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Pulmonary Vein Isolation using a High Density Mesh Ablator Catheter: Incorporation of three-Dimensional Navigation and Mapping

Dr Jiun Tuan, MBChB, MRCP; Dr Mohamed Jeilan, MBChB, MRCP; Dr Faizel Osman, MBChB, MD, MRCP; Dr Suman Kundu, MBChB, MRCP; Dr Rajkumar Mantravadi, MBBS, PhD MRCP; Dr Peter J Stafford*, MBChB, MD, FRCP; Dr G André Ng, MBChB, PhD, FRCP(Glasg), FRCP(London).

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Abstract

Background
We evaluated the use of a novel High Density Mesh Ablator (HDMA) catheter in combination with three-dimensional navigation for the treatment of paroxysmal atrial fibrillation.

Methods
The HDMA catheter was used to carry out pulmonary vein isolation in a consecutive series of patients. Three-dimensional geometry of the left atrial-pulmonary vein (LA-PV) junctions were first created with the HDMA catheter. Ostial, proximal and distal sites within the pulmonary veins were tagged with catheter shadows on the created geometry to allow for re-interrogation of these exact sites after ablation.

Results
The HDMA catheter was successfully used to create three dimensional geometry of the LA-PV junction in a total of 20 pulmonary veins which involved 5 patients. In all cases, ostial ablation alone was sufficient to achieve electrical isolation. No significant pulmonary vein stenosis was seen acutely after ablation.

Conclusion
We describe the successful use of the novel HDMA catheter to create three-dimensional geometry of the LA-PV junction to assist with pulmonary vein isolation.

Keywords: Atrial Fibrillation, pulmonary vein isolation, ablation

Introduction
Since it was first described by Haissaguerre and colleagues,¹ ² catheter ablation of atrial fibrillation (AF) has become an important treatment option in the management of this common arrhythmia. Then very first ablation procedures ³ described made use of conventional catheters with radio-
frequency (RF) energy to deliver lesions point-by-point at sites at the left atrial-pulmonary vein (LA-PV) junction, aiming to isolate atrio-venous and venoatrial conduction i.e. pulmonary vein isolation.

Attempts to improve endocardial ablation efficacy have resulted in modifications to RF energy delivery with the use of irrigated catheter tips \(^3,^4\) and also application of pulsed RF energy. Alternative energy sources that have been explored include cryo\(^6\), microwave \(^7\), laser \(^8\) and ultrasound \(^9\).

To simplify and improve the efficacy of pulmonary vein isolation, several studies have evaluated different energy sources with novel catheter designs. Natale et al reported on the successful use of a through-the-balloon delivery of ultrasound energy for isolation of pulmonary veins. \(^10\) Results of ablation using a high intensity focused ultrasound balloon catheter have also been recently reported. \(^11\) Endoscopic visualization to assist laser energy delivery through a balloon catheter is another technology that is currently being evaluated. \(^12,^13\)

Recently, an expandable multi-electrode HDMA catheter (High Density Mesh Ablator Catheter, Bard Electrophysiology, Lowell, MA, USA) was introduced as a one catheter solution to both mapping and ablation of the LA-PV junction with the use of pulsed RF energy. While it is possible to use the HDMA catheter with fluoroscopic guidance only, the addition of three-dimensional (3-D) navigation and mapping can provide further anatomical information to help guide catheter positioning and ensure delivery of ablation to optimal sites. We hereby describe our technique of using this new ablation catheter in combination with a 3-D navigation and mapping system, with the aim of assessing the technical aspects of using this catheter in this context, and at the same time evaluating acute results achieved with it.

**Methods**

The HDMA catheter was used in a consecutive series of patients who had been referred for catheter ablation of paroxysmal AF. All antiarrhythmic therapies were discontinued for more than 5 half-lives prior to the procedure.

The HDMA catheter utilizes an expandable high density array of wires arranged in 2 helices to form a mesh geometry, carrying a total of 36 electrodes. It is designed to provide high density mapping of the LA-PV junction by being able to conform to different shapes to suit any variation in anatomy. In its low profile configuration, it is able to enter and interrogate within the pulmonary vein itself. In its fully deployed and expanded profile, it adopts a circular, disc shape (30 mm diameter) to fit securely around the pulmonary vein ostium or antral region (Figure 1). It is non-steerable, and is capable of simultaneous delivery of pulsed RF energy at 5ms cycles alternating between its even and odd electrodes to achieve circumferential pulmonary vein ablation. The array of wires is divided into 4 quadrants with a thermocouple at each quadrant to allow for energy delivery under temperature control.

All procedures were carried out with the use of local anaesthesia under conscious sedation. Bilateral femoral venous access was used in all cases. Under fluoroscopic guidance, a steerable decapolar catheter and quadripolar catheter were positioned in the coronary sinus and His position respectively. After baseline electrophysiology study, a single transseptal puncture was carried out using a steerable 9F transseptal sheath (Channel sheath, Bard Electrophysiology, Lowell, MA, USA) to gain access to the left atrium. Following pulmonary vein angiography, the HDMA catheter was advanced into the left atrium via the transseptal sheath. 3-D geometry of the pulmonary veins and the left atrium were created using the Ensite NavX system version 7.0 (St. Jude Medical Inc, St. Paul, Minnesota USA) by moving the HDMA catheter, focusing on the pulmonary vein antral and ostial regions. The HDMA catheter was semi-deployed to enter the pulmonary veins with gradual deployment allowing contact with the pulmonary vein wall on pull-back whilst the ostial / antral / atrial geometry was created with the catheter fully deployed as a circular disc. Due care was taken to ensure that the HDMA catheter was lined up with the long axis of the pulmonary vein to facilitate ease of deployment. This was done by first keeping the HDMA catheter in the transseptal sheath, before cannulating the pulmonary vein with the steerable sheath. The HDMA catheter was then advanced to the tip of the sheath, and gradual withdrawal of the
The sheath was then carried out to expose the HDMA catheter in the vein, which then allowed for pull-back and formation of its circular disc-shaped configuration. As the main areas of interest were around the LA-PV junctions, only limited left atrial wall geometry was created (Figure 2). A unipolar catheter that was actively fixed in the right atrium was used as reference for the geometry. Electrical signals were then recorded from proximal and distal sites within each pulmonary vein as well as at the pulmonary vein ostia using the HDMA catheter, during atrial pacing from the distal coronary sinus electrodes. Each of these sites were tagged by application of a catheter shadow on the 3-D geometry (Figure 3). Once the HDMA catheter was deployed at the LA-PV junction, RF energy was applied using a pulsed RF generator (Tempulse pulsed RF controller, Bard Electrophysiology, Lowell, MA, USA). Each application of energy continued for a total duration of 300 seconds whenever possible, aiming for a maximum target temperature of 58°C, with up to 100 W power output. Satisfactory contact with tissue was maintained by gentle pressure on the catheter or sheath. After ablation, mapping was carried out at each pulmonary vein ostia using the HDMA catheter, during atrial pacing from the distal coronary sinus electrodes. Each of these sites were tagged by application of a catheter shadow on the 3-D geometry to confirm pulmonary vein isolation. The endpoint of ablation for each vein was elimination of all sharp signals (either in the pulmonary veins or at the ostia) suggestive of atrio-venous connection as mapped by the HDMA catheter. Electrical isolation was considered to have been achieved if there was evidence of entrance block or if dissociated pulmonary vein firing was seen. Before ablation of the right sided pulmonary veins, pacing from the electrodes on the HDMA catheter was carried out to exclude any diaphragmatic stimulation. If this was evident, the HDMA catheter is rotated and re-orientated into a new position while ensuring adequate endocardial contact and repeat stimulation carried out. This manoeuvre is repeated until diaphragmatic stimulation was no longer possible. In our experience this is usually adequate to prevent phrenic nerve injury, which was not seen in any of the patients presented here. Pacing manoeuvres (using a steerable decapolar catheter in the left atrium) were also used to differentiate far-field atrial signals from local conduction when checking for pulmonary vein isolation. This was achieved by replacing the decapolar catheter with the quadripolar His catheter in the coronary sinus, followed by advancement of the decapolar catheter into the left atrium through the existing transseptal access. Once all pulmonary veins had been isolated, repeat pulmonary vein angiography in the same...
views was performed to assess for pulmonary vein stenosis. Heparin was administered throughout the procedure to maintain an activated clotting time of around 300s. All electrograms were recorded on an electrophysiology review and recording workstation (Labsystem pro, Bard Electrophysiology, Lowell, MA, USA).

All continuous variables are expressed as mean ± standard deviation. Normally distributed paired data were analysed using paired Student’s t-test. Full consent for the procedure was obtained in all patients.

Results

A total of 20 pulmonary veins in 5 patients were ablated with the HDMA catheter (Table 1). High density mapping and 3-D pulmonary vein and limited left atrial geometry creation with the HDMA catheter were successfully carried out in every patient. No pulmonary venous anomaly or common ostia were noted in any of the patients. All patients had a history of paroxysmal AF and mean left atrial dimensions on echocardiography was 40 ± 5 mm, measured in the parasternal long axis view; all patients were in sinus rhythm at the start of the procedure. One patient developed sustained AF during catheter manipulation in the atrium but this reverted to sinus rhythm during circumferential pulmonary vein ablation. All 20 pulmonary veins were successfully isolated. The number of energy applications per patient was 13.6 ± 4.2 and duration of total energy delivered was 3093 ± 622 s. Number of energy applications per vein was 3.4 ± 1.05 and duration of energy application per vein was 773 ± 156 s. Two patients developed transient bradycardia and lowering of blood pressure consistent with a significant vagal response during ablation of the left upper pulmonary veins but this resolved without the need for specific intervention. Mean fluoroscopy time was 68 ± 97 minutes and procedure duration was 286 ± 30 minutes. Pulmonary vein ostial dimensions before and after ablation showed no statistical difference when comparing measurements obtained from fluoroscopy (Table 2).

In all cases, pulmonary vein signals which were mapped and tagged at proximal and distal por-
tions of each pulmonary vein, were completely abolished after delivery of pulsed RF energy with the HDMA catheter at the pulmonary ostia alone. Examples of intracardiac signals before and after pulmonary vein isolation are shown in Figure 4. Apart from minor groin haematoma in 1 patient, no other significant procedure-related complications were encountered acutely in patients reported in this study.

At the time of writing, 4 out of the 5 patients reported in this series had reported significant symptomatic improvement and were free of AF as assessed by routine 24 hour Holter monitoring more than 3 months after the ablation (3 off anti-arrhythmic medication). One patient had documented recurrence of symptomatic, paroxysmal AF at 3 months post-procedure. No long term procedure-related complications were encountered. Mean duration of follow-up for all patients was 112 ± 19 days.

Discussion

We have hereby described our technique of using the novel High Density Mesh Ablator catheter in conjunction with 3-D navigation and mapping using the Ensite NavX system. While the catheter has been developed with the intention for it to be used as a single mapping and ablation catheter for pulmonary vein isolation without employing 3-D mapping assistance, the HDMA catheter is still a relatively new product and published experience of its use in humans is limited. In our group of patients, we successfully used the HDMA catheter to create high density 3-D geometries of the pulmonary veins and the ostial / antral regions to help guide catheter manipulation and also to re-check specific sites in and around the pulmonary veins when assessing for electrical isolation. Although not encountered in our series, 3-D navigation will be especially useful in the delineation of any anomalous venous anatomy or common ostia which may limit the ability of the catheter to deliver effective lesions at desired sites. This is particularly relevant as the shape of the expanded HDMA catheter is designed to fit normal pulmonary venous ostia and could have difficulty conforming to anatomical variation. Having a 3-D geometry will help guide positioning of the HDMA catheter. In all cases, ablation was limited to only the LA- PV junction as non-pulmonary vein

Figure 3: HDMA catheter shadows marking ostial, proximal and distal left upper pulmonary vein (top) and demonstration of lesions delivered by the HDMA catheter (bottom)
triggers of AF were not encountered in any of the patients. While the HDMA catheter is capable of ablation around pulmonary vein ostial and antral regions, we expect that ablation of non-pulmonary vein foci remote from the LA-PV junction will require the use of standard ablation catheters. These, however, have previously been shown to occur less frequently than pulmonary vein triggers.\(^2\)

The risk of pulmonary vein stenosis is reduced by ablating at the ostium or antral region rather than within the vein.\(^{18,19}\) The further the abla-

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**Figure 4:** Left lower pulmonary vein ostium (a), proximal vein (b), and distal vein (c) signals mapped from odd-numbered electrode pairs of the HDMA catheter before (left panel) and after (right panel) ablation, during distal coronary sinus pacing. The remaining electrical signals seen at the ostium after ablation were found to be from far-field sites by using pacing manoeuvres. Corresponding locations on the 3-D geometry are shown in the bottom panel.
tion catheter is placed from the pulmonary vein, the lower the risk of pulmonary vein stenosis. The HDMA catheter was designed with this in mind and its configuration in the expanded profile prevents the catheter from entering the vein, and ensures that all ablation is delivered from the atrial aspect of the ostium. However, a potential problem with circumferential pulmonary ostial ablation is the persistence of LA-PV conduction. This would not be detectable by mapping the ostium alone and further interrogation within the pulmonary vein itself is desirable and often necessary. In our study the use of 3-D navigation and geometry tagging to mark proximal and distal pulmonary vein and ostial sites allowed these exact locations to be accurately re-visited and assessed post-ablation to ensure complete isolation. Our experience so far, using the above technique, indicates that ostial ablation alone with the HDMA catheter to eliminate ostial potentials can lead to successful isolation of the pulmonary veins, without causing any significant pulmonary venous stenosis. This is in agreement with a feasibility study of a similar HDMA catheter carried out on canine hearts where it was used to successfully isolate the right superior pulmonary vein, without causing any significant pulmonary venous stenosis on both post-ablation and also on follow-up pulmonary vein angiography.

### Limitations

This report consists of a small number of patients with short term follow-up. However, we would like to stress that the intention of this paper is to document the feasibility of combining the HDMA catheter with 3-D navigation and mapping, and to highlight the possible advantages of such an approach. As this is a description of our early experience using the HDMA catheter, a considerable amount of time was spent on setting up equipment, manipulating the catheter, and also checking for pulmonary vein isolation. This will account for the fluoroscopy time and also overall procedure time reported in this study. With more operator experience, the procedure time may decrease.

### Table 1

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Left Atrial Size (mm)</th>
<th>No. of pulmonary veins isolated</th>
<th>Total RF delivery time (s)</th>
<th>Fluoroscopy time (minutes)</th>
<th>Total procedure time (minutes)</th>
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<tr>
<td>1</td>
<td>35</td>
<td>4</td>
<td>3417</td>
<td>66.7</td>
<td>325</td>
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<td>2</td>
<td>47</td>
<td>4</td>
<td>3756</td>
<td>82.2</td>
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<td>3</td>
<td>37</td>
<td>4</td>
<td>3296</td>
<td>73.6</td>
<td>290</td>
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<tr>
<td>4</td>
<td>42</td>
<td>4</td>
<td>2860</td>
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<tr>
<td>5</td>
<td>41</td>
<td>4</td>
<td>2138</td>
<td>57.5</td>
<td>270</td>
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### Table 2

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<th>Pre-Ablation</th>
<th>Post-Ablation</th>
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<tr>
<td></td>
<td>LUPV</td>
<td>LLPV</td>
</tr>
<tr>
<td>1</td>
<td>16</td>
<td>23</td>
</tr>
<tr>
<td>2</td>
<td>28</td>
<td>24</td>
</tr>
<tr>
<td>3</td>
<td>24</td>
<td>28</td>
</tr>
<tr>
<td>4</td>
<td>30</td>
<td>24</td>
</tr>
<tr>
<td>5</td>
<td>30</td>
<td>20</td>
</tr>
<tr>
<td>Mean</td>
<td>25.6*</td>
<td>23.8†</td>
</tr>
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</table>

*P = 0.17, †P = 0.18, ‡P = 0.11, §P = 0.13

LUPV = Left upper pulmonary vein, LLPV = Left lower pulmonary vein, RUPV = Right upper pulmonary vein, RLPV = Right lower pulmonary vein
ence and familiarity, it is anticipated that the procedure time would be significantly reduced.

Conclusion

We have demonstrated that pulmonary vein isolation can be carried out with the HDMA catheter in combination with 3-D navigation to create high density three-dimensional geometry of the LA-PV junction, and that this can assist with catheter placement and confirmation of pulmonary vein isolation. Using this technique, the HDMA catheter is capable of circumferential ostial isolation of the pulmonary veins without causing significant pulmonary vein stenosis acutely on angiography. Our data serves as a favourable feasibility assessment of the above technique and further evaluation of its safety and efficacy in a larger cohort of patients should be performed.

References

Introduction

Incidence und Prevalence

Stroke is a leading cause of death and disability worldwide. About 15-20% of ischemic strokes have a cardioembolic origin. Atrial fibrillation (AF) affects 3-5% of the population older than 65 years and is the most common arrhythmia of clinical relevance. With an aging population, the prevalence is likely to increase 2.5 fold over the next 50 years.¹

Summary: For both devices, a reduction in the risk of stroke was documented and device implantation was shown to be safe and feasible. Provided the ongoing trials show noninferiority to oral anticoagulation, another therapeutic option will become available to prevent ischemic strokes.

Abstract

Purpose: Patients with atrial fibrillation are at an increased risk of having a cardioembolic stroke. Stroke is a leading cause of death and disability worldwide. Current guidelines recommend an antithrombotic regimen to prevent thromboembolism in medium and high risk patients with AF. However, a substantial number of patients are not eligible for this therapy. The exclusion of the left atrial appendage (LAA) from circulation seems to be an alternative strategy for stroke prevention in AF. This review focuses on the different strategies for LAA exclusion with special focus on the WATCHMAN Device.

Two devices are currently in use for percutaneous transcatheter occlusion of the LAA: the WATCHMAN®-device and the AMPLATZER®-septal occluder. For both devices safety and feasibility data are available.

Additionally about 200 patients received a PLAATO®-device- which is currently no more available due to economic reasons. Patients treated with the PLAATO device were at high risk for thromboembolic stroke and had contraindications for oral anticoagulation therapy. The Watchman®-device was implanted in 800 patients that were eligible for long-term anticoagulation therapy with a moderate risk for thromboembolic stroke due to non-valvular AF.

Summary: For both devices, a reduction in the risk of stroke was documented and device implantation was shown to be safe and feasible. Provided the ongoing trials show noninferiority to oral anticoagulation, another therapeutic option will become available to prevent ischemic strokes.

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age from about 2% in patients aged 60-69 years to approximately 8% in patients older than 79 years.\(^2\)

Additionally several risk factors have been described as markers for an increased risk for thromboembolism. The CHADS\(^2\) stroke risk index was developed to estimate the stroke rate in AF patients [Table 1]. The higher the score, the higher the risk of stroke.\(^3\) [Table 2 ]

The current guidelines for therapy of AF recommend an antithrombotic regimen with warfarin as a class 1A indication to prevent thromboembolism in all patients with AF with a CHADS\(^2\) score of >1, except for those with contraindications.\(^4\)

Without anticoagulant therapy the risk of stroke is about 5% per year in patients < 65 years and it increases to over 8% per year in patients over 75.\(^5\) The effectiveness of an anticoagulation therapy to prevent ischemic strokes related to atrial fibrillation was demonstrated in several studies. One of the largest studies- the SPAF – I- trial-demonstrated a risk reduction of about 67% with warfarin as compared with placebo.\(^6\)

Studies assigned the effects of warfarin as compared with aspirin, clopidogrel or a combination of both but none of them were able to show a superiority of one of these therapies over warfarin.\(^6,7\)

The impaired mechanical contraction of the left atrium and especially the LAA in patients with AF leads to a reduced blood flow velocity and is supposed to result in spontaneous echo contrast, thrombus formation, and embolic events.\(^13-18\) In addition, the morphology of the LAA might have an impact on the risk of thrombus formation. The LAA is usually a long, tubular, hooked structure with a large variability in morphology. Its size ranges from 20 to 45 mm in length and 15 to 35 mm in orifice diameter.\(^19\) In atrial fibrillation LAA casts at necropsy had a higher volume, larger orifices, and fewer branches and were broader than those of patients with sinus rhythm.\(^20\)

Functionally, the LAA plays a role as a “decompression” chamber, besides the production of atrial natriuretic peptide. Several studies suggest that the LAA is more distensible then the left atrium.

Therefore many activities are focused on the development of novel therapeutic tools to prevent AF related strokes. Besides new medication, one development that might be promising is the interventional exclusion of the left atrial appendage (LAA) from circulation.

### The Left Atrial Appendage as the target

Ischemic strokes associated with atrial fibrillation are caused by secondary embolisation of thrombi from the left atrial appendage (LAA) in 91% to 98%.\(^12\) The pathophysiology of thromboembolism in patients with AF is uncertain. Although Virchow postulated stasis, hypercoagulation and endothelial dysfunction as the mechanisms leading to thrombus formation, the pathophysiology of thromboembolism in atrial fibrillation remains uncertain.\(^4\)

The discontinuation rate for those under therapy is estimated to be 38% per year approximately\(^11\)

### The Exclusion of the LAA from Circulation as an Alternative Therapy to Warfarin for Thrombus Prevention

For more than half a century physicians try to ex-

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<th>Table 1</th>
<th>CHADS(^2) * Risk Score</th>
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<tr>
<td>Risk factor</td>
<td>CHADS(^2) Score</td>
</tr>
<tr>
<td>Congestive heart failure (LVEF &gt;35%)</td>
<td>1</td>
</tr>
<tr>
<td>History of hypertension</td>
<td>1</td>
</tr>
<tr>
<td>Age &gt; 75 years</td>
<td>1</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1</td>
</tr>
<tr>
<td>Stroke or TIA (prior)</td>
<td>2</td>
</tr>
</tbody>
</table>

* CHADS\(^2\) is an acronym derived from the initial letter from the risk factors and the scoring 2 for prior stroke or TIA. The Score is calculated by the scores of the present risk factors.

## Table 2

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<th>Classification of risk groups through the CHADS2 Score</th>
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<tbody>
<tr>
<td>Risk factor</td>
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<tr>
<td>Low risk</td>
</tr>
<tr>
<td>Intermediate risk</td>
</tr>
<tr>
<td>High risk</td>
</tr>
</tbody>
</table>
clude the LAA from circulation in patients with AF for thromboembolic prophylaxis. Even in the pre-warfarin era 1946 the surgical amputation of the LAA was described in two patients for prevention of thromboembolic events. This procedure of LAA obliteration/amputation has been performed first in patients undergoing mitral valve surgery or maze procedure. In this setting the results of LAA exclusion were inconclusive. In 2003 Garcia – Fernandez reported about a series of 58 patients, in whom ligation of the LAA was performed during mitral valve surgery. He reported about incomplete sealing of the LAA in a transesophageal echo follow up of about 10% of patients. In these patients the risk of late embolism was significant increased with an odds ratio of 6.7. On the other hand, a recently published prospective study by Almahameed et al. could show that also in patients after LAA exclusion the rate of thromboembolism was 15% in those without postoperative warfarin therapy and 10% in those patients with postoperative warfarin therapy after 3.6 years of follow up.

In patients undergoing other cardiac surgery than mitral valve surgery, the amount of available data is limited. First data of the Left Atrial Appendage Occlusion Study-[LAAOS] pilot trial in patients undergoing coronary artery bypass surgery (77 patients) showed that the procedure of LAA occlusion is safe and does not prolong overall length of surgery. However, the benefit of a surgical LAA occlusion/amputation, with respect to mortality and morbidity, is unknown so far, as the study is still ongoing with a planned inclusion rate of 2500 patients.

Given the fact that several studies report an incomplete occlusion of the LAA after surgical ligation in a high percentage of patients underlines the need for further development of the technique. Recently Salzberg and colleagues reported on a new LAA Clip [AtriCure Inc. West Chester, Ohio] that was successfully tested in animals. The clip provided a total exclusion of the LAA from circulation. However, also nonsurgical, interventional devices that exclude the LAA from circulation have been...
developed. Three different interventional devices have been described so far for transcatheter LAA occlusion:

A) PLAATO® System - currently no longer commercially available
B) Amplatzer septal occluder – commercially available but not approved for this indication
C) WATCHMAN® Device – so far available only for studies, but FDA-approval expected for this year

A) PLAATO® System
The PLAATO® System (originally produced by ev3 Inc., Plymouth, Minnesota, USA) consists of a self-expandable nitinol cage covered with a non-thrombogenic ePTFE membrane to exclude blood flow from the LAA. Different sizes (15-32mm) of the device were available, and a 14 French introducer sheath was required for implantation. Nakai et al. was the first to report on the Percutaneous LAA Transcatheter Occlusion (PLAATO®) System. Feasibility and safety of this transseptal system was evaluated in 25 dogs. The LAA could be occluded successfully in all 25 dogs safely and quickly. The sealing of the LAA seemed to be complete in all cases. Sievert et al published the first in man experience with the PLAATO® System. Fifteen patients with chronic atrial fibrillation and contraindication for warfarin therapy were recruited for the study. In all patients the LAA could be successfully occluded. At 1 month follow up there were no complications or embolic events. At present, more than 200 patients were treated with the PLAATO® device so far. 98% of patients could be successfully treated with minor complications. There was one device embolisation and 3% of patients developed pericardial effusions during/after the implantation procedure. One of these patients died due to cerebral hemorrhage after surgical pericardiocentesis. The study group analyzed a follow up of 250 patient years and documented an annual stroke rate of 3.2 % in patients having the PLAATO® device. The expected annual stroke risk according to the CHADS2 Score was 6.5% under aspirin therapy in these individuals. One percent of the PLAATO® patients developed a flat thrombus attached to the surface of the device, which resolved under therapy with aspirin, clopidogrel and low molecular weight heparin. No mobile clots, mitral valve damage or pulmonary vein obstruction was observed. Therefore it was concluded that LAA occlusion with the PLAATO® device reduces the relative risk of stroke by 51%. Currently the device is no longer available, solely due to commer-

Figure 2: Schematic view of an implanted WATCHMAN Device
cial and not to medical reasons.

B) Amplatzer® septal occluder

The first and only study of left atrial appendage occlusion with the Amplatzer® septal occluder (AGA Medical Corp. Golden Valley, MN; USA) devices was published in 2003. The ease use of these devices in occluding patent foramen ovale or atrial septal defects lead to first experimental occlusion of LAA with these devices by Meier et al. \(^\text{30}\) This first report included 16 patients that were treated in four centers with successful implantation in 15 patients. One acute device embolisation occurred. However, the device was surgically removed. At 4 months follow up, there were no further complications, the devices were stable in position and the LAA was completely occluded in all cases. Within this follow up period no thromboembolic complications were reported. Nevertheless, for the Amplatzer ASD Occluder there are no further data available in LAA occlusion and large studies are lacking.

C) WATCHMAN® Device

The Watchman ®- Left Atrial Appendage Occlusion Device (Atritech Inc., Plymouth, Minnesota, USA) is comprised of a self-expanding nitinol frame structure with fixation barbs and a permeable polyester fabric [Figure 1 and 2] that covers the left atrial facing surface of the device. Currently, the device is available in a size ranging from 21 to 33 mm. For WATCHMAN® device implantation, a transseptal access sheath (14 Fr) and a delivery catheter is necessary.

In a pilot trial 75 patients were included to assess safety and feasibility of the device. Patients had an

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**Figure 3:** Implanted WATCHMAN Device

a) CT Scan: the device is in situ in the LAA

b) Fluoroscopy: The device was released in the LAA (arrow), the sheath is positioned in LA for fluoroscopic control (asterisk)
average CHADS² Score of 1.8 points corresponding to a moderate risk for stroke. Patients with impaired left ventricular function (< 35%), congenital heart disease, symptomatic carotid disease, prosthetic heart valves and significant neurological defects after prior stroke were excluded. The implantation procedure was performed under general anesthesia and TEE guidance. In 66 of the 75 patients (88%), the device could be implanted successfully [Figure 3]. Implantation failure occurred in 9 patients due to unsuitable LAA anatomy (7 patients), core wire malfunction (1 patient) and impossible transseptal crossing (1 patient). Complications occurred in 5 of the first 16 patients treated with the first generation of the device. There were two embolisations of the device, one delivery system failure, one surgical device explanation after incorrect positioning, and one patient with transient air embolism. Therefore, the device and the delivery system were modified after these first 16 patients. Fifty-three additional patients were implanted with the second-generation device and no further device embolization occurred. There was one significant pericardial effusion due to an overly vigorous tug test but no other relevant complications. After a mean follow up of 24 months there were no major strokes at all. Two deaths occurred during follow up period, which were not device related. In one patient, who died 9 months after device implantation due to a Type A aortic dissection, a complete endothelialisation of the Watchman device and the LAA was observed at autopsy. These data provide considerable evidence that implantation of the re-designed device is safe and feasible. Another randomized, prospective multicenter study (The WATCHMAN® Left Atrial Appendage System for Embolic PROTECTion in Patients With Atrial Fibrillation (PROTECT AF)- study), which is the first controlled trial in this field, compares Watchman device implantation with standard anticoagulation therapy. The recruitment period for this study ended in summer 2008. The study included 800 patients at 39 centers in Europe and USA. The patients were randomized 2:1 for device implantation vs. medical therapy only. All patients randomized in this study were eligible for standard warfarin therapy. For demonstration of non-inferiority of the WATCHMAN® device compared to warfarin therapy to reduce the incidence of stroke, 900 patient years of follow up were analyzed. The data of this study will be published later in 2009 and are currently not yet available.

Summary and Conclusion

Patients with atrial fibrillation, especially in the older population, are at increased risk of stroke/TIA or PRIND, presumably because of stagnant blood flow within the left atrial appendage-a highly complex structure of the left atrium, leading to thrombus formation. The annual risk of stroke in AF increases with age from about 5% in patients that are younger than 65 years to about 8% at the age over 80. Besides age, cardiovascular diseases, hypertension, ischemic heart disease, congestive heart failure, valvular heart disease, and diabetes, have an impact on the prevalence of AF and also on the risk of stroke. The CHADS² score is a good validated score with a high correlation to the event rate.

Three therapeutic options exist to prevent ischemic strokes in those patients: The first and most popular is chronic anticoagulation therapy with warfarin, which is highly effective in preventing cardioembolic events and which is superior to other pharmacological approaches so far. However, oral anticoagulation is associated with severe problems and significant risks: In about one third of patients this therapy is contraindicated, the rate of discontinuation of therapy is up to 38%/year and there is a narrow therapeutic window with a potential risk of severe bleeding of about 2% per year. Furthermore, less than half of all patients who are receiving anticoagulant treatment are within the therapeutic range with regard to INR. Therefore, new oral medication for anticoagulation without the risks and problems of vitamin K antagonists are under way and were tested at present in phase III-studies.

The second way for prevention of thromboembolism from the LAA is the exclusion of the LAA from circulation by surgical techniques. Regardless of the technique, first established in 1946, there are rare data available regarding the rates of successful LAA occlusion by various surgical techniques and in note of complications. In addition, it has never been shown that such an approach really reduces the incidence of stroke. Further studies with large patient populations and clinical endpoints are required to underline the effectiveness of these sur-
gical interventions. Also for a newly developed clip system (LAA Clip; AtriCure Inc. West Chester, Ohio, USA) there are only safety and feasibility data available in an animal model so far. First in man studies are expected and we have to await the issue.

But all these approaches are only for patients undergoing heart surgery for other reasons. In the last ten years, percutaneous occlusion systems were developed in order to seal the LAA in a less traumatic way as a third way to go for stroke prevention in AF patients. The perinterventional success rates are high for all the devices. However, the number of patients treated with such devices so far is small in relation to the population receiving warfarin and long term follow up data are lacking. The first system specially developed for interventional LAA occlusion was the PLAATO®-System. The safety and feasibility of the system in humans was shown in patients with contraindication for chronic oral anticoagulation therapy. A risk reduction of about 50% for the incidence of ischemic strokes in this patient population was demonstrated after implantation of the device and chronic aspirin administration as compared with their statistically calculated risk. However, procedural complications like pericardial effusions/tamponade, device embolisation and device failure have been described in about 5% of patients.

The second system developed to occlude the LAA, is the WATCHMAN®-device. Implantation of the device was shown to be safe and feasible in a pilot trial in humans with atrial fibrillation. The patient population in this study had a lower risk for ischemic stroke with a CHADS² Score of 1.8 points as compared to 2.5 points in patients treated with the PLAATO®-device. Due to the permeable nature of the membrane of the WATCHMAN®- device (das war nicht der Grund, es war eine Bauchentscheidung, zunächst wegen Fremdkörper Antikoagulation fortzuführen, wegen Thrombenbildung auf Device in der Pilotstudie ASS und Clopidogrel bis 6 Monate, jetzt gibt es ha auch die ASAP-Studie, wo gänzlich auf Marcumar verzichtet wird) an oral anticoagulation after implantation procedure for 45 days and a double therapy with aspirin and clopidogrel for up to 6 months is required. The first generation of the device had a higher complication rate (device embolisation, device failure). After re-design of the WATCHMAN®- device these complications were diminished, at presence stroke rate is 0% at 2 year follow up as compared with an anticipated stroke rate of 1.9% calculated with the CHADS2 Score.

Data from the Protect AF Trial- (FDA approval trial) are under supervision and and not yet published. The third interventional method, implantation of an Amplatzer septal occluder into the orifice of the LAA was shown only in a single center experience with few patients and a high rate of embolisations. Also with this method there are some short term results available, but the device is not approved for this indication and randomized data are lacking, therefore this method was left so far. The AGA-company is also on the way with a specially designed device for LAA closure, but it is not yet commercially available and there are no data in the literature so far about this device.

Conclusions

LAA occlusion with the WATCHMAN®-device, with the Amplatzer® septal occluder as well as with the PLAATO® Occluder are safe and feasible. At present only the Amplatzer septal occluder and the WATCHMAN® occluder are (partially) available. No device is approved by the FDA with the indication occlusion of the LAA in patients with AF, but both devices are CE marked. At present the WATCHMAN technology was submitted to the FDA for assessment and the FDA approval is expected for 2009. Because of the growing prevalence of AF especially in the elderly, in whom anticoagulation carries a high risk or is contraindicated, this device may offer an attractive solution to prevent atrial fibrillation-related thromboembolic events. Nevertheless, both, the PLAATO® and the WATCHMAN®-device, demonstrated that there is a measurable risk in implanting such new devices with an investigators learning curve at the beginning. Provided the PROTECT –AF trial shows non-inferiority to oral anticoagulation with warfarin, another therapeutic option will become available to prevent ischemic strokes.

On the other hand, newly developed drugs like oral Factor Xa Inhibitors like rivaroxaban (Bayer Health Care; Leverkusen Germany); DU-176 b (Daichi-Sankyo Ltd. Tokyo Japan) or Dabigatran (Boehringer Ingelheim GmbH; Ingelheim, Germany) may play an increasing role in the therapy of
AF in the future with much less risk for bleeding and a better therapeutic range without the need for INR control. Studies for anticoagulation therapy in AF with these new drugs are under way. The authors recommend indicating an interventional occlusion of LAA in AF with strict caution only done by centers with experience with those devices. Only patients with high risk for stroke should be implanted until more data are available.

References


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**Introduction**

Despite the vast extent of resources devoted to its understanding and treatment, atrial fibrillation (AF) remains the most significant clinical arrhythmia in terms of its morbidity and continues to challenge us to fully uncover its elusive mechanisms. This is not to say, however, that there has not been significant progress made. On the contrary, remarkable strides have been made both in the basic science laboratory to uncover the mechanisms by which the arrhythmia is generated and sustained, and in clinical studies of treatment. Catheter ablation has emerged as an important therapy in drug refractory AF and has brought with it continuously improving technology in areas including catheter design, mapping systems, and overall ablation strategy.

Catheter-based pulmonary vein isolation as a means to electrically isolate triggers of AF has significantly improved success at maintaining sinus rhythm (particularly in paroxysmal AF) but has not eliminated AF altogether. Permanent maintenance of pulmonary vein electrical isolation can often prove to be challenging, and important sources outside the pulmonary veins and predominantly in the left atrium remain. Targeting areas of complex fractionated atrial electrograms (CFAE), although reported with varying degrees of efficacy, is believed to modify important sites for the mainte
of AF. As an adjunct to pulmonary vein isolation, CFAE ablation has gained some favor as a means to tailor ablation to a given patient.  

Recently, significant attention has been directed toward utilizing dominant frequency (DF) analysis to highlight sites of rapid and consistent periodicity which are believed to represent likely targets for maintenance of AF. 2 This article provides an overview of the basic concepts behind DF analysis, reviews the pertinent data regarding its application to AF, and discusses the current and future status of its clinical application.

Mechanisms of Atrial Fibrillation

Multiple theories regarding the initiation and maintenance of AF have been introduced and evolved our understanding of this arrhythmia since at least the beginning of the twentieth century when Winterberg, et al. in 1907 described AF as due to multiple rapidly firing atrial foci. 3, 4 In 1914, Mines promoted the theory of circus movement as the key reentrant mechanism to perpetuate AF. 5 In 1964, Moe et al. described AF as a self sustaining process of multiple randomly propagating wavelets made possible by an atrial substrate of heterogeneous refractoriness. 6, 7 Challenging this, at least in some cases of AF, has been the theory of mother rotors, described by Jalife, et al. as discrete self sustaining reentrant foci that may provide the engine for the maintenance of AF. These rotors tend to anchor to various anatomical substrates, thereby maintaining a relatively fixed location and giving off multiple randomly circulating wavelets. These wavelets then propagate throughout the atria with varying amounts of degradation (fibrillatory conduction) as they encounter the heterogeneous tissue of the left and right atria and their connections. 8 The presence of these rotors have been studied through optical mapping of the left atrium and their periodicities have been shown to match with electrogram frequencies at those locations. 9 Identifying the sites of these rotors by their rapid and periodic deflections on electrograms is the aim of frequency analysis.

Understanding Dominant Frequencies

In its application with respect to AF, the fundamental goal of DF analysis for any given location is to find the activation rate of the dominant atrial signal at that site. The standard approach during electrophysiology studies utilizes a time domain analysis where the amplitude of the signal as seen on the electrogram is plotted against time. However, during AF, the varying amplitude and morphologies of the atrial signals often preclude accurate measurement of atrial cycle lengths. DF analysis, however, dissects the electrogram into components of varying frequencies and creates a power spectrum based on their amplitudes. Ultimately, the “dominant” or highest amplitude frequency is identified and used to determine the activation rate of the primary atrial signal from that location. 10 Below is a more detailed description on the specific algorithms used in DF analysis.

Initially, an electrogram from a given atrial site is obtained over a period of about five seconds. 11 This “time domain” signal then undergoes a Fast Fourier Transform to display a power spectrum of its frequencies and ultimately to identify a DF. The fundamental principle behind the Fourier Transform is that any time series (such as an atrial electrogram) can be portrayed as a sum of a discrete set of sinusoidal waves of specific frequencies, amplitudes, and phase shifts. After the signal is broken into these compository waves, a power spectrum of their frequencies is created and a DF can be identified (figure 1). The term “Fast” Fourier transformation implies that the time sample analyzed is of a power of 2 which lends itself to a more efficient and quick analysis.

In order to provide a cleaner or more discrete frequency power spectrum from biphasic electrogram recordings, signals need to undergo several processing steps including bandpass filtering, rectification, and signal tapering. Band-pass filtering serves to attenuate signal “noise” outside a specified desired frequency range and highlights deflections that represent local atrial depolarization. Rectification converts the biphasic signal to a monophasic one more easily represented by a sinusoidal wave; and signal tapering reduces to baseline the signals at the two ends of a specified time “window” to prevent incompletely recorded deflections from affecting the data. 10, 12 All these steps serve to “clean” the frequency spectrum and help elucidate the dominant atrial waveform and its periodicity.
Any atrial site can be examined utilizing the methods detailed above and a DF can be assigned to each of these sites. Ultimately, the implication in targeting sites with high DFs for ablation is that they potentially represent the location of rotors that may be responsible for the maintenance of AF.

Several studies have suggested that in both animal and human hearts in AF, left atrium and pulmonary vein sites tend to have higher DFs than the right atrium, thereby representing a left to right DF gradient. Lazar et al. demonstrated the presence of this gradient correlated with a higher probability of successful ablation through pulmonary vein isolation. However, whether high DF sites in the pulmonary veins correlate with their identification as triggering foci remains unclear as the tissue characteristics have not yet been fully described. In an animal model of Langendorff-perfused sheep hearts in AF, Jalife et al. elegantly demonstrated this left to right atrium gradient and showed its path of decrementation as it crossed Bachman’s bundle from the left atrium into the right atrium. All these findings support the theory that periodic and relatively stationary high frequency sources to maintain AF may be present in the left atrium and can therefore represent potential targets for therapy of AF.

Clinical Use of Dominant Frequency Analysis

Based on the concept of high DF sites representing potential sources maintaining AF, its specific clinical application is still being determined. Sanders
et al. demonstrated in a study where the operators during AF ablation were blinded to the DF analysis, ablation at a high DF site was more likely to prolong the AF cycle length. Also, in paroxysmal AF the majority of AF termination occurred while ablating a high DF site. Furthermore, a difference in DF distribution was seen where patients with paroxysmal AF had high DF sites that were more likely to lie in the pulmonary vein whereas in persistent AF, left atrial DFs were often higher. Some groups are also beginning to perform real-time analysis of DF to guide ablation. When targeting high DF sites, Atienza et al. have seen a higher probability of remaining free from (arrhythmia or) AF when successfully ablating DFmax sites or abolishing the left to right atrium DF gradient.

While a definitive role for DF analysis to guide ablation is yet to be established and varying accounts of its efficacy have been presented, this concept is certainly one that warrants further clinical evaluation. Targeting of high DF sites may ultimately have an expanded role in AF ablation, particularly as an adjunct to pulmonary vein isolation. The exact strategy for DF based ablation is still being developed and this process will certainly face a number of challenges. Among these is the dynamic nature of DF spectra during PVI and left atrial ablation which may require remapping of DF sites during the procedure. Software and catheter design may also need to be improved to provide more efficient and accurate real-time DF maps. Also, different strategies may prevail between chronic and paroxysmal AF patients, especially in relation to its use with pulmonary vein isolation. Other potential obstacles to accurate DF analysis such as far-field signals, signal alteration around scars, and prior ablation lesions setting up local reentry will also need to be addressed.

However, with innovations such as catheter systems that can deliver a large number of electrodes to the atria and noncontact mapping, evaluating the substrate for high DF sites will likely become more efficient. Furthermore, ongoing clinical investigation is advancing our understanding of the clinical significance of high DF sites and strategies on how and when to map and ablate at these sites are being developed. If these advancements in design and refinement of strategies to target DF sites prove to increase success rates, curative ablation of AF may be accomplished with less atrial damage than current approaches.

References

Atrial Fibrillation in Hypertrophic Obstructive Cardiomyopathy - Antiarrhythmics, Ablation and More!

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Abstract

Hypertrophic cardiomyopathy (HCM) is a genetic disease of the cardiac sarcomere with an autosomal dominant pattern of inheritance. Patients with HCM are at high risk of developing atrial fibrillation (AF) particularly in the setting of advanced diastolic dysfunction and left atrial enlargement. AF is a marker of increased mortality and morbidity and results in a significant reduction in quality of life. Antiarrhythmic medications improve symptoms and reduce AF recurrence, but few are safe and there exists little data to guide their long-term use in HCM. Non-pharmacologic approaches have emerged and have equal or greater efficacy than pharmacologic approaches. Although these approaches are promising, the long-term impact on atrial function needs to be carefully studied as it may impact quality of life in patients that age in the setting of a progressive diastolic disease disorder. Nonetheless, with the significant impact of AF in HCM, rhythm control strategies are often required. The understanding of rhythm control strategies in HCM, an often rapidly progressive diastolic dysfunction disorder, may provide insight in how to treat the much more prevalent AF patient with hypertensive cardiomyopathy. Regardless of treatment strategy (rhythm or rate control) patients are a moderate to high risk of thromboembolism and until data are available to suggest otherwise require long-term warfarin anticoagulation.

Introduction

Hypertrophic cardiomyopathy (HCM) is a genetic disease of the cardiac sarcomere with an autosomal dominant pattern of inheritance. There are more than 450 familial hypertrophic cardiomyopathy-causing mutations identified in 20 genes, that encode cardiac isoforms of sarcomere and sarcomere-related gene products. 1 Of these, cardiac-myosin binding protein-C is the most commonly affected gene (15–50%); 2,3 followed by mutations in cardiac troponin isoforms I and T(4–15%). 2,5,6,7,8,9

Pathophysiology of HCM

The genetic defects involved in HCM lead to myofibril disarray and cause ventricular hypertrophy over time. Although significant phenotypic variation exists, the most common form of HCM involves hypertrophy of the septum extending to the outflow tract. In approximately 25% of pa-
tients the muscle thickening is evenly distributed throughout the ventricle and in approximately 10%, myocardial thickening is predominantly at the apex of the heart. The myofibril disarray present in the septum and even in other distinct areas of the myocardium that may or may not be hypertrophied but can contribute to ventricular arrhythmogenic substrate and/or diastolic dysfunction and heart failure symptoms.

In patients with HCM, dynamic left ventricular outflow tract obstruction is an important pathophysiologic feature that distinguishes obstructive HCM from nonobstructive disease and is closely correlated with long-term adverse outcomes. Despite structural impairment, outflow obstruction through the Venturi phenomenon during systole can also result in systolic anterior motion of the mitral valve resulting in mitral valve regurgitation, valve leaflet fibrosis, and valve degeneration. The combined state of structural and valvular heart disease can result in heart failure symptoms, ventricular arrhythmias, apical thrombi, and premature death. In patients with the acquisition of other disease states such as coronary artery disease the pathologic process may be accelerated.

Clinical manifestations of HCM

The clinical manifestations of HCM vary considerably resultant from a broad spectrum of morphologic and hemodynamic abnormalities (Figure 1). Common symptoms are dyspnea on exertion, chest pain, orthopnea and paroxysmal nocturnal dyspnea, palpitations, fatigue, postural lightheadedness, presyncope and/or syncope. Most patients are diagnosed with HCM because of routine screening due to a family history of HCM. Overtime, asymptomatic patients can become
symptomatic with 25% developing incapacitating symptoms or death over an 8 year follow-up in one large study. In patients with HCM, age at onset of symptoms, gender, the presence of obstruction, and genetic mutations impact progression of disease and expected outcomes. Patients with familial hypertrophic cardiomyopathy caused by a Phe110Ile missense mutation in the cardiac troponin T gene have variable cardiac morphologies and a favorable prognosis. Nonetheless, in patients specifically referred for evaluation of HCM, heart failure symptoms and outflow tract gradients are common, particularly when exercise testing is used in the diagnostic assessment.

Pathophysiology of Atrial fibrillation in HCM

In patients with HCM, atrial fibrillation (AF) is a common arrhythmia. A few studies have sought to understand the incidence of AF in patients with HCM. In a case-control study of 104 HCM patients, AF was present in approximately 5 percent of patients at the time of diagnosis of HCM and developed in an additional 10 percent during the subsequent five years of follow-up. A second study of 480 consecutive HCM patients, AF occurred in 22 percent over 9 years of follow-up. In both patient populations the AF subtype was more likely paroxysmal likely reflecting closer follow-up and the incidence is significantly higher than that projected from similar age-based general populations. Forty two percent of HCM patients with paroxysmal AF at presentation progress to chronic AF. In one study, the average progression time from paroxysmal to chronic AF was 5 years. Occurrence of AF increased progressively with age and was predominant in patients >60 years of age. Strong predictors of AF in HCM included age, functional class, left atrial size.

It is not surprising that AF is much more common in patients with HCM. These patients have various degrees of left ventricular hypertrophy and diastolic dysfunction, left atrial enlargement, and atrial fibrosis. An interesting observation was the atrial fibrosis present in HCM is often out of proportion to the degree of heart failure present and is similar in extent to that observed non-HCM patients with advanced heart failure. An area that requires further study is if atrial myofibril disarray is due to the ventricular disease only and if it is this atrial myofibril disarray that places patients at increased risk of AF. Similarly, little is known regarding the myocardial anatomic structure of the pulmonary vein ostia in HCM patients. Investigation into the genetic risk of an atrial myopathy and sarcomeric protein mutations in the atrium may help identify patients at early risk of AF.

An interesting finding is that dynamic outflow

<table>
<thead>
<tr>
<th>Medication</th>
<th>Class</th>
<th>Summary</th>
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<tr>
<td>Disopyramide</td>
<td>Ia</td>
<td>Unclear efficacy in the treatment of AF in patients with HCM. Improves outflow tract obstruction and symptoms in HCM. Side effects are common</td>
</tr>
<tr>
<td>Sotalol</td>
<td>III</td>
<td>Short-term efficacy for supraventricular arrhythmias in HCM. Exercise tolerance improvement. No observed toxicities in limited trial data</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>III</td>
<td>Long-term efficacy for AF. Reduces embolic rates and cardioversions in a small study. Long-term toxicities are well known. Lower doses may allow long-term use if side effects develop</td>
</tr>
<tr>
<td>Dofetilide</td>
<td>III</td>
<td>No available data in patients with HCM</td>
</tr>
<tr>
<td>Dronedarone</td>
<td>III</td>
<td>No available data in patients with HCM. Avoid in patients with advanced systolic failure. Unclear safety in patients with advanced diastolic failure</td>
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obstruction in HCM does not predict AF. These data that suggest that patients likely need an atrial predisposition coupled with the ventricular cardiomyopathy to develop early atrial arrhythmias.

Impact of AF in HCM

The occurrence of AF represents an important clinical turning point in a HCM patient and has significant impact on quality of life and mortality with both short and long term consequences. In a case series of 52 patients with HCM and new onset AF, the acute onset of AF was associated with worsening of symptoms in 89% of patients and 93% of patients reverted to their original symptom class after either rhythm restoration or rate control.

The impact of AF has been well studied in a large community based HCM study involving 480 patients that were followed up for 9.1 years. AF developed in 107 patients during this period. AF onset was associated with new or worsening clinical manifestations in 84% of the 107 patients. Clinical manifestations included dyspnea, chest pain, and functional deterioration in a majority of patients as well as severe symptoms of heart failure, pulmonary edema, impaired consciousness and syncope in others. In this study, 74 patients died of HCM-related causes, including 38 (35%) among the 107 AF patients (sudden death in 13, heart failure–related death in 17, and stroke-related death in 8). AF was associated with markedly increased risk for HCM-related death (3% versus 1%, p=0.001) when compared to patients in SR and was explained by an excess stroke- and heart failure–related mortality (p=0.001). There was increased incidence of Ischemic strokes among AF patients than among those in sinus rhythm (21% versus 2.6%, OR 17.7), causing death in 8 patients and permanent disability in 11. Also patients developing AF before 50 yrs of age were at greater risk of strokes. Similar increase in stroke risk was also noted in HCM patients with AF.

Similar findings were noted in an epidemiological study involving 744 consecutively enrolled
and largely unselected patients across 3 centers followed up for 8 years. HCM-related death occurred in 86 patients (12%, sudden and unexpected in 51% of these patients), progressive heart failure (36%), and HCM-related stroke associated with AF (13%). Data from these studies highlight the profound impact of AF in these setting of HCM as it relates to both morbidity and mortality. Although unknown, these findings suggest that efforts to maintain sinus rhythm may improve outcomes by favorably impacting disease related morbidity and mortality.

Treatment of AF in HCM patients

Therapeutic options in HCM patients with AF are similar to those for patients without HCM. However, due to the association between AF and progressive HF symptoms, mortality, and stroke, an aggressive approach to the maintenance of sinus rhythm is often preferred.

There exists a paucity of data to guide antiarrhythmic therapy in patients with HCM (Table 1). There are no systematic randomized trials to compare the efficacy and safety of these medications and the information available is largely gleamed from observational studies of a single drug.

Amiodarone

Due to often significant left ventricular hypertrophy and the potential for proarrhythmia, class III antiarrhythmic medications are often used. Of these agents, amiodarone is effective and often used despite a relatively young population. In a case series of 52 consecutive patients with HCM, 46 developed AF and sinus rhythm was restored in 29 patients (63%) with amiodarone. Of these patients, sinus rhythm was maintained in 22 of 29 patients during a 5.5 year follow up period. Over this follow-up period, patients who were treated with amiodarone had fewer alterations in drug therapy, less embolic episodes, and required less cardioversions. In another small study with 53 patients with HCM, amiodarone successfully
treated paroxysmal AF/supraventricular tachycardia in 8/9 patients without provocation of ventricular arrhythmias over a 27 month follow-up period. In this study, Amiodarone was discontinued in 3 patients secondary to side effects, but was re-started later at a lower dose and was well tolerated. However extrapolation of known side effects of amiodarone that are dose and duration dependent from other AF populations makes use of this medication long term in the young HCM patients concerning.

Sotalol

Sotalol may also be helpful in preventing AF in HCM patients. In a small study of 30 patients, sotalol eliminated supraventricular arrhythmias in 6 of 7 patients and suppressed ventricular arrhythmias in 7 of 13 patients. As important, 25 patients had better exercise tolerance on sotalol than on placebo. At a 6 month follow-up period the anti-arrhythmic medication remained effective. In one patient, sotalol induced bronchospasm and had to be discontinued.

Disopyramide

Disopyramide is a class Ia antiarrhythmic medication that is negatively inotropic. Disopyramide was first used for patients with obstructive HCM in 1982 largely due to its’ effects on inotropy. Disopyramide has been shown to provide symptomatic benefit (at 300 mg to 600 mg per day with a dose-response effect) by reducing systolic anterior motion of the mitral valve, outflow obstruction, and mitral regurgitant volume. Disopyramide has been recommended to be used in conjunction with a low dose beta blocker as it may be potentially pro-arrhythmic by accelerating AV nodal conduction and increasing the ventricular rate in AF. However, disopyramide use in a large multicenter trial of 188 patients with obstructive HCM, 66% of the patients had a 50% reduction in outflow gradient with amelioration of symptoms that was maintained over 3 years and did not increase the risk of sudden cardiac death. However, anticholinergic side effects with disopyramide were common in this study and consisted of constipation (11%), xerostomia (32%), and urinary delay/retention (23%). Unfortunately, in non-HCM populations the long-term maintenance of sinus rhythm with disopyramide is poor, a finding that is likely worse in patients with HCM with co-existent diastolic dysfunction.

New class III antiarrhythmics such as dofetilide and dronedarone may also have utility in the treatment of AF in HCM patients, although their clinical efficacy and safety in this population is not known. Due to the significant limitations of current antiarrhythmic medications in patients with HCM, coupled with the consequences of atrial tachyarrhythmias in HCM, there exists a significant need to define new pharmacologic and nonpharmacologic approaches.

Percutaneous Catheter AF ablation

Catheter ablation with pulmonary vein isolation to treat AF is being performed with increasing frequency and safety. The technique has emerged as a first-line therapy in medically-refractive AF and in one trial was an effective initial treatment compared to medication. In a recent comprehensive systemic review of 63 studies that examined both ablation and antiarrhythmic medications for treatment of AF, the single-procedure success rate of ablation off all antiarrhythmic therapies was 57% and for multiple procedures the success rate increased to 71%. In comparison, the success rate for antiarrhythmic therapies at 1 year was 52%. Of interest, major complications with catheter ablation occurred in 4.9% of patients compared to a rate of 30% of adverse, but less severe, events that occurred with drug therapy. The primary objectives of catheter ablation are to eliminated triggers of AF and modify the underlying substrate that is responsible for arrhythmia maintenance. Often the procedure requires extensive ablation in the left atrium particularly in those with extensive substrate or chronic AF.

Catheter ablation for treatment of AF in patients with HCM has been reported from multiple centers. The procedural success rates vary greatly from the different centers from 45-79%. The variance in reported outcomes from these multiple centers likely is due to patient characteristics, inclusion of patients that had prior ablations, technique approach, and the follow-up duration. In aggregate, there appears to be additive benefit in a more aggressive ablative strategy in those
with more advanced disease (Figure 2). Unfortunately with broad variance in ablation strategy, the optimal approach still needs to be defined. We advocate a stepwise approach with more aggressive linear ablation in those with chronic disease, severe left atrial enlargement, or presentation with prior ablation attempts. In understanding the importance of aggressive rhythm control attempts, in our study, one of the most prominent findings was the significant improvement in quality of life that was sustained over the follow-up period after catheter ablation. This finding reflects not only the procedure as a whole, but the highly symptomatic state of HCM patients with AF.

Given the variable results with catheter ablation we previously tried to understand if echocardiography characteristics and/or progression of diastolic disease helped determine outcomes. The presence of diastolic function and severe left atrial enlargement were associated with worse outcomes. As important, in those patients with advanced diastolic disease and chronic AF the procedural approach impacted outcomes. This finding is reflective of the significant atrial arrhythmia substrate with HCM. If patients had severe left atrial enlargement, advanced diastolic dysfunction, or chronic AF additional linear ablation was required to obtain favorable outcomes as well as multiple ablative attempts (Figure 3). Recently atrial strain has emerged as an intriguing technique to evaluate atrial function. Strain may be additive in understanding atrial myopathy and assist in atrial ablation approach. Most of these HCM patients will require more aggressive ablation approaches as left atrial enlargement and diastolic dysfunction are common. For AF ablation in general, an area that requires study is the long-term effects of aggressive ablation on atrial transport function. In patients highly dependent on the atrial contraction component of ventricular filling, loss of transport may impact quality of life and disease-related morbidity significantly. As we do not understand the long-term consequence of aggressive ablation, a stepwise approach may be preferable to minimize extent of ablation if possible especially in young patients with HCM.

Another area that requires further study is the underlying atrial anatomy in patients with HCM and if this contributes to outcomes. Unfortunately, most of the pathologic data revolves around the ventricular cardiomyopathy. Understanding the anatomy further will help in choice of ablation tools, duration of energy delivery, endpoints sought, and strategy.

**Surgical AF ablation and Maze procedure**

There are less data available regarding surgical based antiarrhythmic procedures in HCM patients. It is unclear if surgical myectomy will favorably impact long-term risk of AF. The impact of the surgical approach, if apparent, will likely require long-term investigation as the presence or severity of an outflow tract gradient does not appear to be associated with an increased incidence of AF. In one small case series of septal alcohol ablation, 3 patients had improvement of AF burden after the procedure.

The surgical Maze procedure, similar to catheter ablation, provides an effective nonpharmacologic approach. In a case series of 10 patients that underwent a combination Maze III procedure and myectomy, 80% were in sinus rhythm at a mean of 15 months. Complications in the relatively higher risk cohort were higher than with catheter ablation in that two developed complete heart block requiring a pacemaker and one died 3 months later due to ventricular fibrillation.

There are no case series to understand the efficacy of a surgical minimally invasive Maze procedure in patients with HCM. This procedure is a potentially attractive option as the left atrial appendage can be removed. Likely the ablation approach, whether with cryothermal or radiofrequency energy sources, will need to be extensive, similar to the catheter-based approaches, in order to treat all the arrhythmia substrate.

**Rate control**

Beta blockers, nondihydropyridine calcium channel blockers or both are usually used to treat the ventricular rate. Digoxin can increase inotropy which may exacerbate heart symptoms in patients with HCM that have preserved systolic function. In patients that have refractory AF with rapid ventricular rates, atrioventricular node ablation and permanent pacing is an alternative.

Unfortunately, patients with HCM have various levels of diastolic dysfunction that progresses in
Patients with HCM are at high risk of developing AF particularly in the setting of advanced diastolic dysfunction and left atrial enlargement. AF is a marker of increased mortality and morbidity and results in a significant reduction in quality of life. Antiarrhythmic medications improve symptoms and reduce AF recurrence, but few are safe and there exists little data to guide their long-term use in HCM. Non-pharmacologic approaches have emerged and have equal or greater efficacy than pharmacologic approaches. Although these approaches are promising, the long-term impact on atrial function needs to be carefully studied as it may impact quality of life in patients that age in the setting of a progressive diastolic disease disorder. Nonetheless, with the significant impact of AF in HCM, rhythm control strategies that are often aggressive with associated risk are required. The understanding of rhythm control strategies in HCM, an often rapidly progressive diastolic dysfunction disorder, may provide insight in how to treat the much more prevalent AF patient with hypertensive cardiomyopathy.

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Thrombo-embolism prevention

Ischemic strokes occur up to eight times more frequently with AF in HCM than in sinus rhythm. The risk of stroke increases with age; in the Framingham Study, the annual risk of stroke attributable to AF increased from 1.5% in participants aged 50 to 59 years to 23.5% for those aged 80 to 89 years. In HCM, the risk of AF is higher with an incidence of 2%/yr and prevalence of 22%. In another large community based cohort of 900 patients with HCM, the overall incidence of stroke and peripheral arterial embolic events was 0.8%/year and 1.9% for patients >60 years. As expected, the cumulative incidence of these events was significantly higher in non-anticoagulated patients as compared with patients on warfarin (31% vs. 18%; p < 0.05). HCM patients who develop AF should be considered to be at moderate to high risk and should be anticoagulated with warfarin. Further study is required to understand if aggressive measures to keep patients in SR decrease stroke risk in the setting of anticoagulation.

With emerging advances and successes of non-pharmacologic approaches to restore sinus rhythm, there arises the question of discontinuing warfarin anticoagulation. The recent Heart Rhythm Society guidelines conclude that the long-term use of warfarin anticoagulation should be based upon the underlying patient risk. Patients with HCM are now low risk, a profile that would suggest they can be effectively and safely treated with aspirin only. Given, their baseline moderate risk status, warfarin should be continued until data are available to suggest otherwise or the risk of bleed is greater than the risk of stroke based upon the presented epidemiologic studies.

Conclusion

Patients with HCM are at high risk of developing AF particularly in the setting of advanced diastolic dysfunction and left atrial enlargement. AF is a marker of increased mortality and morbidity and results in a significant reduction in quality of life. Antiarrhythmic medications improve symptoms and reduce AF recurrence, but few are safe and there exists little data to guide their long-term use in HCM. Non-pharmacologic approaches have emerged and have equal or greater efficacy than pharmacologic approaches. Although these approaches are promising, the long-term impact on atrial function needs to be carefully studied as it may impact quality of life in patients that age in the setting of a progressive diastolic disease disorder. Nonetheless, with the significant impact of AF in HCM, rhythm control strategies that are often aggressive with associated risk are required. The understanding of rhythm control strategies in HCM, an often rapidly progressive diastolic dysfunction disorder, may provide insight in how to treat the much more prevalent AF patient with hypertensive cardiomyopathy.


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Introduction

Atrial fibrillation (AF) is the most common arrhythmia encountered in clinical practice, accounting for approximately one third of hospitalizations for cardiac rhythm disturbances. AF is characterized by seemingly disorganized atrial electrical activity without effective atrial contraction. It was once thought that all AF was caused by a single mechanism of multiple wavelets propagating in random fashion throughout the atria. According to the multiple-wavelet hypothesis, fractionation of wavefronts propagating through the atria results in self-perpetuating “daughter wavelets.” Simultaneous recordings from multiple electrodes supported the multiple wavelet hypothesis in human subjects. However, it has become apparent that there are likely other mechanisms underlying AF. In many patients, AF is caused by a focal discharge at rapid rates. A focal origin of AF was originally supported by experimental models of aconitine and pacing-induced AF, in which the arrhythmia persists only in isolated regions of atrial myocardium. This theory received minimal attention until the important observation that a focal source for AF could be identified in humans and ablation of this source could extinguish AF. The observation that AF could be initiated by ectopic beats originating in the pulmonary veins (PVs) sparked new interest in the focal catheter-based techniques to isolate the PVs from the surrounding left atrium. Initial attempts to identify and ablate the PV foci directly were only moderately successful and were associated with frequent recurrences of AF and a significant risk of PV stenosis. The efficacy and safety have improved using PV electrical isolation coupled with the use of three-dimensional electro-anatomic mapping systems, intracardiac echocardiography (ICE) and special mapping catheters. ICE imaging has become an important player in AF ablation. It guides transseptal catheterization, confirms

Abstract

Radiofrequency catheter ablation of pulmonary veins has emerged as an effective therapy for patients with symptomatic atrial fibrillation. Advances in real-time intracardiac echocardiography with 2D and Doppler color flow imaging have led to its integration in atrial fibrillation ablation procedures. It allows imaging of the left atrium and pulmonary veins, including identification of anatomic variations. It has an important role in guiding transseptal catheterization, imaging the pulmonary vein ostia, assisting in accurate placement of mapping and ablation catheters, monitoring lesion morphology and flow changes in the ablated pulmonary veins, hence allowing titration of energy delivery. Importantly, it allows instant detection of procedural complications.
Figure 1 ICE-guided transseptal puncture.
These ICE images, with the transducer placed in the right atrium (RA), show (a) a transseptal needle (arrow) tenting the interatrial septum at the fossa ovalis; (b) Advancement of the transseptal needle tip to the left atrium (LA) was then performed. After confirmation of optimal position in the LA, a sheath (arrow) was advanced over a wire to the LA.

Figure: 1B
the accurate placement of mapping and ablation catheters, images the PV ostia, and assists in the early detection of procedural complications.

**Intracardiac Echocardiography**

Over the past 30 years, electrophysiological procedures have been performed almost exclusively under fluoroscopic guidance. Although, two-dimensional “cardiac silhouette” imaging correlates reasonably well with cardiac anatomy, it requires substantial operator experience. Moreover, the increased complexity of some ablative procedures requires more accurate imaging tools. Although,

**Figure: 2** ICE images of the pulmonary veins. ICE images with the transducer placed in the right atrium, showing: (a) right upper (RUPV), middle (RMPV), and lower (RLPV) pulmonary veins; (b) separate left upper (LUPV) and lower pulmonary vein (LLPV) ostia; (c) color flow directed to the left atrium from the separate left pulmonary vein ostia; (d) Pulsed Doppler spectrum recording of the left upper pulmonary vein ostium with systolic and diastolic components.
transesophageal echocardiography has been used for such cases, it carries major disadvantages, including prolonged placement requiring heavy sedation, and the risk of vagal nerve stimulation. ICE allows visualization of the heart from within the cardiac chambers or from within the great vessels. Catheter-based ICE has advanced from devices bearing single-element transducers and M-
mode transducers to current technology, which allows for higher resolution two-dimensional imaging with wave Doppler and color flow evaluation of blood vessels and intracardiac structures. This technology was initially limited due to the large size of the lower frequency ICE catheters. Over the past 20 years, technology has progressed with the advent of low frequency (12.5–9 MHz, 9 Fr) transducers allowing enhanced tissue penetration and higher resolution. More recently, a 5.5-10MHz, 9 Fr electronic phase-arrayed ultrasound catheter with pulsed/continuous-wave Doppler and color flow imaging has been developed. This ultrasound catheter has a flexible tip that provides higher resolution and deeper penetration of the left side of the heart from the right atrium.

### Transseptal Catheterization

Mapping and ablation in the left atrium are performed through a transseptal approach. Intracardiac echocardiography provides the best available imaging tool for guiding transseptal catheterization. Patients undergoing AF ablation typically need dual transseptal catheterization (8Fr sheaths). Knowledge of the septal anatomy and its relation ship to adjacent structures is essential for safe and effective access to the left atrium. The true interatrial septum is limited to the floor of the fossa ovalis, flap valve, and anteroinferior rim of the fossa.6 Many apparent septal structures are not truly septal, and inadvertent puncture of some septal structures can lead to perforation of the lateral wall of the left atrium or aortic root. These potentially lethal complications can occur even with the most experienced operator. The challenge for a successful atrial septal puncture is positioning the Brockenbough needle at the thinnest aspect of the atrial septum. ICE provides excellent views of the fossa ovalis and of the transseptal apparatus. Utilization of ICE in conjunction with fluoroscopy allows the electrophysiologist to clearly identify the interatrial septum and adjacent structures. When advanced in the right atrium, the catheter provides a cross-sectional view of the fossa ovalis. It allows checking the position of the Brockenbough needle and the Mullins sheath in the middle of the fossa ovalis and tenting of the membranous septum at the time of fossa ovalis puncture [figure 1].7,8

### Imaging the Pulmonary Vein Ostia

Ablation of AF requires accurate anatomical information of the PVs. The PVs can have variable anatomy, with most heart examined found to have four PVs with discrete ostia, however the remainder (approximately 25%) having a common ostium, either on the left or on the right. The right PV generally has upper, middle, and lower pulmonary veins, with the right upper and middle PVs sharing a common ostium separated from the lower right PV by a carina. The PV ostia in patients with AF tend to be ellipsoid with longer superoinferior dimension, and funnel-shaped ostia.9 ICE provides detailed imaging of the pulmonary veins including ostial diameter, which can assist in selection an appropriately-sized circular multipolar mapping catheter [figure 2].

### Guiding Position of Catheters at the PV Ostia

After successful transseptal catheterization, the circular multipolar mapping catheter and the mapping/ablation catheter are advanced through the sheaths into the different PV ostia. ICE helps to optimally position the catheters in place. Based on the size measured with ICE Doppler color flow imaging, an appropriate circular multipolar catheter is placed on either an individual ostium or a common one. When the common ostial diameter is larger than that of the circular mapping catheter used, the latter can be positioned at the upper portion of the ostium and then moved to the lower portion under ICE imaging guidance. ICE imaging also confirms that delivery of radiofrequency energy via the ablation catheter occurs proximal to the multipolar mapping catheter and not inside the PV.

### Changes in Ostial PV flow Velocity

Doppler color flow imaging has been effectively used for monitoring pulmonary vein ostial narrowing during AF ablation.10 Peak flow velocity at the pulmonary vein ostium is measured at systole and diastole before and after ablation [figure 2D]. The ultrasound beam should be within 1 cm of the PV ostium, and the pulsed Doppler sampling gate should be parallel to the PV ostium. The peak pressure gradient can be estimated us-
ing the simplified Bernoulli equation (ΔP = 4V²). An increase in flow velocity greater than 100 cm/sec warrants redirection of the ablation lesions to a more proximal zone. In our early experience, radiofrequency energy was deployed at a total of 219 PV ostia and changes in PV ostial peak flow velocities and pressure gradients were measured. The peak velocity of PV ostial flow measured 56 ± 12 cm/sec (range 21-98) before and 101 ± 22 cm/sec (range 47-211) after ablation (p<0.001). Turbulent flow features with spectral broadening of Doppler signal recorded at the ablated PV has been observed when the peak velocity was greater than 130 cm/sec [figure 3]. Patients with an acute rise in PV flow velocities following ablation were followed for a period of six to eighteen months. Periodic clinical evaluations for symptoms of PV stenosis (dyspnea, exercise intolerance) were corre-

Figure: 4A Pericardial effusion. These ICE images with the transducer placed near the tricuspid valvular orifice in the right ventricle, showing the interventricular septum (IVS), left ventricular (LV) wall and pericardium (arrow); (b) ICE image of a moderate pericardial effusion (arrow, echo-free space) surrounding the LV free wall.
robated with magnetic resonance imaging (MRI) or contrast-enhanced computed tomography. The study showed that an acute increase in the PV ostial peak flow velocity of up to 158 cm/sec (estimated pressure gradient ≥10 mmHg) appears to be well tolerated. It is our practice to conduct ablation lesions when the peak PV flow velocity change is less than 100 cm/sec. However, a flow velocity change of more than 100 cm/sec will warrant a more proximal approach to lesion deployment. Interestingly, in the majority of patients, the acute rise in PV ostial velocities probably reflects tissue edema, as we noted almost complete reversibility in PV velocities in the subset of who returned for a second ablation procedure.

Monitoring ostial flow velocity during repeated ablation at previously ablated pulmonary veins is also critical. We have previously reported the outcome of our first 13 patients undergoing repeat AF ablation procedure. There were two patients with PV flow velocities >100 cm/sec before subsequent ablation. Following subsequent ablation, in three PV, velocities greater than 158 cm/sec were recorded. In one patient, the left upper PV flow velocity increased from 116 to 194 cm/sec. In another patient, the left upper PV flow velocity increased from 118 to 172 cm/sec and the left lower PV from 83 to 176 cm/sec. In these two patients, MRI was performed at 2 and 4 months after ablation, demonstrating mild to moderate PV stenosis (50–60%). The patient with two PV velocities greater than 158 cm/sec developed exertional dyspnea at 4 months. The second patient had no symptoms or progression of PV stenosis with late MRI imaging. No patient with PV flow velocity < 158 cm/sec has been found to develop symptoms consistent with PV stenosis after a repeat ablation procedure.

The typical Doppler color flow imaging in PV stenosis is characterized by increased ostial PV peak flow followed by a blunted systolic velocity and prolonged and elevated diastolic velocity, resulting in a fused systolic and diastolic components and long pressure half-time.

Isoproterenol infusion is one of the most useful provocative maneuvers for potentiating firing of both PV and non-PV triggers of AF. The effect of isoproterenol on PV flow before and after AF ablation has been studied using ICE with Doppler color flow imaging. This study showed that isoproterenol increases ostial peak flow velocity of both pre-ablated and ablated PVs. Moreover, this effect of isoproterenol appears to be independent of the heart rate effect since atrial pacing at similar rates had no effect on PV flow velocities. However, although isoproterenol leads to higher peak velocity, the pulsed Doppler imaging shows separate systolic and diastolic velocity components with normal pressure half-time. These isoproterenol effects are important to recognize, especially when the peak velocity of PV flow is used as an index of ostial PV stenosis. The clinical implication is that an “isoproterenol effect” on PV ostial flow could potentially be misinterpreted as clinically significant PV stenosis.

Morphological changes of ablation lesions

ICE provides tissue imaging of morphologic changes induced by radiofrequency energy. These changes include tissue swelling, dimpling, crater formation, accelerated bubbles before popping, like lesion development, and increased echogenicity during or immediately after lesion deployment. The left atrial wall thickness can also be assessed with 2D or M-mode imaging. Based on real-time ICE monitoring of lesion development, titration of energy power and/or duration can control lesion formation and prevent tissue overheating or structural perforation. The ligament of Marshall is occasionally an important trigger for AF, and may therefore be a target for ablation. The thickness of the ligament of Marshall is usually greater than the surrounding tissue, and therefore has greater echogenicity, enhancing its identification with ICE.

Monitoring for Complications

ICE imaging is a valuable tool for early detection of complication during AF ablation procedures and consequently allows earlier intervention. Moreover, the recognition of certain complications has paved the way to changes in anticoagulation and power titration protocols. Potential complications include those occurring during transseptal catheterization and left heart mapping and ablation. The major potential complications detected by ICE during left heart ablation include:
Pericardial Effusion and Tamponade

Pericardial effusion is one of the most serious complications associated with catheter ablation for AF. It may occur immediately after transseptal catheterization, during catheter manipulation and ablation and after withdrawal of a coronary sinus catheter. ICE allows early detection of pericardial effusion [figure 4]. This is usually detected along the inferior border of the RV and posterior LA. Early detection allows early intervention with pericardiocentesis and

Damage to Cardiac Structures

Inadvertent manipulation of the catheter during transseptal catheterization or mapping/ablation may cause damage to adjacent non-targeted structures, such as aorta, left atrial appendage, mitral valve, and left atrial wall. As mentioned above, ablation radiofrequency energy may cause intramural superheating and a “crater” lesion during ablation.

Figure: 5A I. Visualizing Thrombi ICE images of the left atrium, showing: (a) a thrombus (arrow) formed at the superior aspect of the right upper pulmonary vein following an ablation lesion; (b) a large thrombus is visualized at the left atrium, extending from the pulmonary valve to the septal leaflet of the tricuspid valve.

Figure: 5B
continuous monitoring of re-accumulation during the drainage process.

Left atrial Thrombus Formation

Atrial thrombus formation has been recognized as one of the major complications during atrial ablation procedures. These thrombi are usually single, linear, and mobile, and are typically attached to the transseptal sheath, and less commonly to the circular mapping or ablation catheters [figure 5]. The incidence of left atrial thrombus formation during left atrial ablation has been reported as high as 10.3% when anticoagulation is maintained at a target activated clotting time of 250–300 sec. In 90% of patients with ICE detected left atrial thrombus, successful withdrawal of the thrombus attached catheter/sheath from the left atrium into the right atrium has been reported to prevent serious systemic embolic consequences. Increased anticoagulation with an activated clotting time ≥350 sec reduces the risk of left atrial thrombus formation during ablation procedures for AF.

Pulmonary Vein Stenosis

One of the most serious complications of AF ablation is the development of PV stenosis. ICE Doppler and color flow imaging are used to accurately evaluate and monitor the flow velocities and pressure gradients before and after ablation lesions [figure 3]. As mentioned above, significant ostial PV stenosis is morphologically characterized by swelling and enhanced echogenicity. Color Doppler may demonstrate turbulence flow, and spectral Doppler shows increased ostial PV peak flow followed by a blunted systolic velocity and prolonged and elevated diastolic velocity, resulting in a fused systolic and diastolic components and long pressure half-time.

Esophageal Injury

The esophagus is contiguous with the thin posterior wall of the left atrium. With the advance in catheter design and higher energy delivery, esophageal injury, with or without left atrio-esophageal fistula, has been described and associated with high mortality rate. Radiofrequency lesions in the posterior and lateral aspect of the right lower PV or posterior and medial aspect of the left PV are within immediate proximity to the esophagus. ICE real-time imaging monitoring of the posterior atrium and esophagus during radiofrequency energy delivery may reduce the risk of

Figure: 3 Pulsed Doppler recorded peak flow velocity of the left superior pulmonary vein (LSPV) ostium shows the maximal velocity measured 50 cm/s with two systolic components (S) as well as early diastolic (D) before ablation (a). Following ablation, the ostial peak flow velocity increased to 134 cm/s (b).
ICE has emerged as an extremely useful tool during electrophysiology procedures. In particular, ICE plays a valuable role in left heart mapping and ablation procedures, and has become standard in AF ablation procedures. It provides real-time imaging of the complex anatomy of the left atrium and PVs, guides transseptal catheterization, assists in accurate placement of mapping and ablation catheters, and monitors lesion morphology and flow changes in the ablated PV. ICE allows early detection of procedural complications, facilitating timely and effective therapy.

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Role of Inflammation in Early AF Recurrence after PV Isolation

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Introduction

Recently, there has been a great deal of interest in the mechanistic role of inflammation in the initiation, maintenance, and perpetuation of atrial fibrillation (AF) 1, 2. Several studies have focused on inflammatory biomarkers and acute-phase proteins to further understand the inflammatory milieu in relation to AF. These studies have demonstrated that both interleukin-6 (IL-6) and C-reactive protein (CRP) are elevated in paroxysmal and persistent AF 3, 4, 5. Chung et al. [4] demonstrated an association between elevated CRP levels and AF in a nonoperative setting. In this study, CRP levels were more than 2-fold higher in patients with AF than in control subjects. Moreover, patients with persistent AF had higher CRP levels than patients with paroxysmal AF, suggesting that inflammation may be more relevant to promoting AF maintenance than its initiation. Similarly, Dernellis and Panaretou 6 demonstrated CRP elevation in patients with paroxysmal AF and that CRP levels were higher in the subgroup that failed pharmacologic cardioversion with amiodarone. Lower CRP levels have been associated with successful cardioversion and maintenance of sinus rhythm. Sata et al. 7 measured inflammatory markers at different time intervals pre and post cardioversion in 15 patients with paroxysmal AF and found that CRP, IL-6, and tumor necrosis factor (TNF-α) were significantly elevated when compared to controls and remained elevated for up to 2 weeks after cardioversion. Although this study was small, the authors suggested that inflammation played a role in the initiation of AF. Whether an increase in inflammatory markers is a cause or a consequence of AF, there is a clear association between the two processes and growing interest in developing therapeutic options to modulate the inflammatory state.

Early recurrence of atrial arrhythmias after pulmonary vein isolation is common and does not necessarily indicate failure of the procedure. 8, 9

Though, there is data to support that early recurrence of AF is associated with a lower long-term success rate. 10, 11 It is not clear how to manage patients with early recurrence after AF ablation and thus, there is uniform interest in developing treatment strategies to deal with this subset of patients, including reablation and/or medications. A recent consensus document on catheter and surgical ablation of AF 12 suggested a blanking period of at least three months in regards to repeat ablation. The document did state that symptomatic, atrial arrhythmias after ablation are difficult to treat with medications and patients are best managed with repeat ablation. Lellouche et al. 13 looked at an early reablation strategy to deal
with early recurrences after AF ablation. The authors found that an early reablation strategy had a lower rate of clinical recurrences, but an overall higher number of ablation procedures compared with patients without an early second ablation, suggesting that the optimal timing for the second procedure remains to be defined.

It is unclear if inflammation plays a role in contributing to the early recurrence of atrial arrhythmias after ablation or if these arrhythmias are secondary to recovery of conduction in a previously isolated PV, incomplete PV isolation, or non-PV arrhythmogenic foci and therefore, a marker of late recurrence. An interesting paper by Koyama et al. 14 in the American Journal of Cardiology entitled “Comparison of Characteristics and Significance of Immediate Versus Early Versus No Recurrence of Atrial Fibrillation After Catheter Ablation” sheds light on this topic. The objective of this study was to clarify the relationship between the inflammatory processes related to catheter ablation and recurrence of AF after ablation and to characterize AF recurring within three days after ablation (immediate-AF-recurrence). In this study, 186 patients with symptomatic, paroxysmal AF, who were refractory to medications, underwent extensive pulmonary vein isolation by a double lasso technique. The end point of ablation was bidirectional, pulmonary vein block and no AF induction lasting > 3min with decremental burst pacing from the coronary sinus to a cycle-length of 180ms on isoproterenol. Specific attention was paid to symptoms, physical findings, and data relative to an inflammatory response within the first three days after ablation. The variables measured included body temperature (BT) and C-reactive Protein (CRP). During the first three days after ablation, patients were monitored for pericarditis, which was confirmed by ECG diagnosis and echocardiography, and any evidence of frequent atrial premature contractions or nonsustained AF. Successful ablation was defined as the absence of AF on no antiarrhythmic drugs (AAD) after a six-month follow-up period.

Patients were divided into immediate-AF-recurrence (within 3 days), early-AF-recurrence (4-30 days) and no AF recurrence groups following ablation. During the initial one-month follow-up period, 45 patients (24%) were in the immediate-AF-recurrence group, 27 patients (14%) were in the early-AF-recurrence group, and 114 patients (61%) were in the no AF recurrence group. In the first 3 days after the ablation procedure, the immediate-AF-recurrence group had the highest body temperature, greatest change in body temperature, highest CRP level, and greatest change in CRP level from baseline compared to the early-recurrence and no recurrence groups. Nonsustained AF and frequent atrial premature contractions were more prevalent in the early-AF-recurrence group compared to the immediate- AF-recurrence and no AF recurrence groups. It is important to note that recurrent AF episodes in the immediate-AF-recurrence group were decreased at the 1 and 6 month follow-up visit. In the immediate-AF-recurrence, 45 patients had recurrent AF in the first three days post ablation, which decreased to 10/45 patients and 11/45 patients at 1 and 6 months of follow-up respectively. In contrast, the prevalence of AF recurrence was > 70% at 1 and 6 months in the early-AF-recurrence group.

In this study, the AF-free rate after 6 months of follow-up was greater in the immediate-AF-recurrence group (76%) than in the early-AF-recurrence group (30%). The authors concluded that immediate- AF-recurrence was associated with an acute inflammatory response after ablation with a high BT, increased CRP levels, and signs and symptoms of pericarditis. In most cases, AF recurrence in the immediate-AF-recurrence group resolved spontaneously within 1 month and AF freedom persisted at 6 months, indicating that immediate- AF-recurrence may have a different mechanism than early-AF-recurrence. In contrast, an early- AF-recurrence (4-30 days) was the most powerful predictor of AF recurrence at the end of the 6 month follow-up period and suggested a different mechanism for AF recurrence: recovery of conduction between the pulmonary veins and the left atrium or the presence of non-pulmonary vein foci.

This study introduces an interesting concept: AF recurrence in the setting of an acute inflammatory response. The majority of patients in the immediate- AF-recurrence group did well at the 6-month follow-up and did not require repeat ablation. Thus, it would have been wrong to assume failure in this select group and from this study, it is apparent that immediate-AF-recurrence had different characteristics than early-AF-recurrence. Nicther
et al. \textsuperscript{15} recently published a study on the prognostic value of early AF recurrence within 48 hours after ablation and its impact on long-term outcome. This study included both paroxysmal and persistent patients using two, different ablation strategies and pulmonary vein entrance block as the endpoint of ablation. Although the authors found that early recurrence of AF within 48 hours after ablation was a significant predictor of a poor long-term ablation outcome, they noted that 46\% of patients with early AF recurrence were AF free during long-term follow-up. These two studies support the concept of an acute inflammatory process at work, which may confer a benefit in the overall outcome as the healing process occurs.

Richter et al. also looked at the use of statins, angiotensin-converting enzyme inhibitors, and angiotensin II receptor blockers in relation to ablation outcome and found that none of these medications resulted in an improved ablation outcome. \textsuperscript{16} Roux et al. recently studied the use of antiarrhythmics after ablation of atrial fibrillation (5A Study). \textsuperscript{17} This study randomized patients with paroxysmal AF undergoing ablation to empiric versus no antiarrhythmic drug (AAD) therapy for the first six weeks after ablation and found that AAD therapy reduced the incidence of clinically significant atrial arrhythmias and need for cardioversion.

In summary, the concept of an acute inflammatory response in relation to early recurrence supports an extended blanking period after the initial ablation procedure. The data from Koyama et al. \textsuperscript{14} suggest that immediate recurrence of AF after ablation may be related to an inflammatory response and that conservative treatment in this group, until the inflammatory state subsides, is prudent. AAD therapy after ablation should be encouraged in the group with immediate recurrence of AF in the short-term. While conservative treatment is also reasonable for patients with early AF recurrence, one should be vigilant for late AF recurrence in this subgroup of patients and have a low threshold for repeat ablation if AF persists. Additional prospective clinical trials utilizing anti-inflammatory treatment after ablation seems warranted to determine if modification of the inflammatory state will diminish early AF recurrences after ablation.

References


