjamin A, HellkampAnne S, LokhnyginaYuliya, PatelManesh R, BreithardtGünter, HankeyGraeme J, BeckerRichard C, SingerDaniel E, HalperinJonathan L, HackeWerner, NesselChristopher C, BerkowitzScott D, MahaffeyKenneth W, FoxKeith A A, CaliffRobert M, PicciniJonathan P. Higher risk of death and stroke in patients with persistent vs. paroxysmal atrial fibrillation: results from the ROCKET-AF Trial. Eur. Heart J. 2015;36 (5):288–96
19. Takabayashi Kensuke, HamataniYasuhiro, YamashitaYugo, TakagiDaisuke, UnokiTakashi, IshiiMitsuru, IguchiMoritake, MasunagaNobutoyo, OgawaHisashi, EsatoMasahiro, ChunYeong-Hwa, TsujiHikari, WadaHiromichi, HasegawaKoji, AbeMitsuru, LipGregory Y H, AkaoMasaharu. Incidence of Stroke or Systemic Embolism in Paroxysmal Versus Sustained Atrial Fibrillation: The Fushimi Atrial Fibrillation Registry. Stroke. 2015;46 (12):3354–61
20. Link Mark S, GiuglianoRobert P, RuffChristian T, SciricaBenjamin M, HuikuriHeikke, OtoAli, CromptonAndrea E, MurphySabina A, LanzHans, MercuriMichele F, AntmanElliott M, BraunwaldEugene. Stroke and Mortality Risk in Patients With Various Patterns of Atrial Fibrillation: Results From the ENGAGE AF-TIMI 48 Trial (Effective Anticoagulation With Factor Xa Next Generation in Atrial Fibrillation-Thrombolysis in Myocardial Infarction 48). Circ Arrhythm Electrophysiol. 2017;10 (1)
21. Marijon Eloi, Le HeuzeyJean-Yves, ConnollyStuart, YangSean, PogueJanice, BrueckmannMartina, EikelboomJohn, ThemelesEllison, EzekowitzMichael, WallentinLars, YusufSalim. Causes of death and influencing factors in patients with atrial fibrillation: a competing-risk analysis from the randomized evaluation of long-term anticoagulant therapy study. Circulation. 2013;128 (20):2192–201
22. Themistoclakis Sakis, CorradoAndrea, MarchlinskiFrancis E, JaisPierre, ZadoErica, RossilloAntonio, Di BiaseLuigi, SchweikertRobert A, SalibaWalid I, HortonRodney, MohantyPrasant, PatelDimpi, BurkhardtDavid J, WazniOussama M, BonsoAldo, CallansDavid J, HaissaguerreMichel, RavieleAntonio, NataleAndrea. The risk of thromboembolism and need for oral anticoagulation after successful atrial fibrillation ablation. J. Am. Coll. Cardiol. 2010;55 (8):735–43
23. Saad Eduardo B, d'AvilaAndré, CostaIeda P, AryanaArash, SlaterCharles, CostaRodrigo E, InácioLuiz A, MaldonadoPaulo, NetoDario M, CamilettiAngelina, CamanhoLuiz E, PolanczykCarisi A. Very low risk of thromboembolic events in patients undergoing successful catheter ablation of atrial fibrillation with a CHADS2 score ≤3: a long-term outcome study. Circ Arrhythm Electrophysiol. 2011;4 (5):615–21
24. Kornej Jelena, HindricksGerhard, KosiukJedrzej, AryaArash, SommerPhilipp, HusserDaniela, RolfSascha, RichterSergio, PiorkowskiChristopher, GasparThomas, LipGregory Y H, BollmannAndreas. Renal dysfunction, stroke risk scores (CHADS2, CHA2DS2-VASc, and R2CHADS2), and the risk of thromboembolic events after catheter ablation of atrial fibrillation: the Leipzig Heart Center AF Ablation Registry. Circ Arrhythm Electrophysiol. 2013;6 (5):868–74
25. Saliba Walid, SchliamserJorge E, LaviIdit, Barnett-GrinessOfra, GronichNaomi, RennertGad. Catheter ablation of atrial fibrillation is associated with reduced risk of stroke and mortality: A propensity score-matched analysis. Heart Rhythm. 2017;14 (5):635–642
26. Yagishita Atsuhiko, YamauchiYasuteru, SatoHironori, YamashitaShu, HiraoTatsuhiko, MiyamotoTakamichi, HiraoKenzo, IsobeMitsuaki. Improvement in the Quality of Life and Exercise Performance in Relation to the Plasma B-Type Natriuretic Peptide Level After Catheter Ablation in Patients With Asymptomatic Persistent Atrial Fibrillation. Circ. J. 2017;81 (4):444–449

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Congenital Absence of Left Atrial Appendage

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Abstract

Isolated absence of left atrial appendage is a very rare entity and is usually encountered as an incidental finding during routine imaging for other purposes. Lately, with increasing fund of knowledge about its potential role in cardio embolic phenomena, we have seen an increased trend in the use different techniques to exclude left atrial appendage from main left atrial chamber, in an effort to alleviate the stroke risk and therefore the need for long term anticoagulation. Clinical implications of absent left atrial appendage in such patients remains a mystery.

Case

67 year old male with history of hypertension (HTN), diabetes mellitus (DM), and persistent atrial fibrillation (AF) who was being evaluated for aMAZE study underwent a Computed tomography angiography (CTA) for screening purposes. Left atrial appendage (LAA) was found to be missing [Figure 1] and patient had no previous history of surgical or percutaneous left atrial appendage exclusion.

Discussion

Left atrial appendage develops in 3rd -4th week of embryonic life from the left wall of the primary atrium and functions like a left atrium during the fetal life [Figure 2] [1]. In adults it is believed to function as a decompression chamber during elevated left atrial pressures including left ventricular systole or volume overload situations. It also contributes towards left atrial reservoir and contractile functions [2]. Its physiological and ultrastructural properties are distinct from the left atrium main chamber. Left atrial appendage (LAA) has particularly drawn attention in the last decade due to its potential role in the atrial fibrillation (AF) and thromboembolic phenomena. Ninety percent of thrombi, in the setting of non-valvular atrial fibrillation, are found in left atrial appendage [3] and around 27% of patients presenting for repeat ablation procedures have triggers in left atrial appendage [4]. Mechanical closure/isolation of LAA for stroke prevention is, therefore, a new trend in the world of electrophysiology. Congenital absence of left atrial appendage is very rare and its impact on electromechanical properties of left atrium are not known. But, of more interest and significance would be, its clinical implications for the patient with atrial fibrillation in terms of anticoagulation or even ablation procedures. These are the areas that would need further studies and /or thorough literature review of such cases, in order to get some answers.

Key Words

Decompression, Hypertension, Left Atrial Appendage.

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Disclosures

None.

References

1. Al-Saady N M, ObelO A, CammA J. Left atrial appendage: structure, function, and role in thromboembolism. Heart. 1999;82 (5):547–54
2. Tabata T, OkiT, YamadaH, IuchiA, ItoS, HoriT, KitagawaT, KatoI, KitahataH, OshitaS. Role of left atrial appendage in left atrial reservoir function as evaluated by left atrial appendage clamping during cardiac surgery. Am. J. Cardiol. 1998;81 (3):327–32
3. Blackshear J L, OdellJ A. Appendage obliteration to reduce stroke in cardiac surgical patients with atrial fibrillation. Ann. Thorac. Surg. 1996;61 (2):755–9
4. Di Biase Luigi, BurkhardtJ David, MohantyPrasant, SanchezJavier, MohantySanghamitra, HortonRodney, GallinghouseG Joseph, BaileyShane M, ZagrodzkyJason D, SantangeliPasquale, HaoSteven, HongoRichard, BeheirySalwa, ThemistoclakisSakis, BonsoAldo, RossilloAntonio, CorradoAndrea, RavieleAntonio, Al-AhmadAmin, WangPaul, CummingsJennifer E, SchweikertRobert A, PelargonioGemma, Dello RussoAntonio, CasellaMichela, SantarelliPietro, LewisWilliam R, NataleAndrea. Left atrial appendage: an underrecognized trigger site of atrial fibrillation. Circulation. 2010;122 (2):109–18

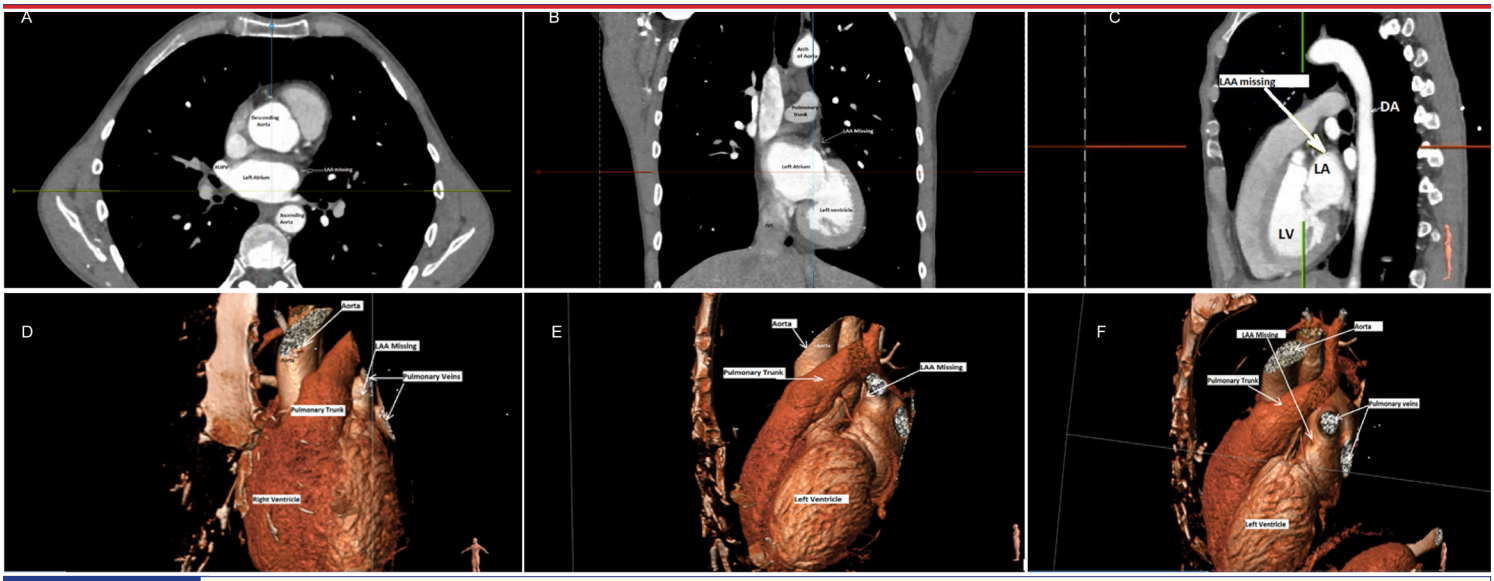

Figure 1: (A,B,C,D,E,F) Multidetector computed tomography imaging of the left atrium marking the structures relative to left atrial appendage using multiplanar reconstruction images (A-axial, B-coronal, C-sagittal) and 3 dimensional volume-rendered images at different angles (D,E,F). LAA: Left atrial appendage, RUPV: Right upper pulmonary vein, LV: Left Ventricle, LA: Left Atrium, DA: Descending Aorta.

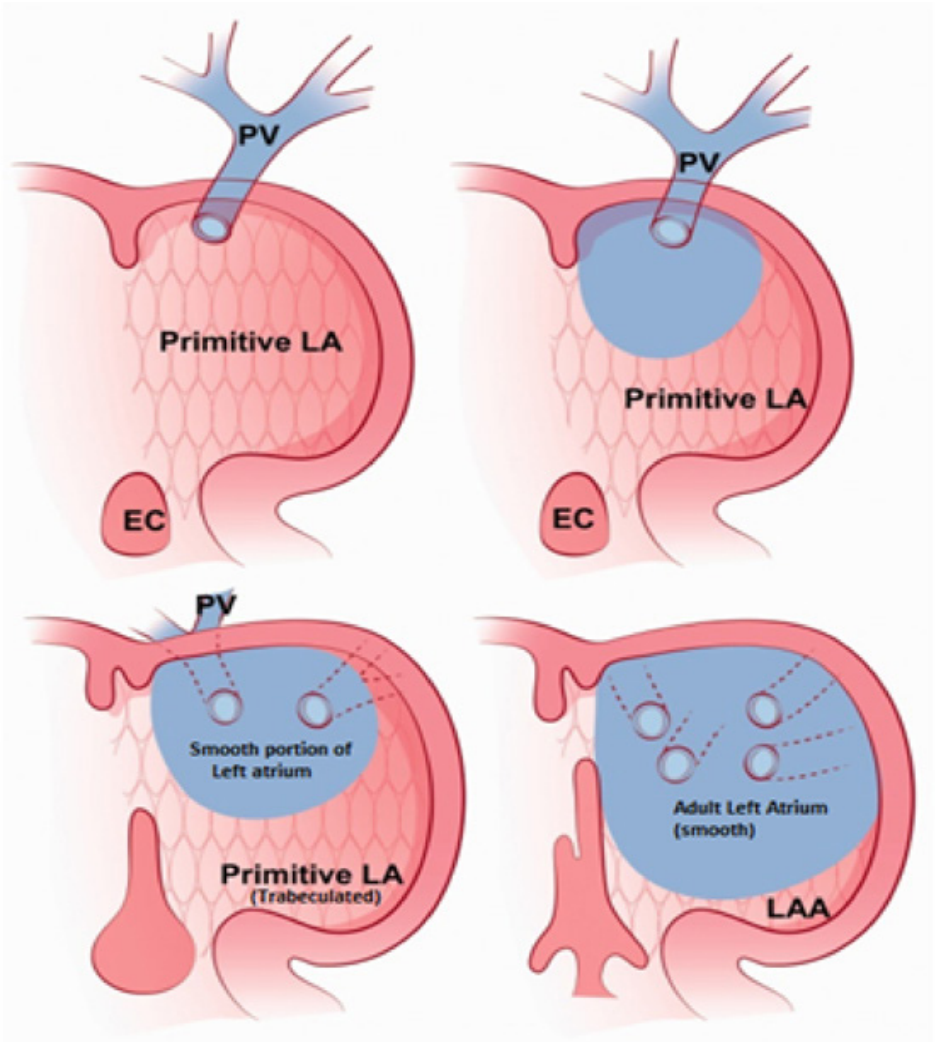

Figure 2: Illustrating embryologic development of the left atrium and left atrial appendage (LAA). Note the primitive left atrium (trabeculated pattern) becomes left atrial appendage (LAA) and part of the pulmonary vein becomes the smooth portion of the left atrium (Blue). EC: Endocardial Cushion, LA : Left atrium, LAA: Left atrial appendage
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Coronary Air Embolism During Cryoablation of Atrial Fibrillation: A Catastrophic Complication and Its Management

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Abstract

Various acute complications and their management during ablation of atrial fibrillation have been described. In the current report, coronary air embolism, its acute adverse effects and management of the problem were presented in a patient underwent cryoballoon ablation of atrial fibrillation.

Introduction

Well-described acute procedure-related adverse effects of cryoablation of atrial fibrillation (AF), resulted clinical conditions including life-threatening events and the acute management of them have been presented previously[1]. Coronary air embolism related to left-sided cardiac procedures, however, has been relatively less described. Herein, a case underwent cryoballoon AF ablation and detected coronary air embolism and its acute management was discussed.

Case report

A 57-year-old female with coronary heart disease and paroxysmal AF was referred to our center for cryoballoon ablation of AF. Following proper patient preparation including transesophageal echo, a transseptal catheter placement using an 8F SL1™ (St. Jude Medical) sheath was performed and the sheath was replaced with a FlexCath Advance™ sheath (Medtronic) to introduce the Arctic Front Advance™ cryoballoon catheter (Medtronic) under conscious sedation. Just seconds after placement of the FlexCath™, the patient reported heavy chest pain. The continuous 12-lead ECG showed ST elevations in leads DII, DIII and aVF with corresponding ST segment depression in other derivations and worsening AV block. The decapolar catheter in the coronary sinus was immediately placed in the right ventricular apex. Urgent coronary angiography of the right coronary artery demonstrated air bubbles in the right coronary cusp and the right coronary artery with total occlusion of the vessel ([Figure 1] and Video). Immediately, a 0.014" guidewire was introduced and a 6F compatible manually controlled thrombus aspiration catheter (Hunter™, IHT Cordynamic) was placed just before the occlusion [Figure 2]. Multiple rapid suctions through the catheter resulted in air filling of the syringe and full patency of the vessel on coronary angiogram with complete resolution of ST segment elevations and diminishing of chest pain [Figure 2]. The left coronary system was also patent. The transseptal sheath was also controlled for any air. After complete hemodynamic stability and no clinical evidence for other organ-system embolism, unfinished procedure was finished with the isolation of all 4 pulmonary veins without any other problem. The day after the procedure was uneventful and the ECG and transthoracic echo showed no abnormality.

Discussion

Air embolism to the systemic circulation via introducing catheters and atrio-esophageal fistula during and/or after AF ablation is always a catastrophic complication[2]. In the acute setting, the majority was due to catheters exposing systemic circulation. Possible mechanisms causing air embolism from introducing catheters are multiple catheter exchanges and rapid removal of catheters and dilators, deep sedation and prolonged apnea periods with deep breaths, and air-opened or loosened hemostasis valves, all causing negative pressure and air transportation through the catheter into the low pressure left atrium[3],[4]. In our case, the most possible mechanism seems as rapid removal of the dilator of the FlexCath™. Because symptoms started just after removal of the dilator and, the patient had no deep sedation causing deep apnea periods. Also, no catheter exchanges were performed before the complication. The management of the complication was through mechanic aspiration of the air using a thrombus aspiration catheter without forceful injection of contrast medium or saline, which may cause distal embolization, vascular damage, or proximal leakage of bubbles causing other organ/system embolization[5]. Various maneuvers to be applied to prevent air embolism are slow removal of dilators and catheters, continuous heparinized saline infusion, no so deep sedation, minimized number

Key Words

ablation, cryoballoon, embolism.

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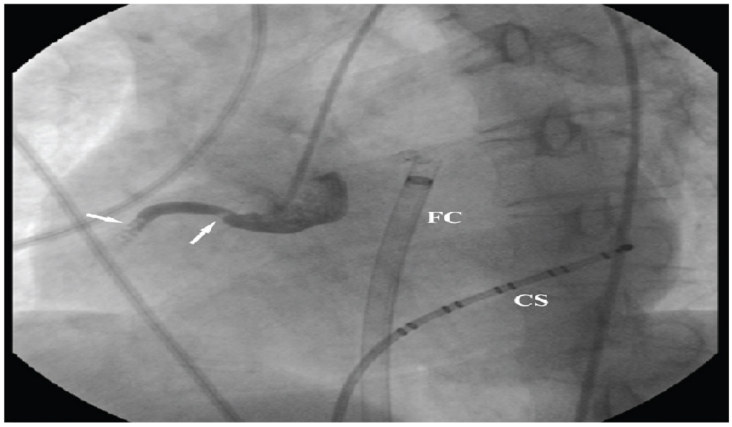

Figure 1: Selective right coronary angiography showed air bubbles (white arrows) in the vessel in the left anterior oblique projection. CS, decapolar coronary sinus catheter; FC, 15F FlexCath™ catheter

of catheter exchanges, and review for loosened hemostatic valves. Lastly, the cause of air embolism to the right sinus of Valsalva and the right coronary artery without involvement of other organ-systems can be more superior position of the right sinus of Valsalva and, so the right coronary artery in supine position.

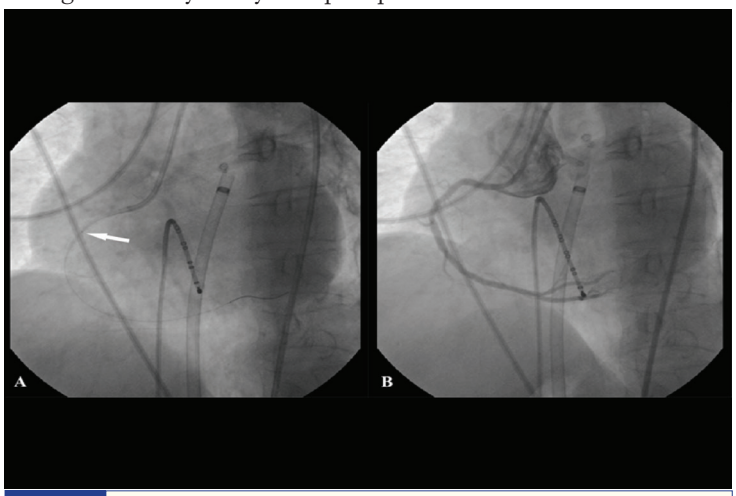

Figure 2: A 0.014" guidewire and the Hunter™ aspiration catheter were introduced in the vessel (A) (white arrow, distal marker of the aspiration catheter). Forceful aspiration was resulted in complete patency of the vessel without residual air (B). Coronary sinus catheter was placed in the right ventricular apex.

Conclusions

In conclusion, air embolism to the coronary artery during cryoablation of AF can cause myocardial infarction and proper aspiration of air bubbles using aspiration catheter can resolve the problem without any sequela.

Disclosures

None.

References

1. Altmann David R, KnechtSven, SticherlingChristian, AmmannPeter, SchaerBeat, OsswaldStefan, KühneMichael. Treating Atrial Fibrillation With Cryoballoon Technology. J Atr Fibrillation. 2012;4 (6)
2. Pappone Carlo, VicedominiGabriele, SantinelliVincenzo. Atrio-Esophageal Fistula After AF Ablation: Pathophysiology, Prevention &Treatment. J Atr Fibrillation. 2013;6 (3)
3. Kuwahara Taishi, TakahashiAtsushi, TakahashiYoshihide, KoboriAtsushi, MiyazakiShinsuke, TakeiAsumi, FujiiAkira, KusaShigeki, YagishitaAtsuhiko, OkuboKenji, FujinoTadashi, NozatoToshihiro, HikitaHiroyuki, SatoAkira, AonumaKazutaka. Clinical characteristics of massive air embolism complicating left atrial ablation of atrial fibrillation: lessons from five cases. Europace. 2012;14 (2):204–8
4. Ahmad Khurram, AsirvathamSamuel, KamathSreenivas, PeckStephen, LiuXiaoke. Successful interventional management of catastrophic coronary arterial air embolism during atrial fibrillation ablation. HeartRhythm Case Rep. 2016;2 (2):153–156
5. Patterson M S, KiemeneijF. Coronary air embolism treated with aspiration catheter. Heart. 2005;91 (5)

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Ashman Phenomenon Dynamicity During Atrial Fibrillation: The Critical Role of the Long Cycles

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Abstract

A case of a patient with Atrial Fibrillation and intermittent wide complex beats. What's the mechanism?

Introduction

A 70-year-old male patient presented to the cardiology consult for a routine follow-up. Prior history of hypertension and permanent atrial fibrillation (AF) treated with Bisoprolol 5 mg once a day and anticoagulation. As part of his workup, a 24-hour Holter monitoring was obtained showing several wide QRS complex beats. What's the mechanism?

Holter analysis revealed AF with an average heart rate of 100 bpm. The patient presented with several wide QRS complex beats that were counted as premature ventricular contractions (PVCs). A closer analysis of the ECG recording allows suspecting aberrancy given the fact that the wide QRS complexes are always preceded by short-long-short sequences and the wideness of the QRS varies depending on the duration of the prior pause.

Ashman phenomenon is usually seen during AF which provides the opportunity for a variation of cycle lengths. In our case, the longer the pause; the wider the QRS complex. In [Figure 1]; a pause of 828 ms followed by a short coupling interval of 375 ms, resulted in a QRS complex of 110 ms; however, a pause of 898 ms followed by the same coupling interval, produced a QRS of 120 ms. It is conceivable, as shown in [Figure 1], that a longer pause (1328 ms) with the same coupling interval, included part of the anterior left fascicle also refractory, thus aberrancy is more remarkable (channels 1, 2, 3 of the Holter represent leads II, III and V5 of the surface ECG). This phenomenon demonstrates Ashman's dynamicity. The fact that the coupling interval of the short interval remains constant, but the preceding long cycle length varies, led us to believe that the degree of aberrancy depends on the longer cycle interval. [Figure 2] shows the comparison of a normally conducted beat (A) followed by progressively wider QRS complexes due to different level of aberration (B to D). The differential diagnosis of Ashman phenomenon should be established with PVCs.

Ashman phenomenon is a physiological response of intraventricular conduction in response to cycle length variations. Short-long-short sequences facilitate aberrancy, however, the dependency of the aberrancy on the long cycle interval, has scarcely been reported. Prolongation of the preceding long cycle generates different degrees of aberrancy (Ashman dynamicity) which is a reflection of involving the anterior fascicle in the mechanism of aberrancy. The most common manifestation of aberrancy during AF seen in clinical practice occurs in the right bundle.

Disclosures

None.

Key Words

Aberrant Conduction, Right Bundle Branch block, Ashman phenomenon.

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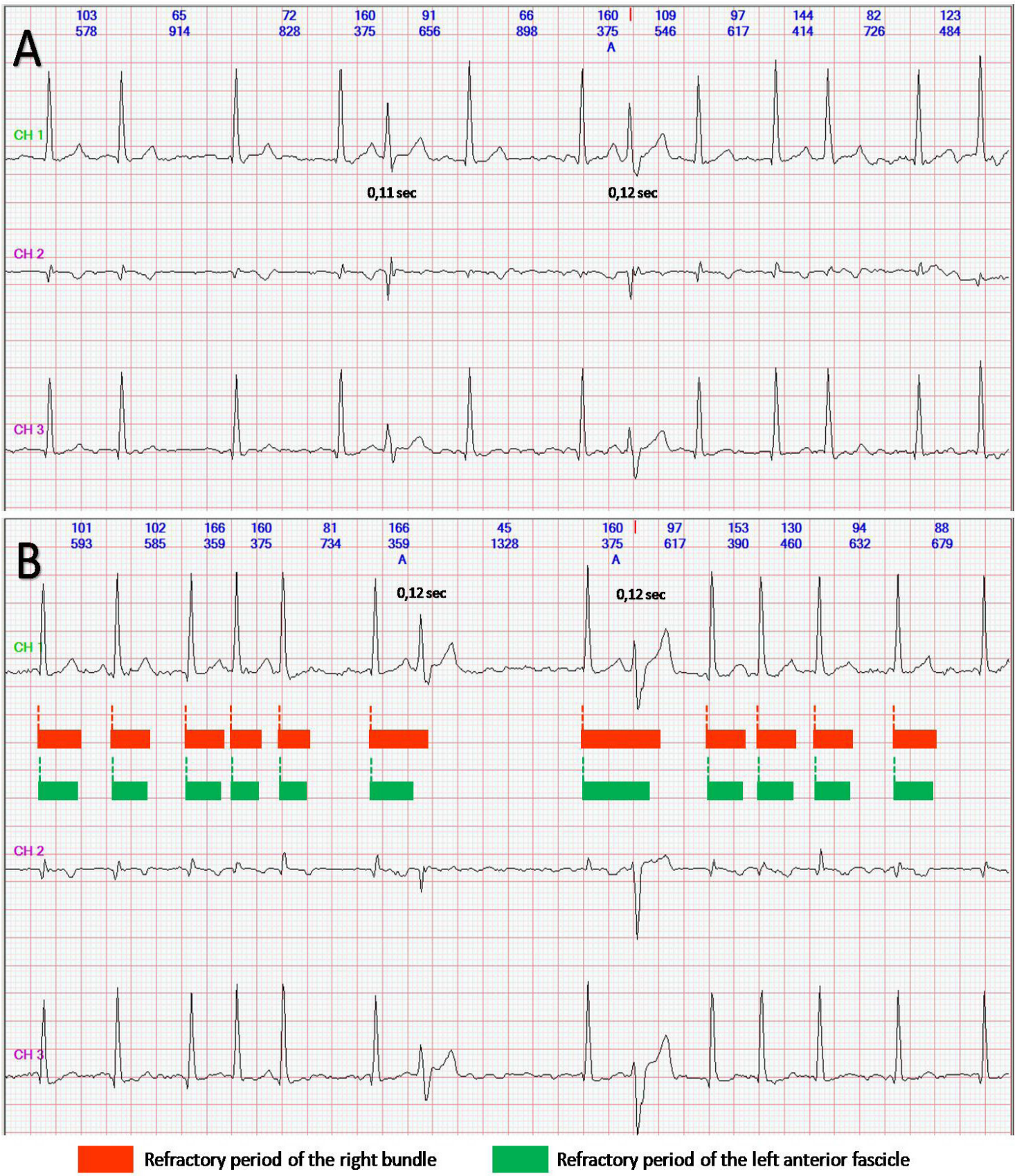

Figure 1: Panel A: Ashman phenomenon: different levels of aberrancy in the right bundle due to variations in the cycle length (See text for details). Ashman's dynamicity.
Panel B: Ashman phenomenon: major degree of aberrancy involving the right bundle and the left anterior fascicle (See text for details).

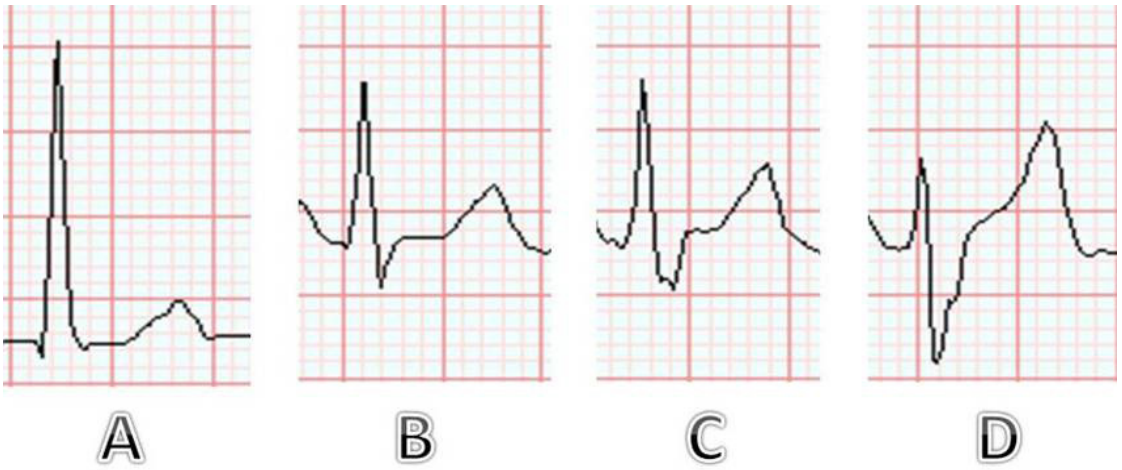

Figure 2: Comparison of a normally conducted beat (A), to different degrees of aberrancy due to Ashman's dynamicity phenomenon (B to D).

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New Migraine with Visual Disturbance after Cryoballoon Ablation of Atrial Fibrillation

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Abstract

We report the case of a 58-year-old woman who developed a headache and visual disturbances after a cryoballoon ablation procedure for atrial fibrillation at our institution. She presented to the emergency department four days post ablation and was admitted the hospital for overnight observation. Serial neurological examinations and neuroimaging were unremarkable for stroke or transient ischemic attack. The patient had some brief transient visual changes which resolved completely after several days, with no further clinical sequelae. She followed up in the outpatient neuro-ophthalmology clinic and had a normal visual field examination. She was given a diagnosis of new onset migraine with visual aura.

Case Report

A 58-year-old woman with a history of hyperlipidemia and drug-refractory paroxysmal atrial fibrillation was referred to our electrophysiology practice for catheter ablation. Her preoperative medications only included digoxin and aspirin, and these were not withheld prior to the procedure. A preoperative transesophageal echocardiogram confirmed the absence of thrombus in the left atrial appendage. Transseptal catheterization of the left atrium was performed with the aid of intracardiac echocardiography (AcuNav, Siemens Medical Solutions, Inc., Mountain View, CA) by direct puncture of the mid-posterior fossa ovalis with a 71-cm Brockenbrough transseptal needle (BRK-1, St. Jude Medical, St. Paul, MN) and an 8.5-French 63-cm guiding introducer sheath (SL-1, St. Jude Medical), followed by an over-the-wire exchange for a 12-French steerable sheath (FlexCath Advance, Medtronic Inc., Minneapolis, MN). Unfractionated heparin was administered via intravenous boluses started prior to transseptal puncture, followed by a continuous infusion to achieve activated clotting times >300 seconds during ablation in the left atrium. Pulmonary vein isolation and superior vena cava isolation were performed under general anesthesia using a 28-mm cryoballoon ablation catheter (Arctic Front Advance, Medtronic Inc.) and a 4-mm radiofrequency ablation catheter (Blazer II, Boston Scientific, Natick, MA), respectively. Left atrial mapping and ablation were completed within 75 minutes exclusively with the cryoballoon sheath and catheter, and an additional 15 minutes were spent with the sheath and a radiofrequency ablation catheter in the right atrium to complete superior vena cava isolation. Heparin anticoagulation was then reversed with protamine, and six hours post procedure she was started on therapeutic oral anticoagulation with rivaroxban. She was discharged the next day in good condition.

On postoperative day#1, she developed a left occipital headache described as sharp but non-pulsatile that was initially mild in severity and relieved with oral acetaminophen. On post-operative day #3, the patient developed the sudden onset of visual symptoms described as bright flashes of light accompanied by blurriness of her peripheral vision bilaterally. Over the next 45 minutes, her vision normalized, at which time she developed recurrence of her left-sided headache. She had the return of similar visual symptoms the following day, and presented to the emergency department. Her blood pressure was 113/73 with a pulse of 94 beats per minute. She was alert and oriented to time, person and place. Her neurologic examination was non-focal. Laboratory studies, including complete blood count, renal function, and serum electrolytes were all normal. Serum digoxin level was 0.6 ng/mL. Electrocardiography and cardiac monitoring confirmed normal sinus rhythm. She underwent computed tomography (CT) imaging of her head, which showed no intracranial hemorrhage or mass lesion; CT angiography demonstrated no intracranial vascular stenosis. Magnetic resonance imaging of her brain was performed, which revealed only minimal nonspecific white matter disease, and no evidence of acute or subacute infarction [Figure 1]. Visualized portions of the orbits, optic nerves and visual pathways were also normal.

She was evaluated by the neurology service, who felt her presentation was consistent with a new onset migraine with visual aura. She had no previous history of migraine headaches. She did not have clinical evidence of an ischemic stroke or transient ischemic

Key Words

atrial fibrillation, catheter ablation, cryoballoon, transseptal catheterization, migraine.

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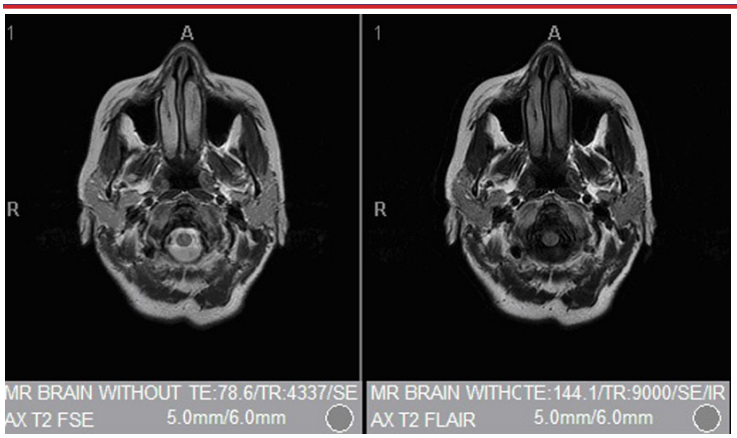

Figure 1: **Magnetic resonance imaging (MRI) of the brain obtained post ablation**

attack after overnight observation. She was discharged home in good condition. Over the next several days, she experienced some transient blurriness in her vision lasting approximately 45 minutes without headache or loss of peripheral vision. She had a follow-up visit in the neuro-ophthalmology clinic one week postoperatively, and both fundoscopic examination and visual field testing were within normal limits [Figure 2]. She had a follow-up visit in the cardiology clinic one month postoperatively, and described no further clinical sequelae.

Discussion

Catheter ablation of atrial fibrillation (AF) has evolved as a safe and highly effective treatment for drug-refractory symptomatic AF.[1]Over the last few years, cryoballoon ablation has become an increasingly utilized technique for the treatment of AF in the electrophysiology laboratory.[2] There have been a number of reports describing headache and migraines after AF ablation, including studies that suggest an increased incidence during and after cryoballoon AF ablation.[3]-[7]

There appears to be a specific link between the iatrogenic atrial septal defect (IASD) caused by transseptal puncture and the development of post-procedure migraines. In a series of 571 consecutive patients undergoing transseptal catheterization at the time of catheter ablation for left-sided cardiac arrhythmias at a single center, isolated migraine aura occurred with an incidence of about 0.5%. In these patients, transient and reversible visual symptoms were noted in the first week, with a negative workup for stroke or transient ischemic attack in all cases.[3] A larger series of 2,069 patients, undergoing radiofrequency catheter ablation for AF, saw a 2.3% incidence of post-procedure headaches, with new-onset definite migraines described in 1.1% of patients.[5] Another study did find an association between new or worsening migraine symptoms and silent cerebral infarcts on brain MRI after AF ablation, which suggest thromboembolism and/or hypercoagulability may play a role in the development of post-procedure migraines. [8] In fact, in this study, therapeutic levels of warfarin anticoagulation maintained during the peri-procedural period were associated with freedom from migraine. Specifically, it is hypothesized that IASD, similar to a native patent foramen ovale, can result in paradoxical embolism of platelets, thrombin and other substances that might contribute to the pathogenesis of migraine. [9]

Cryoballoon AF ablation is performed using a larger transseptal sheath (12 French inner diameter, as opposed to 8 or 8.5 French for radiofrequency AF ablation), which may be associated with a higher risk of persistent post-procedure IASD.[10] In a study of 87 consecutive patients followed for three months after cryoballoon ablation, 8% reported new symptoms of headache with ocular symptoms such as scotoma.[4] Most symptoms had disappeared when patients were reevaluated in the outpatient clinic three months after the ablation procedure. To the extent that the larger transseptal hole may allow for a greater propensity for thrombo-embolism and potentially migraine symptoms, anticoagulation strategies such as uninterrupted and therapeutic pre-procedure oral anticoagulation and intravenous heparinization prior to transseptal puncture, may be even more important for cryoballoon AF ablation than for radiofrequency AF ablation cases. Interestingly, in the study by Mohanty et al., there were no cases of new migraine or silent cerebral infarcts in the cohort that underwent AF ablation with therapeutic INR on the day of the ablation procedure. Pre-procedure warfarin was not utilized in our patient as she opted for an oral anticoagulant that would not require INR monitoring. It is common practice in our institution to suspend anticoagulation with a direct oral anticoagulant such as rivaroxaban 24 to 48 hours pre-procedure, or initiate it postoperatively in patients who have not been previously anticoagulated. This practice is in contradistinction to the management of our patients on warfarin, which is not suspended pre-procedure, and may in retrospect have increased the risk of post-procedure migraine in this patient. Recent data on the use of direct oral anticoagulants during AF ablation suggest that uninterrupted apixaban administration may be a feasible and effective strategy in preventing thromboembolic events without increasing the risk of major bleeding complications. [11]

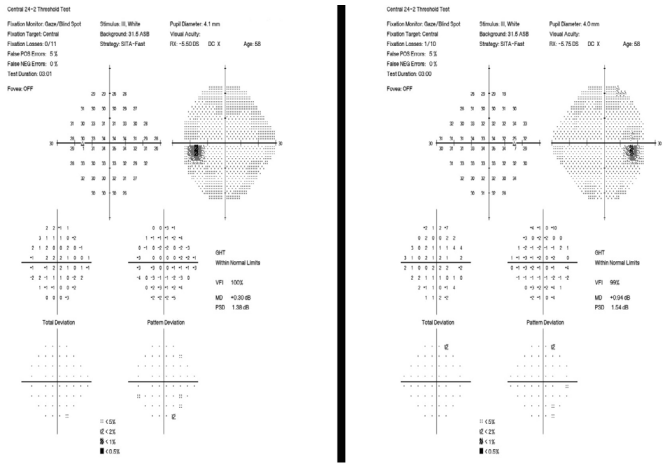

Figure 2: **Visual field testing of left (left panel) and right (right panel) eyes post ablation**

Conclusions

Migraine with visual aura is an increasingly recognized postoperative complication of AF catheter ablation procedures, and may be related to the presence and size of transseptal sheaths used intraoperatively, and the peri-procedural anticoagulant regimen. Neuroimaging and a thorough ophthalmologic examination are necessary to rule out potential thromboembolic and/or vascular causes in patients presenting with acute visual disturbances post ablation.

Disclosures

None.

References

1. Wilber David J, PapponeCarlo, NeuzilPetr, De PaolaAngelo, MarchlinskiFrank, NataleAndrea, MacleLaurent, DaoudEmile G, CalkinsHugh, HallBurr, ReddyVivek, AugelloGiuseppe, ReynoldsMatthew R, VinekarChandan,

LiuChristine Y, BerryScott M, BerryDonald A. Comparison of antiarrhythmic drug therapy and radiofrequency catheter ablation in patients with paroxysmal atrial fibrillation: a randomized controlled trial. JAMA. 2010;303 (4):333–40

2. Packer Douglas L, KowalRobert C, WheelanKevin R, IrwinJames M, ChampagneJean, GuerraPeter G, DubucMarc, ReddyVivek, NelsonLinda, HolcombRichard G, LehmannJohn W, RuskinJeremy N. Cryoballoon ablation of pulmonary veins for paroxysmal atrial fibrillation: first results of the North American Arctic Front (STOP AF) pivotal trial. J. Am. Coll. Cardiol. 2013;61 (16):1713–23
3. Chilukuri Karuna, SinhaSunil, BergerRonald, MarineJoseph E, ChengAlan, NazarianSaman, ScherrDaniel, SpraggDavid, CalkinsHugh, HenriksonCharles A. Association of transseptal punctures with isolated migraine aura in patients undergoing catheter ablation of cardiac arrhythmias. J. Cardiovasc. Electrophysiol. 2009;20 (11):1227–30
4. Jordaens L, JanseP, Szili-TorokT, Van BelleY. Migraine accompagnée after transseptal puncture. Neth Heart J. 2010;18 (7-8):374–5
5. Noheria Amit, RoshanJohn, KapaSuraj, SrivathsanKomandoor, PackerDouglas L, AsirvathamSamuel J. Migraine headaches following catheter ablation for atrial fibrillation. J Interv Card Electrophysiol. 2011;30 (3):227–32
6. Pison Laurent, PeetersPim, BlaauwYuri, VernooyKevin, KumarNarendra, PhilippensSuzanne, CrijnsHarry J, VlaeyenJohan, SchoenenJean, TimmermansCarl. Headache during cryoballoon ablation for atrial fibrillation. Europace. 2015;17 (6):898–901
7. Linhart Markus, BellmannBarbara, Mittmann-BraunErica, SchrickelJan W, BitzenAlexander, AndriéRené, YangAlexander, NickenigGeorg, LickfettLars, LewalterThorsten. Comparison of cryoballoon and radiofrequency ablation of pulmonary veins in 40 patients with paroxysmal atrial fibrillation: a case-control study. J. Cardiovasc. Electrophysiol. 2009;20 (12):1343–8
8. Mohanty Sanghamitra, MohantyPrasant, RutledgeJ Neal, Di BiaseLuigi, YanRachel Xue, TrivediChintan, SantangeliPasquale, BaiRong, CardinalDeb, BurkhardtJ David, GallinghouseJoseph G, HortonRodney, SanchezJavier E, BaileyShane, HranitzkyPatrick M, ZagrodzkyJason, Al-AhmadAmin, NataleAndrea. Effect of catheter ablation and periprocedural anticoagulation regimen on the clinical course of migraine in atrial fibrillation patients with or without pre-existent migraine: results from a prospective study. Circ Arrhythm Electrophysiol. 2015;8 (2):279–87
9. Saravanan Palaniappan, LangChristopher, DavidsonNeil. Migraine following trans-septal access for catheter ablation of cardiac arrhythmias. Headache. 2009;49 (7):1065–7
10. Chan Ngai-Yin, ChoyChi-Chung, LauChun-Leung, LoYing-Keung, ChuPui-Shan, YuenHo-Chuen, MokNgai-Shing, TsuiPing-Tim, LauSuet-Ting. Persistent iatrogenic atrial septal defect after pulmonary vein isolation by cryoballoon: an under-recognized complication. Europace. 2011;13 (10):1406–10
11. Di Biase Luigi, LakkireddyDhanujaya, TrivediChintan, DenekeThomas, MartinekMartin, MohantySanghamitra, MohantyPrasant, PrakashSameer, BaiRong, ReddyMadhu, GianniCarola, HortonRodney, BaileyShane, SigmundElisabeth, DerndorferMichael, SchadeAnja, MuellerPatrick, SzoelloesAtilla, SanchezJavier, Al-AhmadAmin, HranitzkyPatrick, GallinghouseG Joseph, HongoRichard H, BeheirySalwa, PürerfellnerHelmut, BurkhardtJ David, NataleAndrea. Feasibility and safety of uninterrupted periprocedural apixaban administration in patients undergoing radiofrequency catheter ablation for atrial fibrillation: Results from a multicenter study. Heart Rhythm. 2015;12 (6):1162–8

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Scar Homogenization in Atrial Fibrillation Ablation: Evolution and Practice

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Introduction

Atrial fibrillation (AF) ablation has emerged as the preferred rhythm control strategy for symptomatic paroxysmal AF refractory or intolerant to at least one class I or III antiarrhythmic medication[1],[2]. Since the initial observation by Haissaguerre and colleagues, of pulmonary vein triggers initiating atrial fibrillation (AF)[3], pulmonary vein isolation (PVI) has become the cornerstone for paroxysmal AF ablation therapy[4]. Despite technological advances and growing operator experience in performing percutaneous catheter ablation for AF, either by use of radiofrequency(RF) or cryotherapy, the long term procedural success rates for persistent AF and long standing persistent AF have not paralleled those of paroxysmal AF[5]-[8]. Due to the high recurrence rates observed in patients with persistent AF with PVI alone, efforts have been directed towards identifying additional strategies to improve the outcomes of persistent AF ablation. These strategies have included linear ablation lesions in the left and right atria, autonomic ganglionic plexi ablation, ablation directed by complex fractionated electrograms, ablation of non-pulmonary vein triggers, RF or ethanol ablation of the vein of Marshall and most recently, focal impulse and rotor modulation (FIRM). However, there is no consensus nor reproducible multicenter outcome data that would support one strategy over another. The randomized Substrate and Trigger Ablation for Reduction of AF Trial Part II (STAR AF II) failed to demonstrate any significant reduction in AF recurrences when linear ablation lines or complex fractionated electrogram based ablation was performed in addition to pulmonary vein antral isolation (PVAI) as compared to PVAI alone strategy[10]. Regardless of the approach, 40-50% failure rates with catheter ablation were observed over 12 months[10]. The results of this randomized trial form an impetus for researching newer percutaneous approaches for the treatment of persistent AF. The fundamental differences in the pathophysiology of paroxysmal and persistent AF cannot be overemphasized. Anisotropic conduction, triggered activity, autonomic innervation of the heart, embryogenesis of thoracic veins and interspersion of inhomogenous tissue (thoracic veins and heart) are believed to play a major role in initiation and pathogenesis of AF in paroxysmal AF. However, persistent AF pathogenesis is more complex and cannot be siloed into a pathogenic rubric. Observations of atrial substrate characteristics have pointed to a link between atrial fibrosis and AF progression. With rapidly emerging data on this association, ablation strategies have been developed to eliminate low voltage regions that may indicate scar and/or zones of non-uniform anisotropic conduction within the left atrium and convert them into electrically silent regions. This ablation strategy is known as scar homogenization. In this review, we discuss the evidence behind the use of scar homogenization in AF ablation, its evolution and scope in delivering optimal outcomes.

Key Words

Atrial fibrillation, atrial scar, cardiac ablation, scar homogenization, substrate ablation, arrhythmia mapping.

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Association between fibrosis and atrial fibrillation

There is growing evidence that atrial fibrosis plays a key role in maintenance of AF [11]-[13]. Atrial fibrosis may provide a substrate with electrophysiological properties of heterogeneity and nonuniform anisotropy which may help sustain the drivers for wavelet reentry. At a mechanistic level, Maesen et al[14] have shown with animal studies, that propagation of fibrillation waves is promoted by endocardial bundles in acute AF and by epicardial bundles in persistent AF. Remodeling of atrial fiber bundles result in endo to epicardial dissociation of electrical activity and the development of a 3-dimensional AF substrate. This process at least in part contributes to atrial structural remodeling and development of persistence of AF. In a study by Verma et al[15], out of a total of 700 consecutive patients undergoing first-time PVAI, preexisting left atrial (LA) scarring detected by contact voltage mapping with a multipolar circular catheter was a powerful independent predictor of procedural failure and was associated with a lower ejection fraction (EF), larger LA size, and increased inflammatory markers. Another study by Yamaguchi et al showed that the low voltage zone (LVZ) area (defined by bipolar voltage < 0.5 millivolts on electroanatomic mapping) was an independent predictor of recurrence after PVAI without any LA substrate modification[16]. There is growing evidence of significant association between progression of AF and atrial fibrosis as detected

by delayed enhancement MRI imaging (DE- MRI). The DECAAF study by Marrouche et al was a multicenter, prospective, observational cohort study of patients diagnosed with paroxysmal and persistent AF undergoing their first catheter ablation with PVAI[17]. Cardiac MRI was performed before ablation and atrial fibrosis was quantified and classified into stages with stage 1 (<10% of the atrial wall), 2 (≥10%-<20%), 3 (≥20%-<30%), and 4 (≥30%). Cumulative incidence of recurrent arrhythmia by day 325 for stage 1, 2, 3 and 4 fibrosis was 15.3%, 32.6%,45.9% and 51.1% respectively. In another study, atrial fibrosis was measured by late gadolinium enhancement (LGE) cardiac MRI imaging at baseline in patients undergoing PVAI. Patients with LGE ≤ 35% had favorable outcomes, whereas those with a higher LGE had higher AF recurrence rates in the first year after ablation, regardless of whether the initial rhythm was paroxysmal or persistent AF [18]. The studies listed above emphasize the importance of baseline imaging and quantification of atrial scar as a key predictor of procedural outcomes after PVAI. Appropriate patient selection and individualizing decision making based on preprocedural odds of success may be important to consider specifically if PVAI alone strategy is planned. These studies also lay down the platform for other investigations looking at substrate modification in addition to PVAI, specifically in patients with severe LA scarring as detected by MRI imaging or electroanatomic mapping. While there is an abundance of basic science and clinical data emphasizing association between AF and fibrosis, the concept behind ablation strategies targeting 'the atrial scar' seems reasonable, although some important questions remain unanswered, such as "What comes first- the chicken or the egg?, the scar or the AF?" and "To what degree is one required for the other to occur?" or "Are they coexistent but independent of each other?". If AF is the result of scar, does modifying the scar prevent further AF-induced scar formation, or harm by creating more scar?

Defining the 'Atrial Scar'

In a study by Kapa et al[19], LA bipolar voltage was measured in sinus rhythm (SR) and values lower than the amplitude of 95% of sampled points was used as the upper cutoff value for an abnormal signal. Delayed enhancement (DE) cardiac magnetic resonance imaging (CMRI) sequences were performed to validate voltage cutoffs. The authors showed that a voltage range of 0.2-0.45 mV can demarcate LA scar distribution during SR. Most studies have defined severely affected fibrotic areas as those with bipolar voltage on electroanatomic mapping of < 0.5 millivolts. However, the limitations of using bipolar voltage to define scar are well understood. Bipolar voltage amplitude depends on the type of mapping electrode, electrode tip size, orientation, interelectrode spacing and tissue contact[20]. Moreover, voltage in the same areas of the atrium do not follow the same cutoffs in AF as in SR or paced rhythm. Yagashita et al have shown that using electroanatomic mapping, mean bipolar voltage for same areas are lower in AF than in SR[21]. However, they found a linear voltage correlation between SR and AF, suggesting that LA fibrotic substrate may also be estimated in AF if the voltage cutoff is adjusted. In another study, there was no correlation between mean voltage or percentage low voltage during AF and paced rhythm[22]. Areas of complex fractionated electrograms and low voltage during AF frequently demonstrated normal atrial myocardial characteristics during SR. In addition, mean bipolar LA voltages, whether measured during AF, SR or pacing were lower in patients with persistent and long standing persistent AF than paroxysmal AF thereby correlating with AF severity and disease progression[23],[24],[25]. Recognizing the limitations of bipolar LA voltage as a marker of atrial scar is important as at least some of these limitations are avoidable. Standardization of mapping protocols, use of same catheter for building entire LA geometry and mapping with different voltage cutoffs based on the atrial rhythm as well as correlating with cardiac MRI when available include some of these measures that may potentially improve our ability to accurately define atrial scar.

Targeting the atrial substrate for AF ablation – Evidence 'For' and 'Against'

[Table 1] summarizes the studies assessing the role of substrate modification in AF ablation. Rolf et al in 2014[26] studied 178 patients with paroxysmal or persistent AF who first underwent voltage mapping during SR after circumferential pulmonary vein isolation. Subsequently substrate modification was performed in the same procedure and confined to the presence of low voltage zones (LVZ) defined by bipolar voltage<0.5mV. They identified LVZs in 35% and 10% of patients with persistent and paroxysmal AF respectively, most commonly in the LA roof followed by anterior, septal, and posterior wall. A twelve-month AF-free survival was 62% for patients without LVZs undergoing PVAI alone and 70% for patients with LVZs who also underwent tailored substrate modification (P=0.3). In addition, this success rate was significantly higher than in a control group of 26 patients with LVZ in whom no substrate modification was performed (27%, p value<0.001). The authors concluded that sinus rhythm voltage mapping is a useful tool to guide personalized AF substrate modification in patients undergoing AF ablation. Substrate modification in this study mostly involved posterior box isolation, roof lines and anterior mitral isthmus lines.

Jadidi et al[27] reported outcomes in 85 consecutive patients with persistent AF who underwent voltage mapping, PVI, and ablation at low-voltage zones (<0.5 millivolts while in AF) that were associated with electric activity lasting >70% of AF cycle. The procedural endpoint was AF termination. Freedom from arrhythmia was compared with a control group undergoing PVI only (66 patients). In the study population, 23 of 85 (27%) patients had small area of LVZ (<10% of left atrial surface area) and thus underwent PVI alone. In the remaining 62 patients with higher scar burden, PVI was performed followed by ablation of LVZs. In this subgroup, the procedural AF-termination rate was 73%. At a median follow-up of 13 months, arrhythmia free survival after single procedure was 69%, compared with a PVI-only approach (47%). In addition, there was no significant difference in the success rate of patients in the study group with a low amount of LVZ undergoing PVI only and patients requiring PVI + selective LVZ ablation.

Yamaguchi et al[28] performed voltage mapping of the LA during SR in 101 persistent AF patients. LVZ was defined as an area with bipolar electrograms <0.5 mV covering at least 5% of the left atrial surface excluding the pulmonary vein antrum. In patients with LVZs, PVI was performed along with substrate homogenization (LVZ-Abl) as opposed to PVI alone strategy in non-LVZ persistent AF patients. A historical control group included 16 patients who underwent PVI and left atrial scar mapping with the same method but without ablation of the scar areas (LVZ non-abl). During a mean follow-up period of 18 ± 7 months, the study reported an AF free survival of 72% in LVZ abl and 79% in PVI alone group, a statistically nonsignificant result. A second ablation procedure, when performed resulted in subsequent

Table 1: Studies of substrate guided AF ablation. See text for additional details.

Study (author/yr)	Design	Description	Follow up duration	Results	Favors Substrate modification
Rolf et al (2014)24	Nonrandomized, observational study	178 patients with paroxysmal or persistent AF underwent voltage mapping during sinus rhythm after circumferential PVI and then subsequent substrate modification confined to the presence of LVZ (<0.5 mV).	12 months	12 month AF-free survival - 62% for patients without LVZs undergoing PVAI alone - 70% for patients with LVZs who also underwent tailored substrate modification (P=0.3). -27% patients with LVZ in whom no substrate modification was performed	True
Jadidi et al (2016)25	Nonrandomized observational study	-85 consecutive patients with persistent AF underwent voltage mapping, PVI, and ablation at LVZ (<0.5 millivolts while in AF) associated with electric activity lasting >70% of AF cycle length. -Control group- PVI only	13 months	Study group with high-procedural AF termination rate. At follow up, arrhythmia free survival after single procedure was 69%, compared with a PVI-only approach (47%) in patients with persistent AF.	True
Yamaguchi et al (2016)26	Nonrandomized observational study	-101 persistent AF patients underwent voltage mapping to identify LVZ. -In patients with LVZs identified, PVI was performed along with substrate homogenization (LVZ-Abl) -PVI alone strategy in non-LVZ persistent AF patients. -A historical control group of 16 patients with PVI and left atrial scar mapping with the same method but without ablation of the scar areas (LVZ non-abl)	18+/-7 months	-AF free survival of 72% in LVZ abl and 79% in PVI alone group and AF free survival of 90% and 84% respectively with second procedure if required. -In LVZ-non Abl controls, AF free survival remained low (38% at mean follow-up 32 ± 7 months)	True
Yang et al (2016)27	Nonrandomized observational study	-86 consecutive patients with nonparoxysmal AF underwent PVI followed by LVZ guided substrate homogenization (Study) - 78 consecutive sex- and age-matched patients with nonparoxysmal AF who underwent stepwise ablation approach(Control)	24 months	The probability to maintain SR at 24 months was 69.8% versus 51.3% in the two groups respectively.	True
Kottkamp et al(2015)28	Nonrandomized observational	-10 patients with PAF with durable PVI for redo ablation underwent box isolation of fibrotic areas (BIFA). -31 patients with nonparoxysmal AF for first AF ablation underwent PVI alone (if no LVZ) or PVI + BIFA (if LVZ present)	Mean follow-up was 12.5 ± 2.4 months	In pts with paroxysmal AF despite durable PVI and in 60% of patients with nonparoxysmal AF, individually localized LVZ were identified and targeted successfully with the BIFA strategy.	True
Wang et al (2014)28	Randomized	One hundred and twenty-four patients were randomized to individualized substrate modification (ISM) group (n = 64) or stepwise ablation (SA) group (n = 60). All patients underwent PVAI first.	12- month	Sinus rhythm was maintained in 65.5% of patients in the ISM group and in 45.0% of patients in the SA group after a single procedure (P = 0.04)	True
Blandino et al (2017)29	Meta-analysis	-6 studies including 885 patients (517 in study group and 368 in control group). Aim to assess the impact of a voltage-guided substrate modification by targeting low-voltage zones (LVZ) in addition to pulmonary vein isolation (PVI). 92% patients with nonparoxysmal AF.	17 months	70% of patients in the study group vs. 43% in the control group were free from AF/atrial tachycardia (AT) recurrences (odds ratio [OR] = 3.41, 95% confidence interval [CI] 2.22-5.24).	True
Mohanty et al (2016)30	Nonrandomized observational study	-177 consecutive patients with PAF and severe LA scarring undergoing first AF ablation. - Success rates (no recurrence of AF while off antiarrhythmic drugs through average follow up.	27+/-5 months	-PVAI only (n=45), PVAI + scar homogenization (n=66) or PVAI + ablation of non-PV triggers (n=66) resulted in success rates of 18%, 21% and 61% respectively -Scar homogenization combined with PVAI did not provide any additional advantage compared with PVAI alone	False

AF free survival of 90% and 84% (LVZ abl vs. PVI). In LVZ-non Abl controls, AF free survival remained low (38% at mean follow-up 32 ± 7 months). However, a significant decline in left atrial function in 13% of LVZ patients and higher procedural and fluoroscopy times were noted in LVZ-Abl cohort. Authors concluded that LVZ-based substrate modification after PVI improved the outcomes in persistent AF patients with LVZs, whereas PVI alone strategy worked well in patients without LVZs, even those with persistent AF. In another investigation by Yang et al[29], 86 consecutive patients with non-paroxysmal AF were studied. After circumferential pulmonary vein isolation, cavo-tricuspid isthmus ablation and cardioversion to SR, high-density electroanatomic mapping of left atrium was performed to identify LVZs and abnormal potentials in SR. Seventy eight consecutive sex- and age-matched patients with non-paroxysmal AF who underwent stepwise ablation (SA) approach were included in the historical control group. In the study group, patients underwent PVI followed by LVZ guided substrate homogenization. In control group, PVI was performed followed by linear ablation at LA roof,

mitral isthmus and cavo-tricuspid isthmus if AF persisted, followed by complex fractionated atrial electrograms (CFAEs) ablation and finally DCCV. The probability to maintain SR at 24 months was 69.8% versus 51.3% in the two groups respectively. Authors concluded that for non-paroxysmal AF, electrophysiological substrate-guided LA ablation during SR in addition to PVI, significantly improved single procedural success rates compared to the widely practiced stepwise approach. Kottkamp et al[30] reported high success rates with box isolation of fibrotic substrate (BIFA) in both non-paroxysmal AF patients and in patients with paroxysmal AF undergoing redo procedure. First, PVI was performed in all patients. Then, based on left atrial voltage mapping, the authors classified patients into different stages of fibrotic atrial cardiomyopathy (FACM). Left atria with no or very limited low-voltage areas were classified as fibrotic atrial cardiomyopathy (FACM) 0–1, left atria with regional areas of low voltage as FACM 2, and atria with large confluent areas as FACM 3. The procedure involved circumferential isolation of confluent LVZs identified by point-by-point voltage mapping. In 60% of the non-paroxysmal AF patients who were classified as FACM 2–3, BIFA ablation was performed. In this subgroup, single-procedure success rate measured 72% with a 1-year follow-up and 83% with only 1.2 procedures/patient. However, one limitation was that the study lacked a comparative group for the patients with FACM 2–3 (solely PVI without BIFA).

All the above studies were observational nonrandomized trials and hence suffer from limitations inherent to the study design; incorporating data from historical controls introduces further bias. In a randomized trial, Wang et al[31] reported success with a novel individualized substrate modification approach when compared to a stepwise approach in patients with long standing persistent AF. One hundred and twenty-four patients were randomized to individualized substrate modification (ISM) group (n = 64) or stepwise ablation group (n = 60). All patients underwent PVAI first. In ISM group, ablation strategy included creating LA roof line in all patients and substrate ablation based on the extent of scar. Only abnormal potentials (AP) within LVZs were ablated in patients with mild substrate abnormality (LVZ< 10%). In patients with moderate (LVZ =10—20%) and large substrate areas (LVZ>20%), AP within LVZ were ablated and additional individualized lines were created to connect scar areas with each other and/or to anatomical structures. In SA group, PVI was followed by linear ablation at the LA roof, mitral isthmus and cavo-tricuspid isthmus, followed by ablation of complex fractionated atrial electrograms (CFAE) with a goal to terminate AF. If AF did not terminate, DCCV was applied. At end of 12-month follow up, the intention-to-treat analysis showed that sinus rhythm was maintained in 65.5% of patients in the ISM group and in 45.0% of patients in the SA group after a single procedure (P = 0.04). The total procedural time was significantly shorter in ISM than that in SA group. This study highlights that even with extensive ablation performed in both groups, targeting the low voltage zone and individualizing scar modification strategy in patients may produce better outcomes with a shorter procedural time than PVI with additional lines and CFAE and non-PV trigger guided ablation strategy in patients with long standing persistent AF. However, the study results were limited by small sample size and short duration of follow up. Most recently, a meta-analysis, including 6 studies of 885 predominantly non-paroxysmal AF patients (92%), looked at outcomes of freedom from AF or AT in patients with PVI+LVZ ablation vs. PVI and other conventional ablation techniques (control). The results indicated that LVZ ablation in addition to PVI was more effective than PVI +/- traditional ablation (70% vs. 43%) with comparable rates of adverse events (2.5% vs. 6%) [32].

There is emerging data that additional substrate guided ablation may not add much benefit to conventional PVAI alone strategy. A nonrandomized prospective study of 177 consecutive patients with paroxysmal AF and severe LA scarring (scar >60% of LA area as defined by electroanatomic voltage mapping during procedure) underg oing first AF ablation showed that PVAI only (n=45), PVAI + scar homogenization (n=66) or PVAI + ablation of non-PV triggers (n=66) resulted in success rates (no recurrence of AF while off antiarrhythmic drugs through average follow up duration of 27+/-5 months) of 18%, 21% and 61% respectively33. Scar homogenization combined with PVAI did not provide additional benefit when compared with PVAI alone and both approaches had very low-success rate after single procedure in patients with extensive scarring. Interestingly, a PVAI + trigger based ablation strategy was not only safe but also provided significantly higher success rate than PVAI alone or PVAI + scar homogenization. Non-PV trigger ablation is yet another extensively studied strategy for persistent AF ablation which is beyond the scope of this review.

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However, the results of STAR AF II trial do merit some discussion[10]. Five hundred and eighty nine patients with persistent AF were randomized to PVI alone (67 patients), PVI plus CFAE ablation (263 patients), or PVI and linear ablation across the left atrial roof and mitral valve isthmus (259 patients). After 18 months, AF free survival was 59%, 49% and 46% in group 1, 2 and 3 respectively (P=0.15). There was no significant difference among the three groups in freedom from AF even after a redo procedure. Procedure time was significantly shorter for PVI alone than for the other two procedures (P<0.001). From this study, it appears that neither complex electrograms nor linear ablation lines are the correct ancillary targets for ablation. Thus, the authors concluded that the role of more extensive ablation in persistent AF patients is of dubious benefit. It is very important to remember that in this study, scar modification or homogenization was not performed in either study group. Ablation targeting CFAE or roof/isthmus lines cannot be equated with individualized substrate modification approach. The

results of the trial emphasize the need for future research looking at selective ablation targets based on an individual patient's specific arrhythmic substrate.

In the 2017 HRS expert consensus document[34], the usefulness of mapping and ablation of areas of abnormal myocardial tissue identified with voltage mapping or MRI as an initial or repeat ablation strategy for persistent or longstanding persistent AF was given a class IIb recommendation. A class IIb recommendation was given to creation of linear ablation lines (in absence of documented macro-reentrant flutter), CFAE ablation, rotor ablation, extensive posterior wall ablation or targeting of autonomic ganglionic plexi in persistent AF. The document did however give a class IIa recommendation to ablation of non-PV triggers, if found.

Pitfalls of a substrate guided approach

Scar modification/homogenization approach is not without pitfalls. Some of these include

1. Variation in accuracy and reproducibility of scar maps by electroanatomic mapping or MRI

We have discussed the pitfalls of bipolar voltage mapping earlier in this review. Voltage maps may look different in the same patient with different mapping catheters and in different rhythms. Specific cutoffs for different catheters, mapping systems and rhythms may apply which are yet to be identified. The same problem is noted with MRI imaging where considerable differences in operator and center experience exists. Recent data regarding use of MRI for fibrosis imaging is conflicting. Most recently, a prospective single center experience of 149 consecutive patients (64 persistent, 85 paroxysmal) undergoing AF ablation showed that delayed enhancement detected by cardiac MRI within LA walls using standard clinical scanners and typical pulse sequence parameters was uncommon (five patients, prevalence 3%) and when present, did not correlate with AF type or risk of AF recurrence.[35] These results are contrary to other investigational data.[17],[18] Developing standardized fibrosis specific protocols and uniform cutoffs for fibrosis detection may lead to improved accuracy and reproducibility.

2. What are the end points of substrate modification?

End point of substrate modification is not well established and best ablation approach would likely depend on the distribution and extent of the fibrosis. For example, it may be reasonable to expect to completely homogenize a scar that comprises 5% of the atrium but it is unreasonable to do so if the scar is 40% or more. In those cases, a box lesion set may be more feasible but anatomic location of the scar could further complicate the task, an example would be a septal extension of the scar. The power, duration, extent and end-point of scar-homogenization ablation may also have to be tailored to the adjacent structures such as the esophagus and posterior wall to minimize risk of damage.

3. Is atrial scar really a 'static' substrate?

Targeting the scar at the time of AF ablation may potentially eliminate the 'electrical substrate' at that time point but scar recovery and progression of fibrosis should be considered. In one study, atrial fibrosis quantified by LGE-MRI was stable in the majority of AF patients at one-year follow-up[36]. However, about one third of patients evaluated in the study exhibited progression of atrial fibrotic disease over time. Specific risk predictors for progression of fibrosis could not be identified in this study. In another report by the same group[37], scar recovery and presence of new fibrosis as detected by LGE MRI scans were significant risk factors for late recurrence of AF after initial ablation. If the substrate is not static, scar progression should be considered as a potential risk factor and whether modifying this process can be a long term solution remains to be seen. It is uncertain as to what may be the best approach for ablation in patients with large atrial scars and what would be the endpoint of ablation. Additionally, to what extent right atrial scars correlate with AF progression and whether these need to be targeted remains to be determined.

4. Does scar define all the abnormal substrate? What about the' hidden' substrate?

Even if we consider that imaging or voltage mapping can accurately define the scar and that scar represents the static substrate, it must be understood that fibrosis may just be the final step of a remodeling cascade including myocyte architectural changes, ion channel dysfunction, connexin disarray and disruption of fiber orientation all of which may precede scarring but may not be seen on voltage mapping or imaging. However, it is possible that these areas may still exhibit properties of electrical heterogeneity and may sustain reentrant drivers. This may be referred to as the hidden substrate and at this time remains non-quantifiable. Whether or not this hidden substrate can be detected or targeted to make a clinically relevant difference remains to be seen.

5. Procedural times and fluoroscopy times with additional substrate mapping and modification are longer than PVAI alone

This is a particularly concerning issue at the present time when minimizing fluoroscopy exposure is a principle safety goal during AF ablation procedure. However, as 'low' fluoroscopy and 'no' fluoroscopy techniques for AF ablation become widespread, this issue may not remain as important.

6. Risk–benefit ratio of additional ablation

The risk- benefit ratio of substrate modification would conceivably vary depending on extent of fibrosis, classification and duration of AF, operator and center experience, and expected chances of success with PVAI alone strategy. For example, in a paroxysmal AF patient with first ablation of AF and mild scar, considering that PVAI alone may have high success rates, it may be better to stay away from additional ablation. On the contrary, during redo ablation in long standing persistent AF patients with extensive scar, an individualized substrate modification approach may be necessary. However, a risk benefit model may be most useful in patients such as those with long standing persistent AF going for first AF ablation with moderate scar or paroxysmal AF patients with severe LA scarring. At this time, evidence from large randomized trials is not available to answer these questions.

7. Substrate based ablation may potentially affect LA diastolic function- The "Stiff left atrial syndrome"

Gibson et al[38] first reported the syndrome of dyspnea, congestive heart failure, pulmonary hypertension, and large V waves recorded on PCWP or LA pressure tracings in the absence of significant mitral regurgitation. This syndrome is seen despite absence of pulmonary vein stenosis and is a result of abnormal LA diastolic function due to extensive ablation. Small LA size, obstructive sleep apnea, diabetes mellitus, atrial scarring, and high LA pressure were predictors of this complication of AF ablation. It is conceivable that the syndrome may become more important if operators were to perform extensive ablations beyond PVI alone as the LA diastolic function is more

likely to be affected. While there is data suggesting abnormalities of LA diastolic function after substrate ablation[28], whether this difference is clinically relevant between PVI alone versus PVI with substrate homogenization remains to be seen.

The 'Future role' of substrate guided ablation in management of AF

Voltage and MRI guided substrate modification in addition to pulmonary vein isolation during AF ablation have been performed successfully. However, data is confined to small, mostly non-randomized observational studies. In face of conflicting results from these studies, longer procedural times and possible increased risk of complications with extensive ablation, the rates at which this strategy is employed have remained low, even for repeat ablation in persistent and long standing persistent AF[33]. The currently ongoing large, multicenter randomized DECAAF II trial is designed to study the efficacy of DE-MRI detected fibrosis guided AF ablation strategy (involving PVI +/-scar homogenization based on fibrosis extent) in comparison to conventional catheter ablation of AF. The results of this trial will likely provide further insight in substrate guided AF ablation and more specifically, the role of scar homogenization in AF. However, as previously mentioned in this manuscript, there is lack of consistent reproducibility of MRI detected scar in the atrium and results from recent data regarding use of MRI for LA fibrosis imaging using current standard MRI equipment and protocols have not been entirely encouraging.

Results of a recent investigation indicate that a wholly patient tailored approach may be successful in trigger based ablation in all AF types. In a recent prospective nonrandomized pilot study of 105 patients undergoing AF ablation, Seitz et al[39] have shown that spatiotemporal dispersion of electrograms may represent an electrical footprint of waves that emanate from AF drivers and that these areas may further represents sites of interstitial fibrosis and atrial muscle heterogeneity. The authors demonstrated a novel approach involving recording regions exhibiting spatiotemporal electrogram dispersion by multipolar catheter mapping (Pentaray, Biosense Webster) during AF and then targeting such regions without additional PVI or any other anatomy-based ablation lines. An average of 49 ± 21 mins ablation duration and a mean of 1.4 ± 0.5 procedures resulted in a 95% rate of acute AF termination and 85% AF free survival during an 18 months follow-up. These results showed that the novel approach allowed for efficacious, nonextensive, and wholly patient-tailored ablation in all AF types. The nonrandomized design of this pilot study limited author conclusions. There were other limitations including comparison to a historical cohort and high use of anti-arrhythmic drug (44%). However, the study provides a new hypothesis that needs to be further tested and which may provide a significant step forward in the field of trigger based ablation. It also brings forth evidence supporting an overlap between anatomic substrate and electrical drivers of AF. A larger randomized trial to study this approach against conventional approaches of AF ablation is now warranted.

Since the results of the randomized Fire and ICE trial[40] which showed cryoballoon ablation was noninferior to radiofrequency ablation with respect to efficacy and safety for the treatment of patients with drug-refractory paroxysmal atrial fibrillation, there is growing use of cryoablation for pulmonary vein isolation worldwide. Multiple small nonrandomized studies[41]-[45] have been conducted to assess the efficacy and safety of this technique in persistent AF patients and initial results have been encouraging. Shorter procedural and fluoroscopy times have been reported[45] when compared with RF ablation in persistent AF patients. Larger randomized trials of cryoablation in persistent and long standing persistent AF ablation are underway. As the role of substrate modification in AF ablation remains controversial and pulmonary vein isolation by cryoablation is a growing trend, willingness of operators to perform additional ablation which may require a different ablation technique altogether or a different catheter will be important factors that may determine the future of substrate or trigger based ablation as a first line therapy, even with growing evidence in support of these techniques. There is increasing emphasis on fluoroless ablation techniques and shorter procedural times and hence the benefits of substrate guided ablation will need to be weighed against safety profile and long term outcomes that will determine whether these techniques gain widespread acceptability among electrophysiologists.

Conclusions

Despite technological advances and growing operator experience in performing percutaneous catheter ablation for AF, the long term procedural success rates for persistent AF and long standing persistent AF have not paralleled those of paroxysmal AF. A thorough understanding of the AF substrate requires standardized techniques for defining the static and dynamic substrates of AF. Our most-studied modalities for scar mapping include electroanatomic mapping and cardiac MRI. Currently, the use of either of these techniques has significant pitfalls. In the future, the ability to integrate imaging information with emerging technologies like body surface mapping, ripple mapping and very high-density mapping with closely spaced bipoles and improving the spatial resolution and accuracy of cardiac MR imaging with development of fibrosis specific protocols might provide further understanding of the pathophysiologic interrelation between "scar" and abnormal electrophysiologic substrate in persistent and long standing persistent AF. Multiple studies have reported success with novel trigger and substrate based ablation techniques and larger randomized trials are underway. However, due to lack of data from large multicenter randomized trials, these techniques have not yet gained widespread acceptability. Even as evidence of benefit from substrate based ablation in persistent AF patients grows, there will be practical barriers that will need to be overcome before these techniques can become standard of care (risk-benefit ratio, operative training and experience, requirement for additional ablation techniques in case cryoablation used for PVI, procedural times, fluoroscopy times). Nevertheless, as we embark on our efforts to improve outcomes of AF ablation, especially in patients with persistent and long standing persistent AF, the role of substrate guided AF ablation strategies remains promising.

Disclosures

The authors do not have any conflicts of interest in relation to this manuscript.

References

1. January Craig T, WannL Samuel, AlpertJoseph S, CalkinsHugh, CigarroaJoaquin E, ClevelandJoseph C, ContiJamie B, EllinorPatrick T, EzekowitzMichael D, FieldMichael E, MurrayKatherine T, SaccoRalph L, StevensonWilliam G, TchouPatrick J, TracyCynthia M, YancyClyde W. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines and the Heart Rhythm Society.

Circulation. 2014;130 (23):2071–104

2. Calkins Hugh, ReynoldsMatthew R, SpectorPeter, SondhiManu, XuYingxin, MartinAmber, WilliamsCatherine J, SledgeIsabella. Treatment of atrial fibrillation with antiarrhythmic drugs or radiofrequency ablation: two systematic literature reviews and meta-analyses. Circ Arrhythm Electrophysiol. 2009;2 (4):349–61
3. Haïssaguerre M, JaïsP, ShahD C, TakahashiA, HociniM, QuiniouG, GarrigueS, Le MourouxA, Le MétayerP, ClémentyJ. Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins. N. Engl. J. Med. 1998;339 (10):659–66
4. Calkins Hugh, KuckKarl Heinz, CappatoRiccardo, BrugadaJosep, CammA John, ChenShih-Ann, CrijnsHarry J G, DamianoRalph J, DaviesD Wyn, DiMarcoJohn, EdgertonJames, EllenbogenKenneth, EzekowitzMichael D, HainesDavid E, HaissaguerreMichel, HindricksGerhard, IesakaYoshito, JackmanWarren, JalifeJosé, JaisPierre, KalmanJonathan, KeaneDavid, KimYoung-Hoon, KirchhofPaulus, KleinGeorge, KottkampHans, KumagaiKoichiro, LindsayBruce D, MansourMoussa, MarchlinskiFrancis E, McCarthyPatrick M, MontJ Lluis, MoradyFred, NademaneeKoonlawee, NakagawaHiroshi, NataleAndrea, NattelStanley, PackerDouglas L, PapponeCarlo, PrystowskyEric, RavieleAntonio, ReddyVivek, RuskinJeremy N, SheminRichard J, TsaoHsuan-Ming, WilberDavid. 2012 HRS/EHRA/ECAS expert consensus statement on catheter and surgical ablation of atrial fibrillation: recommendations for patient selection, procedural techniques, patient management and follow-up, definitions, endpoints, and research trial design: a report of the Heart Rhythm Society (HRS) Task Force on Catheter and Surgical Ablation of Atrial Fibrillation. Developed in partnership with the European Heart Rhythm Association (EHRA), a registered branch of the European Society of Cardiology (ESC) and the European Cardiac Arrhythmia Society (ECAS); and in collaboration with the American College of Cardiology (ACC), American Heart Association (AHA), the Asia Pacific Heart Rhythm Society (APHRS), and the Society of Thoracic Surgeons (STS). Endorsed by the governing bodies of the American College of Cardiology Foundation, the American Heart Association, the European Cardiac Arrhythmia Society, the European Heart Rhythm Association, the Society of Thoracic Surgeons, the Asia Pacific Heart Rhythm Society, and the Heart Rhythm Society. Heart Rhythm. 2012;9 (4):632–696.e21
5. Elayi Claude S, VermaAtul, Di BiaseLuigi, ChingChi Keong, PatelDimpi, BarrettConor, MartinDavid, RongBai, FahmyTamer S, KhaykinYaariv, HongoRichard, HaoSteven, PelargonioGemma, Dello RussoAntonio, CasellaMichela, SantarelliPietro, PotenzaDomenico, FanelliRaffaele, MassaroRaimondo, ArrudaMauricio, SchweikertRobert A, NataleAndrea. Ablation for longstanding permanent atrial fibrillation: results from a randomized study comparing three different strategies. Heart Rhythm. 2008;5 (12):1658–64
6. Brooks Anthony G, StilesMartin K, LaborderieJulien, LauDennis H, KuklikPawel, ShippNicholas J, HsuLi-Fern, SandersPrashanthan. Outcomes of long-standing persistent atrial fibrillation ablation: a systematic review. Heart Rhythm. 2010;7 (6):835–46
7. Tilz Roland Richard, RilligAndreas, ThumAnna-Maria, AryaAnita, WohlmuthPeter, MetznerAndreas, MathewShibu, YoshigaYasuhiro, WissnerErik, KuckKarl-Heinz, OuyangFeifan. Catheter ablation of long-standing persistent atrial fibrillation: 5-year outcomes of the Hamburg Sequential Ablation Strategy. J. Am. Coll. Cardiol. 2012;60 (19):1921–9
8. Providência Rui, LambiasePier D, SrinivasanNeil, Ganesh BabuGirish, BronisKonstantinos, AhsanSyed, KhanFakhar Z, ChowAnthony W, RowlandEdward, LoweMartin, SegalOliver R. Is There Still a Role for Complex Fractionated Atrial Electrogram Ablation in Addition to Pulmonary Vein Isolation in Patients With Paroxysmal and Persistent Atrial Fibrillation? Meta-Analysis of 1415 Patients. Circ Arrhythm Electrophysiol. 2015;8 (5):1017–29
9. Cox J L, BoineauJ P, SchuesslerR B, KaterK M, LappasD G. Five-year experience with the maze procedure for atrial fibrillation. Ann. Thorac. Surg. 1993;56 (4):814–823
10. Verma Atul, JiangChen-yang, BettsTimothy R, ChenJian, DeisenhoferIsabel, MantovanRoberto, MacleLaurent, MorilloCarlos A, HaverkampWilhelm, WeerasooriyaRukshen, AlbenqueJean-Paul, NardiStefano, MenardiEndrj, NovakPaul, SandersPrashanthan. Approaches to catheter ablation for persistent atrial fibrillation. N. Engl. J. Med. 2015;372 (19):1812–22
11. Heijman Jordi, AlgalarrondoVincent, VoigtNiels, MelkaJonathan, WehrensXander H T, DobrevDobromir, NattelStanley. The value of basic research insights into atrial fibrillation mechanisms as a guide to therapeutic innovation: a critical analysis. Cardiovasc. Res. 2016;109 (4):467–79
12. Zahid Sohail, CochetHubert, BoylePatrick M, SchwarzErica L, WhyteKaitlyn N, VigmondEdward J, DuboisRémi, HociniMélèze, HaïssaguerreMichel, JaïsPierre, TrayanovaNatalia A. Patient-derived models link re-entrant driver localization in atrial fibrillation to fibrosis spatial pattern. Cardiovasc. Res. 2016;110 (3):443–54
13. Andrade Jason, KhairyPaul, DobrevDobromir, NattelStanley. The clinical profile and pathophysiology of atrial fibrillation: relationships among clinical features, epidemiology, and mechanisms. Circ. Res. 2014;114 (9):1453–68
14. Maesen Bart, ZeemeringStef, AfonsoCarlos, EcksteinJens, BurtonRebecca A B, van HunnikArne, StuckeyDaniel J, TylerDamian, MaessenJos, GrauVicente, VerheuleSander, KohlPeter, SchottenUlrich. Rearrangement of atrial bundle architecture and consequent changes in anisotropy of conduction constitute the 3-dimensional substrate for atrial fibrillation. Circ Arrhythm Electrophysiol. 2013;6 (5):967–75
15. Verma Atul, WazniOussama M, MarroucheNassir F, MartinDavid O, KilicaslanFethi, MinorStephen, SchweikertRobert A, SalibaWalid, CummingsJennifer, BurkhardtJ David, BhargavaMandeep, BeldenWilliam A, Abdul-KarimAhmad, NataleAndrea. Pre-existent left atrial scarring in patients undergoing pulmonary vein antrum isolation: an independent predictor of procedural failure. J. Am. Coll. Cardiol. 2005;45 (2):285–92
16. Yamaguchi Takanori, TsuchiyaTakeshi, NagamotoYasutsugu, MiyamotoKoji, MurotaniKenta, OkishigeKaoru, TakahashiNaohiko. Long-term results of pulmonary vein antrum isolation in patients with atrial fibrillation: an analysis in regards to substrates and pulmonary vein reconnections. Europace. 2014;16 (4):511–20
17. Marrouche Nassir F, WilberDavid, HindricksGerhard, JaisPierre, AkoumNazem, MarchlinskiFrancis, KholmovskiEugene, BurgonNathan, HuNan, MontLluis, DenekeThomas, DuytschaeverMattias, NeumannThomas, MansourMoussa, MahnkopfChristian, HerwegBengt, DaoudEmile, WissnerErik, BansmannPaul, BrachmannJohannes. Association of atrial tissue fibrosis identified by delayed enhancement MRI and atrial fibrillation catheter ablation: the DECAAF study. JAMA. 2014;311 (5):498–506
18. Khurram Irfan M, HabibiMohammadali, Gucuk IpekEsra, ChrispinJonathan, YangEunice, FukumotoKotaro, DewireJane, SpraggDavid D, MarineJoseph E, BergerRonald D, AshikagaHiroshi, RickardJack, ZhangYiyi, ZipunnikovVadim, ZimmermanStefan L, CalkinsHugh, NazarianSaman. Left Atrial LGE and Arrhythmia Recurrence Following Pulmonary Vein Isolation for Paroxysmal and Persistent AF. JACC Cardiovasc Imaging. 2016;9 (2):142–8
19. Kapa Suraj, DesjardinsBenoit, CallansDavid J, MarchlinskiFrancis E, DixitSanjay. Contact electroanatomic mapping derived voltage criteria for characterizing left atrial scar in patients undergoing ablation for atrial fibrillation. J. Cardiovasc. Electrophysiol. 2014;25 (10):1044–52
20. Tschabrunn Cory M, RoujolSebastien, DormanNicole C, NezafatReza, JosephsonMark E, AnterElad. High-Resolution Mapping of Ventricular Scar: Comparison Between Single and Multielectrode Catheters. Circ Arrhythm Electrophysiol. 2016;9 (6)
21. Yagishita Atsuhiko, DE OliveiraSamer, CakulevIvan, GimbelJ Rod, SparanoDina, ManyamHarish, Manrique-GarciaAlvaro, ArredondoMichael, MackallJudith, ArrudaMauricio. Correlation of Left Atrial Voltage Distribution Between

Sinus Rhythm and Atrial Fibrillation: Identifying Structural Remodeling by 3-D Electroanatomic Mapping Irrespective of the Rhythm. J. Cardiovasc. Electrophysiol. 2016;27 (8):905–12

22. Teh Andrew W, KistlerPeter M, LeeGeoffrey, MediCaroline, HeckPatrick M, SpenceSteven J, SparksPaul B, MortonJoseph B, SandersPrashanthan, KalmanJonathan M. The relationship between complex fractionated electrograms and atrial low-voltage zones during atrial fibrillation and paced rhythm. Europace. 2011;13 (12):1709–16
23. Teh Andrew W, KistlerPeter M, LeeGeoffrey, MediCaroline, HeckPatrick M, SpenceSteven J, SparksPaul B, MortonJoseph B, KalmanJonathan M. Electroanatomic remodeling of the left atrium in paroxysmal and persistent atrial fibrillation patients without structural heart disease. J. Cardiovasc. Electrophysiol. 2012;23 (3):232–8
24. Lin Yazhou, YangBing, GarciaFermin C, JuWeizhu, ZhangFengxiang, ChenHongwu, YuJinbo, LiMingfang, GuKai, CaoKejiang, CallansDavid J, MarchlinskiFrancis E, ChenMinglong. Comparison of left atrial electrophysiologic abnormalities during sinus rhythm in patients with different type of atrial fibrillation. J Interv Card Electrophysiol. 2014;39 (1):57–67
25. Fiala Martin, WichterleDan, ChovancíkJan, BulkováVeronika, WojnarováDorota, NevralováRenáta, JanuskaJaroslav. Left atrial voltage during atrial fibrillation in paroxysmal and persistent atrial fibrillation patients. Pacing Clin Electrophysiol. 2010;33 (5):541–8
26. Rolf Sascha, KircherSimon, AryaArash, EitelCharlotte, SommerPhilipp, RichterSergio, GasparThomas, BollmannAndreas, AltmannDavid, PiedraCarlos, HindricksGerhard, PiorkowskiChristopher. Tailored atrial substrate modification based on low-voltage areas in catheter ablation of atrial fibrillation. Circ Arrhythm Electrophysiol. 2014;7 (5):825–33
27. Jadidi Amir S, LehrmannHeiko, KeylCornelius, SorrelJérémie, MarksteinViktor, MinnersJan, ParkChan-Il, DenisArnaud, JaïsPierre, HociniMélèze, PotocnikClemens, AllgeierJuergen, HochholzerWillibald, Herrera-SidlokyClaudia, KimSteve, OmriYoussef El, NeumannFranz-Josef, WeberReinhold, HaïssaguerreMichel, ArentzThomas. Ablation of Persistent Atrial Fibrillation Targeting Low-Voltage Areas With Selective Activation Characteristics. Circ Arrhythm Electrophysiol. 2016;9 (3)
28. Yamaguchi Takanori, TsuchiyaTakeshi, NakaharaShiro, FukuiAkira, NagamotoYasutsugu, MurotaniKenta, EshimaKenichi, TakahashiNaohiko. Efficacy of Left Atrial Voltage-Based Catheter Ablation of Persistent Atrial Fibrillation. J. Cardiovasc. Electrophysiol. 2016;27 (9):1055–63
29. Yang Gang, YangBing, WeiYouquan, ZhangFengxiang, JuWeizhu, ChenHongwu, LiMingfang, GuKai, LinYazhou, WangBenqi, CaoKejiang, KojodjojoPipin, ChenMinglong. Catheter Ablation of Nonparoxysmal Atrial Fibrillation Using Electrophysiologically Guided Substrate Modification During Sinus Rhythm After Pulmonary Vein Isolation. Circ Arrhythm Electrophysiol. 2016;9 (2)
30. Kottkamp Hans, BergJan, BenderRoderich, RiegerAndreas, SchreiberDoreen. Box Isolation of Fibrotic Areas (BIFA): A Patient-Tailored Substrate Modification Approach for Ablation of Atrial Fibrillation. J. Cardiovasc. Electrophysiol. 2016;27 (1):22–30
31. Wang Xin-Hua, LiZheng, MaoJia-Liang, HeBen. A novel individualized substrate modification approach for the treatment of long-standing persistent atrial fibrillation: preliminary results. Int. J. Cardiol. 2014;175 (1):162–8
32. Blandino Alessandro, BianchiFrancesca, GrossiStefano, Biondi-ZoccaiGiuseppe, ConteMaria Rosa, GaidoLuca, GaitaFiorenzo, ScaglioneMarco, RamettaFrancesco. Left Atrial Substrate Modification Targeting Low-Voltage Areas for Catheter Ablation of Atrial Fibrillation: A Systematic Review and Meta-Analysis. Pacing Clin Electrophysiol. 2017;40 (2):199–212
33. Mohanty Sanghamitra, MohantyPrasant, Di BiaseLuigi, TrivediChintan, MorrisEli Hamilton, GianniCarola, SantangeliPasquale, BaiRong, SanchezJavier E, HranitzkyPatrick, GallinghouseG Joseph, Al-AhmadAmin, HortonRodney P, HongoRichard, BeheirySalwa, ElayiClaude S, LakkireddyDhanunjaya, Madhu ReddyYaruva, Viles GonzalezJuan F, BurkhardtJ David, NataleAndrea. Long-term follow-up of patients with paroxysmal atrial fibrillation and severe left atrial scarring: comparison between pulmonary vein antrum isolation only or pulmonary vein isolation combined with either scar homogenization or trigger ablation. Europace. 2017;19 (11):1790–1797
34. Calkins Hugh, HindricksGerhard, CappatoRiccardo, KimYoung-Hoon, SaadEduardo B, AguinagaLuis, AkarJoseph G, BadhwarVinay, BrugadaJosep, CammJohn, ChenPeng-Sheng, ChenShih-Ann, ChungMina K, NielsenJens Cosedis, CurtisAnne B, DaviesD Wyn, DayJohn D, d'AvilaAndré, de GrootN M S Natasja, Di BiaseLuigi, DuytschaeverMattias, EdgertonJames R, EllenbogenKenneth A, EllinorPatrick T, ErnstSabine, FenelonGuilherme, GerstenfeldEdward P, HainesDavid E, HaissaguerreMichel, HelmRobert H, HylekElaine, JackmanWarren M, JalifeJose, KalmanJonathan M, KautznerJosef, KottkampHans, KuckKarl Heinz, KumagaiKoichiro, LeeRichard, LewalterThorsten, LindsayBruce D, MacleLaurent, MansourMoussa, MarchlinskiFrancis E, MichaudGregory F, NakagawaHiroshi, NataleAndrea, NattelStanley, OkumuraKen, PackerDouglas, PokushalovEvgeny, ReynoldsMatthew R, SandersPrashanthan, ScanavaccaMauricio, SchillingRichard, TondoClaudio, TsaoHsuan-Ming, VermaAtul, WilberDavid J, YamaneTeiichi. 2017 HRS/EHRA/ECAS/APHRS/SOLAECE expert consensus statement on catheter and surgical ablation of atrial fibrillation: Executive summary. J Arrhythm. 2017;33 (5):369–409
35. Bois John P, GlocknerJames, YoungPhillip M, FoleyThomas A, SheldonSeth, NewmanDarrell B, LinGrace, PackerDouglas L, BradyPeter A. Low incidence of left atrial delayed enhancement with MRI in patients with AF: a single-centre experience. Open Heart. 2017;4 (1)
36. Yamaji K, FujimotoS, YutaniC, IkedaY, MizunoR, HashimotoT, NakamuraS. Does the progression of myocardial fibrosis lead to atrial fibrillation in patients with hypertrophic cardiomyopathy?. Cardiovasc. Pathol. 2002;10 (6):297–303
37. Kottkamp Hans. Human atrial fibrillation substrate: towards a specific fibrotic atrial cardiomyopathy. Eur. Heart J. 2013;34 (35):2731–8
38. Gibson Douglas N, Di BiaseLuigi, MohantyPrasant, PatelJigar D, BaiRong, SanchezJavier, BurkhardtJ David, HeywoodJ Thomas, JohnsonAllen D, RubensonDavid S, HortonRodney, GallinghouseG Joseph, BeheirySalwa, CurtisGuy P, CohenDavid N, LeeMark Y, SmithMichael R, GopinathDevi, LewisWilliam R, NataleAndrea. Stiff left atrial syndrome after catheter ablation for atrial fibrillation: clinical characterization, prevalence, and predictors. Heart Rhythm. 2011;8 (9):1364–71
39. Seitz Julien, BarsClément, ThéodoreGuillaume, BeurtheretSylvain, LelloucheNicolas, BremondyMichel, FerracciAnge, FaureJacques, PenarandaGuillaume, YamazakiMasatoshi, AvulaUma Mahesh R, CurelLaurence, SiameSabrina, BerenfeldOmer, PisapiaAndré, KalifaJérôme. AF Ablation Guided by Spatiotemporal Electrogram Dispersion Without Pulmonary Vein Isolation: A Wholly Patient-Tailored Approach. J. Am. Coll. Cardiol. 2017;69 (3):303–321
40. Kuck Karl-Heinz, BrugadaJosep, FürnkranzAlexander, MetznerAndreas, OuyangFeifan, ChunK R Julian, ElvanArif, ArentzThomas, BestehornKurt, PocockStuart J, AlbenqueJean-Paul, TondoClaudio. Cryoballoon or Radiofrequency Ablation for Paroxysmal Atrial Fibrillation. N. Engl. J. Med. 2016;374 (23):2235–45
41. Ciconte Giuseppe, OttavianoLuca, de AsmundisCarlo, BaltogiannisGiannis, ConteGiulio, SieiraJuan, Di GiovanniGiacomo, SaitohYukio, IrfanGhazala, MugnaiGiacomo, StortiCesare, MonteneroAnnibale Sandro, ChierchiaGian-Battista, BrugadaPedro. Pulmonary vein isolation as index procedure for persistent atrial fibrillation: One-year clinical outcome after ablation using the second-generation cryoballoon. Heart Rhythm. 2015;12 (1):60–6
42. Lemes C, WissnerE, LinT. One-year clinical outcome after pulmonary vein isolation in persistent atrial fibrillation using the second-generation 28 mm

cryoballoon: a retrospective analysis. Europace. 2015;18:201–205

43. Koektuerk Buelent, YorgunHikmet, HengeoezOezlem, TuranCem H, DahmenAlina, YangAlexander, BansmannPaul M, GorrEduard, HoppeChristian, TuranRamazan G, HorlitzMarc. Cryoballoon Ablation for Pulmonary Vein Isolation in Patients With Persistent Atrial Fibrillation: One-Year Outcome Using Second Generation Cryoballoon. Circ Arrhythm Electrophysiol. 2015;8 (5):1073–9
44. Guhl Emily N, SiddowayDonald, AdelsteinEvan, VoigtAndrew, SabaSamir, JainSandeep K. Efficacy of Cryoballoon Pulmonary Vein Isolation in Patients With Persistent Atrial Fibrillation. J. Cardiovasc. Electrophysiol. 2016;27 (4):423–7
45. Ciconte Giuseppe, BaltogiannisGiannis, de AsmundisCarlo, SieiraJuan, ConteGiulio, Di GiovanniGiacomo, SaitohYukio, IrfanGhazala, MugnaiGiacomo, HunukBurak, ChierchiaGian-Battista, BrugadaPedro. Circumferential pulmonary vein isolation as index procedure for persistent atrial fibrillation: a comparison between radiofrequency catheter ablation and second-generation cryoballoon ablation. Europace. 2015;17 (4):559–65

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Towards a Mechanistic Understanding and Treatment of a Progressive Disease: Atrial Fibrillation

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Abstract

Atrial fibrosis appears to be a key factor in the genesis and/or perpetuation of atrial fibrillation (AF). The pathological distribution of atrial fibrosis is geographically consistent with the attachments between the posterior left atrium and the pericardium along the reflections where wall stiffness is increased and structural changes are found. While there is a wide range of complex etiological factors and electrophysiological mechanisms in AF, there is evidence for a common pathophysiological pathway that could account for deliberate substrate formation and progression of AF. Anatomical stresses along the atrium, mediated by the elastic modulus mismatch between atrial tissue and the pericardium, result in inflammatory and fibrotic changes which create the substrate for atrial fibrillation. This may explain the anatomical predominance of pulmonary vein triggers earlier in the development of atrial fibrillation and the increasing involvement of the atrium as the disease progresses. Ablative treatments that address the progressive nature of atrial fibrillation and fibrosis may yield improved success rates.

Introduction

Atrial Fibrillation (AF) is the most commonly encountered clinical arrhythmia requiring treatment, and results in multiple adverse sequelae including stroke, heart failure, cognitive decline, dementia, diminished quality of life and a rising incidence of death. [1], [2] With increasing life expectancy and the upsurge of underlying factors that affect progressive atrial remodeling, AF has become a global pandemic, evidenced by a worldwide prevalence of 33.5 million and 5 million new cases annually. [3]

The mechanisms for development of persistent atrial fibrillation are not known, although conjecture is widespread. [4] While many viable theories to account for the development and occurrence of atrial fibrillation (AF) have been suggested, a unifying explanation that puts all of the acknowledged pathological explanations into perspective is lacking. Dominant theories revolve around ganglionated plexi, ectopic foci, rotors, and macro re-entrant circuits that enable arrhythmogenic wavefronts. [5] Curiously, none of these explanations focus on the consistent geographic distribution of substrates responsible for AF.

Computational models, real time voltage mapping and advanced imaging studies have consistently demonstrated geographically similar atrial remodeling in progressive patterns. [6] This atrial remodeling emanates from proposed high stress regions where the pericardium secures the posterior left atrium. The progression of atrial fibrosis relative to the pericardial reflections and stress points about the posterior left atrium, as depicted in [Figure 1], appears clinically significant and may offer clues to underlying mechanisms in AF. Understanding the role played by the pericardial reflections in the genesis of AF may unlock additional treatment considerations and clinical algorithms.

Treatment of atrial fibrillation: A changing target

Endocardial catheter ablation has become a primary treatment modality for drug resistant, symptomatic paroxysmal AF (PAF), but has demonstrated a limited, temporally related efficacy in non-paroxysmal atrial fibrillation (NPAF) patients. [7] The 3 year arrhythmia-free survival in NPAF for a single endocardial catheter ablation procedure has been reported at 28.4% with the efficacy after multiple procedures at 51.1%. [8] The Hamburg sequential ablation strategy of PVI plus linear lesions and SVC isolation for long-standing persistent AF patients yielded 5-year single and multiple procedure success rates of 20% and 45% respectively. [9] Recently, the StarAF II study demonstrated that PVI only ablation in patients with persistent AF resulted in a single-procedure 49% freedom from atrial tachyarrhythmias off antiarrhythmics at 18 months. The addition of CFAE or linear lesions actually yielded an even lower ~30% freedom from atrial tachyarrhythmias. Additional ablations and antiarrhythmic therapy increased the success rate to only ~60%. Even an open surgical approach has not yielded much higher success. A recent study by Gillinov et al. examined the outcomes of surgical atrial fibrillation ablation in patients with persistent AF undergoing mitral-valve surgery. Biatrial maze resulted in only a 66% freedom from AF at 1 year. [10]

Key Words

Atrial Fibrillation, Ablation, Fibrosis.

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Detailed investigation into potential explanations for the failure of AF ablation frequently indicts reconnections of pulmonary vein tissue and substrates along the posterior left atrium. Fibrosis progresses predictably from the heavily invested pulmonary veins to the posterior left atrium, evolving additional AF substrates [Figure 1]. Attempts to ablate localized rotors or complex fractionated atrial electrograms may actually create patchy, heterogeneous fibrosis capable of initiating or sustaining arrhythmogenic circuits as illustrated. A better understanding of the mechanisms for AF is needed to tailor a more effective treatment.

Pulmonary Vein Triggers of Atrial Fibrillation

The atrial muscle sleeves at the pulmonary vein-left atrial junction are the most common source of focal triggers for atrial fibrillation. [11] There is a predominance of pulmonary vein ectopy in the superior veins versus the inferior veins and the left superior vein was noted to have the highest frequency of ectopy. There may be an anatomical reason for this unequal distribution of PV ectopy. Anatomically, the

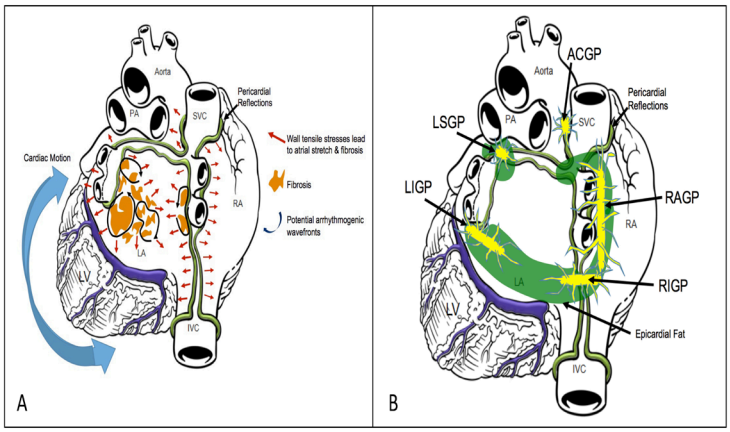


Figure 1: **Panel A: Schematic of progressive atrial remodeling. Pericardial reflections (green lines), their attachments to the posterior left atrium, and their relation to proposed high stress regions. Panel B: Ganglionated plexi (yellow) and epicardial fat (green). Left superior ganglionated plexi (LSGP), left inferior ganglionated plexi (LIGP), right anterior ganglionated plexi (RAGP), right inferior ganglionated plexi (RIGP), aortocaval ganglionated plexi (ACGP)**

superior veins are better developed and longer than the inferior veins. The longest sleeve is usually the left superior vein. [12] Histologically, patients with atrial fibrillation have a significantly increased presence of atrial myocardial extension into the pulmonary veins. In addition, patients with AF also have a higher frequency of discontinuity, hypertrophy, and fibrosis of these extensions. [13] Fibrosis was more prominent in the periphery of the sleeves and often are completely sclerotic distally. This may be due to chronic hypoxia at these distal sleeves since they are at the periphery of the coronary circulation. Development of extensive collagenous septa may create nonuniform anisotropic electrical propagation that could result in micro re-entry and automaticity. [14] Since the left superior pulmonary vein frequently has the longest atrial myocardial extension, placing it at the highest risk for tissue hypoxia, this may explain the increased propensity for LSPV ectopy. Additionally, since the atrial and pulmonary veins are autonomically innervated, sympathovagal imbalance can cause additional anisotropic changes in the action potential duration and PV myocyte refractory periods, increasing the potential for re-entry. [15]

Persistent Atrial Fibrillation and Non-Pulmonary Vein Atrial Fibrillation Substrate

As atrial fibrillation increases in chronicity, so does the proportion of the patients who have non-pulmonary vein substrate. The posterior left atrium is the most anatomically concentrated location of arrhythmogenic mechanisms that are consistently demonstrated with nonparoxysmal AF. [16] Kalifa et al. demonstrated that, in an ovine model, the posterior left atrium frequently contains sites of fast-organized activity with the highest dominant frequency. [17] Patients with AF demonstrated a significantly greater anatomic distribution and degree of conduction slowing, heterogeneity, and anisotropy in the posterior left atrium, culminating in circuitous patterns of propagation. [18]

Atrial Fibrosis/ Tailored Atrial substrate modification

There is increasing data that point to the development of atrial fibrosis in the progression of atrial fibrillation. An underlying cardiac abnormality or metabolic disorder associated with atrial fibrosis and atrial enlargement can be found in approximately 85% of patients with atrial fibrillation. [19] Atrial fibrosis usually extends beyond the pulmonary veins and appears to be a significant reason why simple pulmonary vein isolation is not adequate in treating the majority of persistent atrial fibrillation patients.

Despite the current limitations in spatial resolution with cardiac MRI, there appears to be a pattern of atrial fibrosis in patients with atrial fibrillation. Cochet et al. elegantly described the distribution of atrial fibrosis in patients with and without atrial fibrillation. [20] The predominant location of fibrosis was noted to be in the posterior LA wall rather than the septal, anterior, and lateral segments. More specifically, delayed-enhancement likelihood maps showed that the region around the left inferior pulmonary vein ostium was most frequently to have fibrosis. [Figure 2] There was a lesser degree of fibrosis at the right veins ostia. Fibrosis in the anterior wall was less common but when present was more often found in the septum below and anterior to the right pulmonary veins.

Treatment strategies which isolate a larger area of the posterior wall appear to have increased rates of success. [21], [22] This is the theory of why a wide antral circumferential ablation has been more successful than ostial pulmonary vein isolation. Posterior wall isolation via the creation of a roof line and posterior box line to the usual PVI circles has also been demonstrated to have better long term outcomes than PVI alone for persistent AF. Unfortunately, isolation of the posterior left atrium is frequently challenging with endocardial catheter ablation alone since a breakdown in the PVI or either linear line may be arrhythmogenic and can result in recurrence. [23] Additionally, even if durable lines are created, some arrhythmogenic areas of fibrosis may be missed by empiric anatomical lines. As a result, there has been recent interest in developing an individualized strategy for ablating atrial fibrillation. [24] In this strategy, a pre-procedural MRI is performed to delineate the atrial scar substrate and ablation to box these additional regions is performed. This strategy has been termed Box Isolation of Fibrotic Areas (BIFA).

The Stretch-Inflammation-Fibrosis-Fibrillation (StIFF) Axis

Anatomical Stress mediated by the Pericardial Reflections

Interestingly the common sites of atrial fibrosis appears to be centered around regions of high stress. There appears to be an anatomical reason for this. The pericardium supports the heart

Table 1: Left atrial wall thickness and fat thickness

	Left atrial wall thickness (mm)	Left atrial fat thickness (mm)
LAA	2.2±0.6	4.3±1.8
Roof	2.0±0.6	4.3±2.1
Anterior Wall	1.8±0.3	1.3±0.7
Posterior Wall	1.7±0.3	3.6±2.0
Floor	1.7±0.3	9.6±3.9
Lateral Wall	1.8±0.4	6.3±3.1
Septum	2.4±0.8	

Adapted from Park et al. Int J Cardiol 2014; 172(3):e411-3.

against gravity and is attached to the posterior left atrium, inferior vena cava, superior vena cava, and pulmonary veins, as shown in [Figure 1]. These reflections secure the heart to the chest wall and vertebral column and confer specific plasticity and elasticity that allow cardiac excursion during acceleration and deceleration. The reflections anchor the heart and limit translational and rotational excursion of the heart with activity.

The pericardium is a strong, dense, fibrotic layer that blends with the adventitia of the roots of the great vessels and the central tendon of the diaphragm. [25]The pericardial reflections of the human heart derive from the same mesodermal fetal tissue as functional cardiac tissue. Histologically, however, the pericardium contains more abundant fibroblasts and has a higher modulus of elasticity than adjoining atrial and venous tissue, resulting in a material mismatch. Because of the tethering of the pericardium, motion of the heart is limited and high stresses at the pericardial attachment points lead to reactive fibrosis adjacent to these regions [Figure 2]. To compound the stress issue, the posterior left atrium and the pulmonary veins are substantially thinner than the left atrial roof, the ridge, or the lateral left atrium. [26] [Table 1] Laplace's law reasons that these regions would experience the highest pressure and stress. This may explain why dense fibrosis appears to be more common within the oblique sinus rather than on the other side of the pericardial reflection (ie in the borderzone of the transverse sinus, Waterston's sulcus anteriorly, and the posterior left atrial appendage). Additionally, the pericardial attachment points may also explain why fibrosis around the region of the sinus node and thus sinus node dysfunction coexist with atrial fibrillation. It may also explain why the SVC frequently harbors sites of AF triggers. Although the pericardial reflections are frequently found near fibrosis prone regions, fibrosis may also be located at other regions due to regional pressure, stretch, and stress.

Cardiac Motion

Since DE-MRI data indicate that the region outside the left inferior pulmonary veins are most frequently associated with fibrosis, perhaps there is an anatomic reason for this region being statistically problematic. Since the pericardial reflections at the inferior pulmonary veins help tether the heart in place, cardiac motion may place significant strain at these regions. The base of the left ventricle twists in a counterclockwise motion. The heart's rotational motion during systole as well as the longitudinal and translational motion may put particular strain on the left inferior antrum. Anteriorly, this may translate to annular fibrosis and coronary sinus substrate as there is also a material mismatch of atrial and ventricular tissue at the annulus.

Regional atrial wall stresses

Finite element analysis has been used to predict wall stress distribution based on left atrial geometry from CT. Peaks in walls stress were concentrated at the pulmonary venous ostia, the appendage ridge, the high posterior wall and septal regions. [Figure 3] Peaks in wall stress were consistent with low voltage areas suggestive of focal remodeling and fibrosis. [27] These high stress regions correlate with locations of the pericardial reflections. The pericardial reflections outlined in green in [Figure 1] extend along the right heart from the SVC to the right pulmonary vein ostia to the IVC, across the high posterior roof from the superior aspect of the RPV ostium to the superior aspect of the left pulmonary veins, and incorporate the LPV ostium. Delayed-Enhancement Magnetic Resonance Imaging (DE-MRI) has illustrated progressive fibrosis formation in the same regions of finite element analysis documented increased wall stress suggesting a correlation [Figure 2].

Stretch, Inflammation and fibrosis

In preclinical animal models, atrial stretch induces increased atrial fibrosis that causes regional remodeling and conduction slowing. Atrial stretch causes release of ANP, calcium overload, calcineurin activation, engagement of the AT1 receptor and alterations in MMP and TIMP levels, which are implicated in tissue turnover and remodeling. [28] Importantly, atrial stretch results in inflammation that contribute to fibroblast proliferation, collagen elaboration and scar formation. [29] Structural remodeling is ongoing with AF and thought to be partially mediated by transforming growth factor **β**1 (TGF-**β**1), which is a potent stimulator of collagen-producing cardiac fibroblasts. [30]

Atrial structural changes observed in animal models of AF include atrial enlargement, cellular hypertrophy, dedifferentiation, fibrosis, apoptosis, loss of contractile apparatus (myolysis), changes in size and shape of the mitochondria, disruption of the sarcoplasmatic reticulum, and homogeneous distribution of nuclear heterochromatin. [31] The changes in structural, contractile, and electrical properties disrupt interconnections between cardiac muscle bundles produces anisotropy that causes micro-reentry circuits. The resulting electrophysiological substrate is characterized by shortening of atrial refractoriness and reentrant wavelength or by local conduction heterogeneities caused by disruption of electrical interconnections between muscle bundles, which predisposes patients to develop AF. [32], [33] [16] [34]

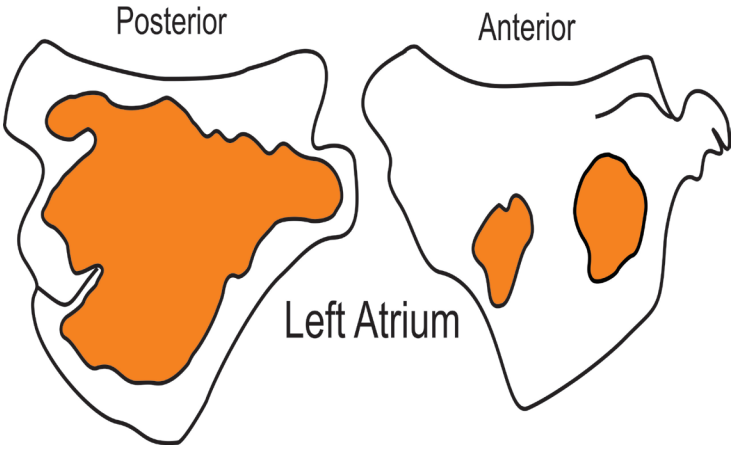


Figure 2: Common regions of fibrosis
Adapted from Cochet et al. J Cardiovasc Electrophysiol 2015; 26: 489

Anatomical Enhancers of Atrial Fibrillation substrate

Ganglionated plexi

Epicardial fat also contains a rich supply of autonomic ganglionated plexi (GP), which has gained attention in the creation of AF substrate. GPs are found embedded along the ligament of Marshall, along the great vessels, at the right superior PV-atrial junction, at the left superior PV-atrial junction, at the left inferior PV-atrial junction, and at the junction of the inferior vena cava and both atria. [35], [36] [Figure 1] GP stimulation by the autonomic nervous system has been hypothesized to release neurotransmitters that increase PV ectopy [37], reduce PV sleeve action potential duration [38], and shorten the fibrillation cycle length.[39] These factors appear to stimulate triggers and enable the perpetuation of AF. [40] The ablation of GP in addition to PVI may result in higher success rates in patients with paroxysmal and persistent AF. [41] Neural remodeling may allow for regrowth of ganglionated plexi [42], however even temporary suppression of ganglionated plexi may have long-term effects in suppressing of AF by breaking the cyclical progression of AF. [43]

Epicardial fat

Recent studies have also implicated epicardial fat in the creation of AF substrate. [44] Adipose tissue is frequently found in the atrioventricular and interventricular grooves extending to the apex of the heart. There are also minor regions of fat that are located subepicardially around the 2 appendages and in the free walls of the atria. [Figure 1] Epicardial fat may have direct electrophysiologic effects as well as possible paracrine effects by cytokines or other signaling molecules. [45] Epicardial adipose tissue express a wide range of inflammatory mediators and demonstrate increased activity of matrix metalloproteinases which likely contribute to interstitial fibrosis, [46] Since epicardial fat is often associated with fatty infiltration deep into the myocardial tissue, this disorganized tissue may contribute to local arrhythmogenic substrate.

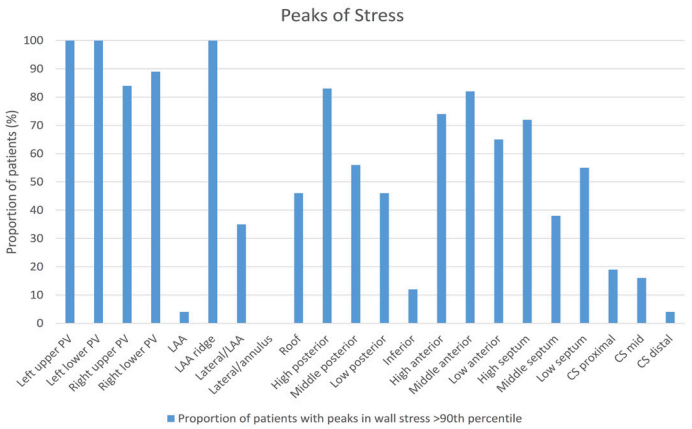


Figure 3: **Peaks of atrial wall stress Adapted from Hunter et al. Circ Arrhythm Electrophysiol. 2012;5(2):354.**

Contribution of Comorbidities and Environmental Factors towards the Development of Atrial Fibrillation: Accelerators of Fibrosis

Hypertension

Stress from any source, whether endocardial or epicardial, applied to the left atrium leads to tissue remodeling and fibrogenesis. [47] The most common stressor is hypertension. In the DECAAF trial, hypertension was the only predictor of the degree of atrial fibrosis in patients with atrial fibrillation. [6] As an independent predictor of AF, hypertension causes remodeling of small and large vessels where low-grade inflammation and associated elaboration of C-Reactive Protein are thought to play important roles in triggering fibrosis. A chronic increase in internal atrial pressure also causes atrial stretch that has been implicated in inflammation, apoptosis and atrial remodeling.

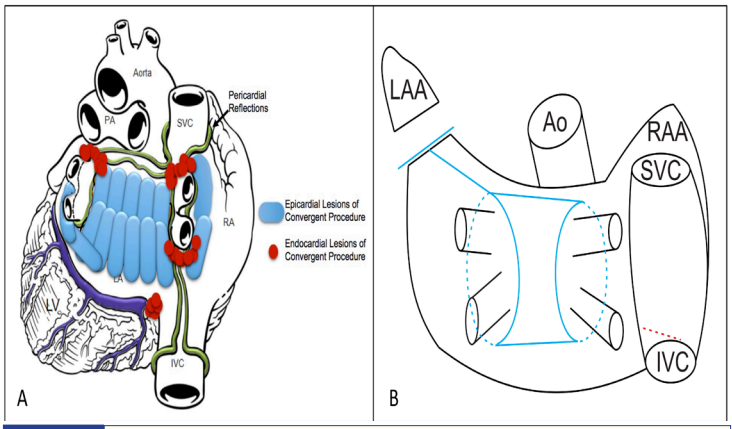


Figure 4: **Panel A: Schematic of the Convergent procedure lesion pattern relative to the high stress regions. Panel B: Thoracoscopic hybrid AF ablation lesion set. Hybrid AF ablation utilizing a thoracoscopic approach commonly involves pulmonary vein isolation, a roof line, posterior box line, exclusion of the left atrial appendage (blue lines). Endocardial ablation is performed to confirm bi-directional block across the lines and create a cavotricuspid isthmus line (red dotted line). Additional ablation may be performed to create an intercaval line, mitral line, and at ganglionated plexi.**

Pressure induced fibrosis has been studied in an experimental porcine animal model. Ventricular tachypacing resulted in an increase in atrial volume of 60%, a two-fold rise in pressure and a complex pattern of local mechanical, histological and biochemical changes including fibrosis. The authors used a comparison of the stress distribution in healthy versus ventricular tachypacing cases to determine how volume overload and stress affects and modifies left atrial mechanics. The largest areas of stretch-induced changes were around the lower pulmonary veins and the appendage boundaries. [48] Similar to the pressure overload of hypertension, the pressure and volume overload of mitral regurgitation and mitral stenosis, sleep apnea, or congestive heart failure creates stress in the atria that predispose patients to atrial remodeling, fibrosis, and atrial fibrillation.

Obesity

Obesity as a risk factor for AF has been documented with a two-fold increase in AF compared to age- and sex-matched individuals having a normal weight; this risk of developing AF increases progressively with rising Body Mass Index. [49] With a 2.4 fold increased risk of left atrial enlargement, obesity has the potential to cause stress-mediated progressive atrial remodeling that produces substrates known to initiate or maintain AF. [50] The hemodynamic alterations in obesity such as increased intravascular volume and increased cardiac output may lead to LA volume overload, stress and LA dilatation. Interstitial and epicardial fat may accumulate and contribute to atrial fibrosis enhanced by paracrine effects. Studies have shown that the expansion of adipose tissue with obesity are accompanied by inadequate capillarization, resulting in hypoxia. [51] The increased leptin and reduced adiponectin levels of obesity may contribute to the adverse atrial remodeling. [52] Obesity is also associated with a proinflammatory state and oxidative stress, as evidenced by increased

CRP, IL-6, and TNF-α. Finally, the autonomic dysfunction of obesity (increased sympathetic activity and decreased vagal tone) may also contribute to AF inducibility. [53], [54]

AF in Endurance Athletes

In endurance athletes, atrial fibrillation is more common than their age, sex and activity matched peers. The increased left atrial pressure loading and constant supra-physiologic acceleration/deceleration movements placed on the cardiac reflections may cause acute stretch induced electrical changes, fibrosis, and AF. [55] Deconditioning reverses expression of cardiac fibrosis markers in animal models of endurance suggesting that once training is halted and load is removed from the pericardial attachments, the fibrotic process is retarded. [56]

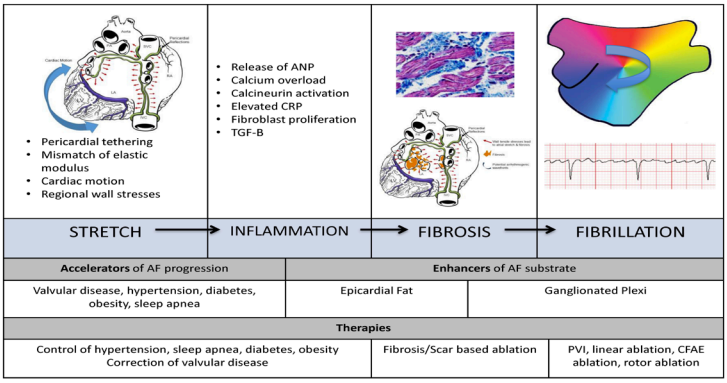
Treatment of Progressive Atrial fibrillation

Current therapies in the ablation of atrial fibrillation focus on the creation of durable lesions (contact force catheters, laser balloon, cryoballoon, nMarq ablation catheter) and the assessment of real-time arrhythmogenic substrate (CFAE and rotor mapping). In centers with expertise in cardiac MRI, pre-ablation substrate assessment and tailored ablation isolating regions of fibrosis shows an appreciation for atrial fibrotic substrate. However all of these therapies generally deal with a patient's atrial fibrillation at its present state of substrate. As long as the causative factors for atrial stress continue to exist, it would not be surprising that atrial fibrosis would progress, exposing the patient to continued risk for developing atrial fibrillation. Certainly patients with sleep apnea, obesity, and hypertension need to be treated, however complete control of AF risk factors is usually impossible.

Patients with enlarged atrial and heterogeneous AF substrate will likely have more than just focal pulmonary vein triggers as the driver for their disease. This is the reason why more extensive ablation is usually required to treat these patients. Using an endocardial approach only, creation of additional lines to isolate the posterior wall and prevent mitral annular, septal, or right atrial substrate can better address the non-PV substrate of AF, however it is currently limited by issues inherent in the creation of lines using a point-by-point technique. Additionally, an endocardial approach may not address GP, epicardial fat, and other non-PV substrate as thoroughly or as easily as an epicardial approach.

Hybrid procedures have been utilized to treat patients with difficult AF substrate.

The Convergent atrial fibrillation procedure treats a high proportion of left atrial territory that is at high risk for fibrosis and addresses multiple non-PV mechanisms of AF. [57] The Convergent multidisciplinary procedure applies closed chest epicardial ablation of the posterior left atrium via a subxiphoid approach in combination with standard endocardial catheter ablation. This multidisciplinary procedure allows for electrosilencing the posterior wall using epicardial ablation at relevant points juxtaposing the pericardial reflections at their attachments to the left atrium. [Figure 4] The homogenization of the posterior and inferior wall tissue should theoretically prevent further progression of arrhythmogenic patchy atrial fibrosis. Fortunately, ablation of the posterior wall appears to have a minimal impact on left atrial function since the posterior wall contributes less to the left atrial ejection fraction than the anterior, septal and lateral walls.



Stretch-Inflammation-Fibrosis-Fibrillation (StIFF) Axis Progression

Figure 5: Stretch-Inflammation-Fibrosis-Fibrillation (StiFF) Axis

The promising clinical results utilizing this more comprehensive lesion set may lead credence to the role of ablating a wider territory of the left atrium. [58]-[62] Despite the fact that many patients had complex disease and frequently failed prior ablations, operators have reproducibly been reporting success rates in the 73% to 95% range on or off antiarrhythmic therapy at 1-year follow up amongst a mixed population of paroxysmal and persistent AF patients. [63] Although long-term data is pending, homogenization of the posterior wall should prevent posterior wall substrate development. Additionally, epicardial ablation of ganglionated plexi and epicardial fat may aid in the current treatment of and further progression of AF substrate.

Similar to the Convergent procedure, hybrid procedures utilizing a thoracoscopic approach also seek to provide durable isolation of the pulmonary veins and posterior wall. [Figure 4] The ligament of Marshall is easily dissected from a thoracoscopic approach and ligation of the left atrial appendage may yield anti-arrhythmic benefit as well as reducing stroke risk. Additionally, ganglionated plexi may be more readily targeted, and additional linear lesions may also be created and verified across the mitral isthmus and cavotricuspid isthmus. Success rates utilizing a hybrid thoracoscopic technique have also been very favorable in the 84% to 94% range on or off antiarrhythmic therapy at 1-year follow up amonst a mixed population of paroxysmal and persistent AF patients. [64]

Conclusions

In contrast to other organized arrhythmias, atrial fibrillation is an electrically disorganized arrhythmia that is frequently the end product of unfavorable atrial remodeling. Ablative therapy initially began targeting triggers which were frequently found in the pulmonary veins however we have subsequently learned that atrial fibrillation involves much more of the atrium and attention has expanded to additional mechanisms of atrial fibrillation genesis and perpetuation. Recent focus has been on the targeting of functional mechanisms of AF however it remains to be seen if these interventions will result in long-term arrhythmia-free success.

There appears to be a plausible anatomical mechanism for the progression of atrial fibrillation. Mechanical stress placed on the atrium due to its pericardial tethers and repetitive cardiac motion appear to cause stress induced inflammatory changes and fibrosis. These fibrotic changes predispose the atrium to fibrillate. [Figure 5] The failure of current ablative strategies particularly to treat persistent atrial fibrillation may be due to the fact that PVI, linear ablation, CFAE ablation, and rotor ablation probably does not reduce the mechanical nor inflammatory stresses upon the remodeling atrium, and thus does not halt the anatomical progression of atrial fibrillation. This enforces the importance of risk factor reduction:

control of hypertension, obesity, sleep apnea. However it also brings to question if there is an anatomic method to reduce the mechanical stresses upon the atrium or pre-treat the areas of atrium most prone to anisotropic fibrosis and AF substrate formation. Since AF is recognized as a progressive disease, treatments that target the progressive nature of fibrosis may result in improved outcomes. Scar-based, or empiric ablation to cover regions of fibrosis prone areas such as BIFA ablation or the homogenization or durable isolation of the posterior wall through a hybrid ablation procedure may better address the progressive nature of AF. Additionally, ablative strategies that target ganglionated plexi and epicardial fat may adjunctively treat and prevent the progression of AF.

Disclosures

None.

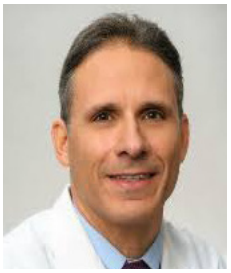
References

1. Lloyd-Jones Donald, AdamsRobert J, BrownTodd M, CarnethonMercedes, DaiShifan, De SimoneGiovanni, FergusonT Bruce, FordEarl, FurieKaren, GillespieCathleen, GoAlan, GreenlundKurt, HaaseNancy, HailpernSusan, HoP Michael, HowardVirginia, KisselaBrett, KittnerSteven, LacklandDaniel, LisabethLynda, MarelliAriane, McDermottMary M, MeigsJames, MozaffarianDariush, MussolinoMichael, NicholGraham, RogerVéronique L, RosamondWayne, SaccoRalph, SorliePaul, StaffordRandall, ThomThomas, Wasserthiel-SmollerSylvia, WongNathan D, Wylie-RosettJudith. Executive summary: heart disease and stroke statistics--2010 update: a report from the American Heart Association. Circulation. 2010;121 (7):948–54
2. Fuster Valentin, RydénLars E, CannomDavis S, CrijnsHarry J, CurtisAnne B, EllenbogenKenneth A, HalperinJonathan L, KayG Neal, Le HuezeyJean-Yves, LoweJames E, OlssonS Bertil, PrystowskyEric N, TamargoJuan Luis, WannL Samuel, SmithSidney C, PrioriSilvia G, EstesN A Mark, EzekowitzMichael D, JackmanWarren M, JanuaryCraig T, LoweJames E, PageRichard L, SlotwinerDavid J, StevensonWilliam G, TracyCynthia M, JacobsAlice K, AndersonJeffrey L, AlbertNancy, BullerChristopher E, CreagerMark A, EttingerSteven M, GuytonRobert A, HalperinJonathan L, HochmanJudith S, KushnerFrederick G, OhmanErik Magnus, StevensonWilliam G, TarkingtonLynn G, YancyClyde W. 2011 ACCF/AHA/HRS focused updates incorporated into the ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. Circulation. 2011;123 (10):e269–367
3. Chugh Sumeet S, HavmoellerRasmus, NarayananKumar, SinghDavid, RienstraMichiel, BenjaminEmelia J, GillumRichard F, KimYoung-Hoon, McAnultyJohn H, ZhengZhi-Jie, ForouzanfarMohammad H, NaghaviMohsen, MensahGeorge A, EzzatiMajid, MurrayChristopher J L. Worldwide epidemiology of atrial fibrillation: a Global Burden of Disease 2010 Study. Circulation. 2014;129 (8):837–47
4. Calkins Hugh, KuckKarl Heinz, CappatoRiccardo, BrugadaJosep, CammA John, ChenShih-Ann, CrijnsHarry J G, DamianoRalph J, DaviesD Wyn, DiMarcoJohn, EdgertonJames, EllenbogenKenneth, EzekowitzMichael D, HainesDavid E, HaissaguerreMichel, HindricksGerhard, IesakaYoshito, JackmanWarren, JalifeJose, JaisPierre, KalmanJonathan, KeaneDavid, KimYoung-Hoon, KirchhofPaulus, KleinGeorge, KottkampHans, KumagaiKoichiro, LindsayBruce D, MansourMoussa, MarchlinskiFrancis E, McCarthyPatrick M, MontJ Lluis, MoradyFred, NademaneeKoonlawee, NakagawaHiroshi, NataleAndrea, NattelStanley, PackerDouglas L, PapponeCarlo, PrystowskyEric, RavieleAntonio, ReddyVivek, RuskinJeremy N, SheminRichard J, TsaoHsuan-Ming, WilberDavid. 2012 HRS/EHRA/ECAS Expert Consensus Statement on Catheter and Surgical Ablation of Atrial Fibrillation: recommendations for patient selection, procedural techniques, patient management and follow-up, definitions, endpoints, and research trial design. Europace. 2012;14 (4):528–606
5. Marrouche Nassir F, WilberDavid, HindricksGerhard, JaisPierre, AkoumNazem, MarchlinskiFrancis, KholmovskiEugene, BurgonNathan, HuNan, MontLluis, DenekeThomas, DuytschaeverMattias, NeumannThomas, MansourMoussa, MahnkopfChristian, HerwegBengt, DaoudEmile, WissnerErik, BansmannPaul, BrachmannJohannes. Association of atrial tissue fibrosis identified by delayed enhancement MRI and atrial fibrillation catheter ablation: the DECAAF study. JAMA. 2014;311 (5):498–506
6. Weerasooriya Rukshen, KhairyPaul, LitalienJean, MacleLaurent, HociniMeleze, SacherFrederic, LelloucheNicolas, KnechtSebastien, WrightMatthew, NaultIsabelle, MiyazakiShinsuke, ScaveeChristophe, ClementyJacques, HaissaguerreMichel, JaisPierre. Catheter ablation for atrial fibrillation: are results maintained at 5 years of follow-up?. J. Am. Coll. Cardiol. 2011;57 (2):160–6
7. Chao Tze-Fan, TsaoHsuan-Ming, LinYenn-Jiang, TsaiChin-Feng, LinWei-Shiang, ChangShih-Lin, LoLi-Wei, HuYu-Feng, TuanTa-Chuan, SuenariKazuyoshi, LiCheng-Hung, HartonoBeny, ChangHung-Yu, AmbroseKibos, WuTsu-Juey, ChenShih-Ann. Clinical outcome of catheter ablation in patients with nonparoxysmal atrial fibrillation: results of 3-year follow-up. Circ Arrhythm Electrophysiol. 2012;5 (3):514–20
8. Chao Tze-Fan, TsaoHsuan-Ming, LinYenn-Jiang, TsaiChin-Feng, LinWei-Shiang, ChangShih-Lin, LoLi-Wei, HuYu-Feng, TuanTa-Chuan, SuenariKazuyoshi, LiCheng-Hung, HartonoBeny, ChangHung-Yu, AmbroseKibos, WuTsu-Juey, ChenShih-Ann. Clinical outcome of catheter ablation in patients with nonparoxysmal atrial fibrillation: results of 3-year follow-up. Circ Arrhythm Electrophysiol. 2012;5 (3):514–20
9. Gillinov A Marc, GelijnsAnnetine C, ParidesMichael K, DeRoseJoseph J, MoskowitzAlan J, VoisinePierre, AilawadiGorav, BouchardDenis, SmithPeter K, MackMichael J, AckerMichael A, MullenJohn C, RoseEric A, ChangHelena L, PuskasJohn D, CoudercJean-Philippe, GardnerTimothy J, VargheseRobin, HorvathKeith A, BollingSteven F, MichlerRobert E, GellerNancy L, AscheimDeborah D, MillerMarissa A, BagiellaEmilia, MoqueteEllen G, WilliamsPaula, Taddei-PetersWendy C, O'GaraPatrick T, BlackstoneEugene H, ArgenzianoMichael. Surgical ablation of atrial fibrillation during mitral-valve surgery. N. Engl. J. Med. 2015;372 (15):1399–409
10. Tilz Roland Richard, RilligAndreas, ThumAnna-Maria, AryaAnita, WohlmuthPeter, MetznerAndreas, MathewShibu, YoshigaYasuhiro, WissnerErik, KuckKarl-Heinz, OuyangFeifan. Catheter ablation of long-standing persistent atrial fibrillation: 5-year outcomes of the Hamburg Sequential Ablation Strategy. J. Am. Coll. Cardiol. 2012;60 (19):1921–9
11. Haïssaguerre M, JaïsP, ShahD C, TakahashiA, HociniM, QuiniouG, GarrigueS, Le MourouxA, Le MétayerP, ClémentyJ. Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins. N. Engl. J. Med. 1998;339 (10):659–66
12. Ho S Y, Sanchez-QuintanaD, CabreraJ A, AndersonR H. Anatomy of the left atrium: implications for radiofrequency ablation of atrial fibrillation. J. Cardiovasc. Electrophysiol. 1999;10 (11):1525–33
13. Hassink Rutger J, AretzH Thomas, RuskinJeremy, KeaneDavid. Morphology of atrial myocardium in human pulmonary veins: a postmortem analysis in patients with and without atrial fibrillation. J. Am. Coll. Cardiol. 2003;42 (6):1108–14
14. Spach M S, BoineauJ P. Microfibrosis produces electrical load variations due to loss of side-to-side cell connections: a major mechanism of structural heart disease arrhythmias. Pacing Clin Electrophysiol. 1997;20 (2 Pt 2):397–413
15. Ogawa Masahiro, ZhouShengmei, TanAlex Y, SongJuan, GholmiehGhassan, FishbeinMichael C, LuoHuai, SiegelRobert J, KaragueuzianHrayr S, ChenLan S, LinShien-Fong, ChenPeng-Sheng. Left stellate ganglion and vagal nerve activity and cardiac arrhythmias in ambulatory dogs with pacing-induced congestive heart failure. J. Am. Coll. Cardiol. 2007;50 (4):335–43
16. Allessie Maurits, AusmaJannie, SchottenUlrich. Electrical, contractile and

structural remodeling during atrial fibrillation. Cardiovasc. Res. 2002;54 (2):230–46

17. Kalifa Jérôme, TanakaKazuhiko, ZaitsevAlexey V, WarrenMark, VaidyanathanRavi, AuerbachDavid, PanditSandeep, VikstromKaren L, Ploutz-SnyderRobert, TalkachouArkadzi, AtienzaFelipe, GuiraudonGérard, JalifeJosé, BerenfeldOmer. Mechanisms of wave fractionation at boundaries of high-frequency excitation in the posterior left atrium of the isolated sheep heart during atrial fibrillation. Circulation. 2006;113 (5):626–33
18. Roberts-Thomson Kurt C, StevensonIrene, KistlerPeter M, HaqqaniHaris M, SpenceSteven J, GoldblattJohn C, SandersPrashanthan, KalmanJonathan M. The role of chronic atrial stretch and atrial fibrillation on posterior left atrial wall conduction. Heart Rhythm. 2009;6 (8):1109–17
19. Janse M J. Why does atrial fibrillation occur?. Eur. Heart J. 1997;18 Suppl C ():C12–8
20. Cochet Hubert, MouriesAmaury, NivetHubert, SacherFrederic, DervalNicolas, DenisArnaud, MerleMathilde, RelanJatin, HociniMélèze, HaïssaguerreMichel, LaurentFrançois, MontaudonMichel, JaïsPierre. Age, atrial fibrillation, and structural heart disease are the main determinants of left atrial fibrosis detected by delayed-enhanced magnetic resonance imaging in a general cardiology population. J. Cardiovasc. Electrophysiol. 2015;26 (5):484–92
21. Ouyang Feifan, BänschDietmar, ErnstSabine, SchaumannAnselm, HachiyaHitoshi, ChenMinglong, ChunJulian, FalkPeter, KhanedaniAfsaneh, AntzMatthias, KuckKarl-Heinz. Complete isolation of left atrium surrounding the pulmonary veins: new insights from the double-Lasso technique in paroxysmal atrial fibrillation. Circulation. 2004;110 (15):2090–6
22. Verma Atul, MarroucheNassir F, NataleAndrea. Pulmonary vein antrum isolation: intracardiac echocardiography-guided technique. J. Cardiovasc. Electrophysiol. 2004;15 (11):1335–40
23. Chilukuri Karuna, ScherrDaniel, DalalDarshan, ChengAlan, SpraggDavid, NazarianSaman, BarcelonBernadette D, MarineJoseph E, CalkinsHugh, HenriksonCharles A. Conventional pulmonary vein isolation compared with the "box isolation" method: a randomized clinical trial. J Interv Card Electrophysiol. 2011;32 (2):137–46
24. Kottkamp Hans, BenderRoderich, BergJan. Catheter ablation of atrial fibrillation: how to modify the substrate?. J. Am. Coll. Cardiol. 2015;65 (2):196–206
25. Laizzo P. Handbook of Cardiac Anatomy, Physiology, and Devices. 2nd Edition ed. Humana Press. 2009
26. Suenari Kazuyoshi, NakanoYukiko, HiraiYukoh, OgiHiroshi, OdaNoboru, MakitaYuko, UedaShigeyuki, KajiharaKenta, TokuyamaTakehito, MotodaChikaaki, FujiwaraMai, ChayamaKazuaki, KiharaYasuki. Left atrial thickness under the catheter ablation lines in patients with paroxysmal atrial fibrillation: insights from 64-slice multidetector computed tomography. Heart Vessels. 2013;28 (3):360–8
27. Hunter Ross J, LiuYankai, LuYiling, WangWen, SchillingRichard J. Left atrial wall stress distribution and its relationship to electrophysiologic remodeling in persistent atrial fibrillation. Circ Arrhythm Electrophysiol. 2012;5 (2):351–60
28. Saygili Erol, RanaObaida R, MeyerChristian, GemeinChristopher, AndrzejewskiMichael G, LudwigAndreas, WeberChristian, SchottenUlrich, KrüttgenAlexander, WeisJoachim, SchwingerRobert H G, MischkeKarl, RassafTienush, KelmMalte, SchauertePatrick. The angiotensin-calcineurin-NFAT pathway mediates stretch-induced up-regulation of matrix metalloproteinases-2/-9 in atrial myocytes. Basic Res. Cardiol. 2009;104 (4):435–48
29. Schotten Ulrich, DuytschaeverMattias, AusmaJannie, EijsboutsSabine, NeubergerHans-Ruprecht, AllessieMaurits. Electrical and contractile remodeling during the first days of atrial fibrillation go hand in hand. Circulation. 2003;107 (10):1433–9
30. Khan Razi, SheppardRichard. Fibrosis in heart disease: understanding the role of transforming growth factor-beta in cardiomyopathy, valvular disease and arrhythmia. Immunology. 2006;118 (1):10–24
31. Schotten Ulrich, VerheuleSander, KirchhofPaulus, GoetteAndreas. Pathophysiological mechanisms of atrial fibrillation: a translational appraisal. Physiol. Rev. 2011;91 (1):265–325
32. Verheule Sander, WilsonEmily, BanthiaSmriti, EverettThomas H, ShanbhagSujata, SihHaris J, OlginJeffrey. Direction-dependent conduction abnormalities in a canine model of atrial fibrillation due to chronic atrial dilatation. Am. J. Physiol. Heart Circ. Physiol. 2004;287 (2):H634–44
33. Verheule Sander, WilsonEmily, EverettThomas, ShanbhagSujata, GoldenCatherine, OlginJeffrey. Alterations in atrial electrophysiology and tissue structure in a canine model of chronic atrial dilatation due to mitral regurgitation. Circulation. 2003;107 (20):2615–22
34. Casaclang-Verzosa Grace, GershBernard J, TsangTeresa S M. Structural and functional remodeling of the left atrium: clinical and therapeutic implications for atrial fibrillation. J. Am. Coll. Cardiol. 2008;51 (1):1–11
35. Chevalier Philippe, TabibAlain, MeyronnetDavid, ChalabreysseLara, RestierLioara, LudmanValérie, AlièsAlexandre, AdeleinePatrice, ThivoletFrançoise, BurriHaran, LoireRobert, FrançoisLaurent, FantonLaurent. Quantitative study of nerves of the human left atrium. Heart Rhythm. 2005;2 (5):518–22
36. Tan Alex Y, LiHongmei, Wachsmann-HogiuSebastian, ChenLan S, ChenPeng-Sheng, FishbeinMichael C. Autonomic innervation and segmental muscular disconnections at the human pulmonary vein-atrial junction: implications for catheter ablation of atrial-pulmonary vein junction. J. Am. Coll. Cardiol. 2006;48 (1):132–43
37. Zhou Jing, ScherlagBenjamin J, EdwardsJeffery, JackmanWarren M, LazzaraRalph, PoSunny S. Gradients of atrial refractoriness and inducibility of atrial fibrillation due to stimulation of ganglionated plexi. J. Cardiovasc. Electrophysiol. 2007;18 (1):83–90
38. Patterson Eugene, PoSunny S, ScherlagBenjamin J, LazzaraRalph. Triggered firing in pulmonary veins initiated by in vitro autonomic nerve stimulation. Heart Rhythm. 2005;2 (6):624–31
39. Scherlag Benjamin J, NakagawaHiroshi, JackmanWarren M, YamanashiWilliam S, PattersonEugene, PoSunny, LazzaraRalph. Electrical stimulation to identify neural elements on the heart: their role in atrial fibrillation. J Interv Card Electrophysiol. 2005;13 Suppl 1 ():37–42
40. Jiang Ru-Hong, JiangChen-Yang, ShengXia, ZhangZu-Wen, SunYa-Xun, LiuQiang, FuGuo-Sheng, PoSunny S. Marked suppression of pulmonary vein firing after circumferential pulmonary vein isolation in patients with paroxysmal atrial fibrillation: is pulmonary vein firing an epiphenomenon?. J. Cardiovasc. Electrophysiol. 2014;25 (2):111–8
41. Katritsis Demosthenes G, PokushalovEvgeny, RomanovAlexander, GiazitzoglouEleftherios, SiontisGeorge C M, PoSunny S, CammA John, IoannidisJohn P A. Autonomic denervation added to pulmonary vein isolation for paroxysmal atrial fibrillation: a randomized clinical trial. J. Am. Coll. Cardiol. 2013;62 (24):2318–25
42. Wang Ximin, ZhangMing, ZhangYujiao, XieXinxing, WangWeizong, LiZhan, GaoMei, WangZhongsu, HouYinglong. Long-Term Effects of Ganglionated Plexi Ablation on Electrophysiological Characteristics and Neuron Remodeling in Target Atrial Tissues in a Canine Model. Circ Arrhythm Electrophysiol. 2015;8 (5):1276–83
43. Lo Li-Wei, ChangHung-Yu, ScherlagBenjamin J, LinYenn-Jiang, ChouYu-Hui, LinWei-Lun, ChenShih-Ann, PoSunny S. Temporary Suppression of Cardiac Ganglionated Plexi Leads to Long-Term Suppression of Atrial Fibrillation: Evidence of Early Autonomic Intervention to Break the Vicious Cycle of "AF Begets AF". J Am Heart Assoc. 2016;5 (7)
44. Hatem Stéphane N, RedheuilAlban, GandjbakhchEstelle. Cardiac adipose tissue and atrial fibrillation: the perils of adiposity. Cardiovasc. Res. 2016;109 (4):502–9

45. Hatem Stéphane N, SandersPrashanthan. Epicardial adipose tissue and atrial fibrillation. Cardiovasc. Res. 2014;102 (2):205–13
46. Mazurek Tomasz, ZhangLiFeng, ZalewskiAndrew, MannionJohn D, DiehlJames T, ArafatHwyda, Sarov-BlatLea, O'BrienShawn, KeiperElizabeth A, JohnsonAnthony G, MartinJack, GoldsteinBarry J, ShiYi. Human epicardial adipose tissue is a source of inflammatory mediators. Circulation. 2003;108 (20):2460–6
47. Everett Thomas H, OlginJeffrey E. Atrial fibrosis and the mechanisms of atrial fibrillation. Heart Rhythm. 2007;4 (3 Suppl):S24–7
48. Di Martino Elena S, BelliniChiara, SchwartzmanDavid S. In vivo porcine left atrial wall stress: Effect of ventricular tachypacing on spatial and temporal stress distribution. J Biomech. 2011;44 (16):2755–60
49. Frost Lars, HuneLone Juul, VestergaardPeter. Overweight and obesity as risk factors for atrial fibrillation or flutter: the Danish Diet, Cancer, and Health Study. Am. J. Med. 2005;118 (5):489–95
50. Stritzke Jan, MarkusMarcello Ricardo Paulista, DuderstadtStefanie, LiebWolfgang, LuchnerAndreas, DöringAngela, KeilUlrich, HenseHans-Werner, SchunkertHeribert. The aging process of the heart: obesity is the main risk factor for left atrial enlargement during aging the MONICA/KORA (monitoring of trends and determinations in cardiovascular disease/cooperative research in the region of Augsburg) study. J. Am. Coll. Cardiol. 2009;54 (21):1982–9
51. Ye Jianping, GaoZhanguo, YinJun, HeQing. Hypoxia is a potential risk factor for chronic inflammation and adiponectin reduction in adipose tissue of ob/ob and dietary obese mice. Am. J. Physiol. Endocrinol. Metab. 2007;293 (4):E1118–28
52. Ochiai Hirotaka, ShirasawaTakako, NishimuraRimei, NanriHinako, OhtsuTadahiro, HoshinoHiromi, TajimaNaoko, KokazeAkatsuki. Abdominal obesity and serum adiponectin complexes among population-based elementary school children in Japan: a cross-sectional study. BMC Pediatr. 2014;14
53. Musaad Salma, HaynesErin N. Biomarkers of obesity and subsequent cardiovascular events. Epidemiol Rev. 2007;29 ():98–114
54. Karason K, MølgaardH, WikstrandJ, SjöströmL. Heart rate variability in obesity and the effect of weight loss. Am. J. Cardiol. 1999;83 (8):1242–7
55. Hoogsteen Jan, SchepGoof, Van HemelNorbert M, Van Der WallErnst E. Paroxysmal atrial fibrillation in male endurance athletes. A 9-year follow up. Europace. 2004;6 (3):222–8
56. Benito Begoña, Gay-JordiGemma, Serrano-MollarAnna, GuaschEduard, ShiYanfen, TardifJean-Claude, BrugadaJosep, NattelStanley, MontLluis. Cardiac arrhythmogenic remodeling in a rat model of long-term intensive exercise training. Circulation. 2011;123 (1):13–22
57. Geršak Borut, ZembalaMichael O, MüllerDirk, FolliguetThierry, JanMatevz, KowalskiOskar, ErlerStefan, BarsClement, RobicBoris, FilipiakKrzysztof, Wimmer-GreineckerGerhard. European experience of the convergent atrial fibrillation procedure: multicenter outcomes in consecutive patients. J. Thorac. Cardiovasc. Surg. 2014;147 (4):1411–6
58. Gersak Borut, PernatAndrej, RobicBoris, SinkovecMatjaz. Low rate of atrial fibrillation recurrence verified by implantable loop recorder monitoring following a convergent epicardial and endocardial ablation of atrial fibrillation. J. Cardiovasc. Electrophysiol. 2012;23 (10):1059–66
59. KC Civello, CASmith, BoedefeldW. Combined endocardial and epicardial ablation for symptomatic atrial fibrillation: single center experience in 100+ consecutive patients. J Innov Cardiac Rhythm Mgmt. 2013;0:1–7
60. DM Gilligan, CAJoyner, GMGundy. Multidisciplinary collaboration for the treatment of atrial fibrillation: Convergent procedure outcomes from a single center. J Innov Cardiac Rhythm Mgmt. 2013;0:1–8
61. Thosani Amit J, GerczukPaul, LiuEmerson, BeldenWilliam, MoracaRobert. Closed Chest Convergent Epicardial-Endocardial Ablation of Non-paroxysmal Atrial Fibrillation - A Case Series and Literature Review. Arrhythm Electrophysiol Rev. 2013;2 (1):65–8
62. Zembala Michal, FilipiakKrzysztof, KowalskiOskar, BuchtaPiotr, NiklewskiTomasz, NadziakiewiczPawel, KobaRafał, GąsiorMariusz, KalarusZbigniew, ZembalaMarian. Staged hybrid ablation for persistent and longstanding persistent atrial fibrillation effectively restores sinus rhythm in long-term observation. Arch Med Sci. 2017;13 (1):109–117
63. Zembala Michael O, SuwalskiPiotr. Minimally invasive surgery for atrial fibrillation. J Thorac Dis. 2013;5 Suppl 6 ():S704–12
64. Kumar Prabhat, KiserAndy C, GehiAnil K. Hybrid treatment of atrial fibrillation. Prog Cardiovasc Dis. 2015;58 (2):213–20



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