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Intracardiac ECHO Integration with Three Dimensional Mapping: Role in AF Ablation

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Abstract

Background
Catheter ablation of atrial fibrillation (AF) is typically guided by 3D mapping. This involves point-by-point reconstruction of the 3D virtual anatomy and may be time consuming and require substantial fluoroscopy exposure. Intracardiac echocardiography (ICE) affords real time imaging of the cardiac structures during mapping and ablation.

Methods
Between February and May 2007, 15 patients (100% men, 10 with paroxysmal AF) presenting for AF ablation were offered mapping using a novel system integrating 3D mapping and ICE. A modified ICE probe with a location sensor tracked by the mapping system was positioned in the right atrium (RA). This allowed acquisition of ECG gated images of the left atrium (LA). Endocardial contours were traced on each image and were used to generate a registered 3D map.

Results
3D maps took a mean of 51+/−25 minutes to create, PRIOR to entering the LA and without fluoroscopy. Pulmonary veins and the esophagus were rendered in 3D. A complete map was built from a mean of 46+/−19 contours. Upon instrumentation of the left atrium, the maps were easily distorted if points collected by the mapping catheter were combined with the original map, due to deformation of the left atrial geometry by the relatively stiff ablation catheter. Pulmonary vein antrum isolation was guided by a circular mapping catheter. Since this catheter could not be visualized on the CARTO map, fluoroscopy was used to track its position and the contact between the ablation catheter and the circular mapping catheter. No substantial reduction in fluoroscopy time was thus realized, as expected. At 10+/−1 months of followup, 73% of the patients were in sinus rhythm after the initial three month blanking period. No patient suffered any complications related to the procedure or in follow-up.

Conclusions
A mapping system combining ICE and 3D electroanatomical mapping can feasibly reconstruct a 3D shell of the LA and the pulmonary veins without the need to enter the left heart. The map created is sensitive to distortion during point-by-point mapping with the standard ablation catheter.

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Introduction

Pulmonary vein antrum isolation guided by intracardiac echocardiography (ICE) and circumferential pulmonary vein ablation guided by electroanatomical imaging are established therapeutic modalities in patients with atrial fibrillation (AF). While the ICE guided technique affords real time imaging of the cardiac structures and monitoring for complications, this technique does not allow registration of the ablation lesions or other sites of interest during the study. Imaging of the tip of a linear catheter is also difficult using intracardiac echocardiography because of the reverberation artefact. Three-dimensional electroanatomical mapping allows recording of special site positions in space but relies on point-by-point reconstruction of 3D virtual anatomy of the left atrium (LA) or registration of CT / MRI images. Depending on the imaging modality used, the true ostium of the pulmonary veins may be proximal to the ostium reconstructed using the CARTO system or distal to the ostium reconstructed using Navex. There is accumulating body of evidence suggesting that registration of pre-acquired CT and MRI images to improve the accuracy of point-by-point mapping is difficult and may be imprecise. A novel mapping system integrating intracardiac echocardiography and electroanatomical imaging (CARTOSOUND™; Biosense Webster Inc, Diamond Bar, CA, USA; Siemens AG, Munich, Germany) was developed to bridge the gap between real time imaging using intracardiac echocardiography and virtual three dimensional electroanatomic mapping.

Mapping And Ablation

Intracardiac ECHO Generated Left Atrial Geometry

Dual venous access to the right femoral vein was achieved along with a single access to each of the left femoral and the right internal jugular veins. A decapolar coronary sinus catheter was placed via the latter vessel. A 64 element linear phased array intracardiac echocardiography probe with a CARTO navigation sensor imbedded close to the
phased array (SoundStarä, Biosense Webster) was positioned in the right atrium via the left femoral vein and allowed sequential acquisition of ECG gated 2D images of the left atrium (LA) without having to be advanced into the left atrium. In patients who were in sinus rhythm during mapping, gating was set to the best atrial electrogram seen within the coronary sinus. Whenever patients were in atrial fibrillation during mapping, gating was set to the QRS. Images were acquired in end-expiration to minimize distortion due to cardiac motion with the respiratory cycle. Endocardial surface of the LA was traced on each image (Figure 1A). A family of these contours was then summed by the system to generate a registered 3D geometry of the LA cavity without the need for a trans-septal puncture or point-by-point mapping (Figure 1B). Integration of ICE and 3D electroanatomic mapping allowed for rapid real-time non-contact registered reconstruction of the left atrial anatomy (Figure 1C). Three-dimensional rendering of the esophagus helped track its course along the posterior wall of the left atrium and estimate the distance between the two structures (Figure 2). Contours of multiple structures such as the left atrium, pulmonary veins and the esophagus could be concurrently acquired from the same ultrasound “slice”. No fluoroscopy was required to construct the map.

**Pulmonary Vein Antrum Isolation**

Left atrium was then instrumented with a circular mapping catheter and an ablation catheter via two independent ICE guided trans-septal punctures and the patient was systemically anticoagulated. Pulmonary vein antrum isolation was performed using a previously described approach. The ablation catheter was manipulated within the ultrasound derived 3D shell of the left atrium without either having to create a point-by-point anatomy or having to select and superimpose key anatomical sites as is the case with CartoMerge and Ensite Fusion technologies. In brief, a circular mapping catheter was sequentially positioned in each of the anatomical pulmonary vein antra guided by intracardiac echocardiography and fluoroscopy, since the catheter could not be visualized using the CARTO system. Wherever high frequency pulmonary vein potentials were seen, radiofrequency energy was delivered immediately next to the roaming electrode pair of the circular mapping catheter using either a Navistar Thermacool (Biosense Webster) set to the power of 30 – 40 Watt and flow of 30 cc/min or a Navistar DS 8mm tip catheter with power titrated from 40 – 50 Watt and temperature capped at 50ºC. In both instances, energy was delivered to the endpoint of disappearance of pulmonary vein potentials as seen by the circular mapping catheter. In the case of the 8mm tip catheter, energy was titrated down in 5 Watt decrements whenever microbubbles were seen on ICE. Ablation lesion tags were collected towards the 3D map of the left atrium for later correlation with the ICE generated anatomy.

Ablation catheter position was verified using fluoroscopy and 2D real-time intracardiac echo imaging. Catheter position verified using standard

![Figure 2: Reconstruction of oesophagus: Panel A illustrates an ultrasound snapshot through the mid left atrium. The red contour behind the posterior wall of the left atrium represents a “slice” through the Esophagus. Panel B shows a 3D reconstruction of the left atrium, the pulmonary veins and the Esophagus built on the basis of ultrasound derived contours.](image-url)
means correlated with that seen on the 3D ultrasound-derived left atrial reconstruction throughout the ablation procedure.

In each vein, the circular mapping catheter was initially positioned at the anatomical pulmonary vein ostium, starting at the ridge with the left atrial appendage in the case of the left pulmonary veins and the septal border in the case of the right pulmonary veins. Once no pulmonary vein potentials were seen by the circular mapping catheter at any given position, it was moved towards the roof or the floor of the vein ostium, and ultimately towards the posterior wall of the left atrium, thus covering the entire pulmonary vein antrum.

At the end of the procedure, the veins were re-mapped using the circular mapping catheter to ensure disappearance of potentials in all PV antra. In patients who were still in atrial fibrillation at the end of the procedure, limited mapping of the complex fractionated atrial electrogram (CFAE) regions took place. The version of software used did not have an automated CFAE mapping algorithm and so identification and ablation of CFAE was at the operator discretion. Those who were still in atrial fibrillation after CFAE ablation were cardioverted and the PV antra were re-mapped in sinus rhythm.

Once the procedure in the left atrium was complete, patients with history of atrial flutter had a
Cavo-tricuspid isthmus ablation to the endpoint of bidirectional block. Superior vena cava was isolated as well whenever high output stimulation did not suggest that SVC isolation would incur the risk of phrenic nerve palsy.

Results

Fifteen patients, all men, 10 with paroxysmal AF were offered ablation guided using CARTOSOUND technology between February and May of 2007. Average age of the patients was 57 +/- 7 years. Five patients had previously failed Class IC drugs, seven had failed sotalol, nine were refractory to amiodarone and two to dofetilide. Four patients had mild to moderate left ventricular dysfunction. Left atrial size was 44 +/- 5 mm on average.

3D maps took 51 +/- 25 min to create, prior to entering the left atrium and without fluoroscopy. Complete maps of the left atrium, the pulmonary vein and the esophagus were built from 46 +/- 19 contours. Figure 3 illustrates the relative position of the ablation tags with respect to the map in one of the patients. It became apparent that catheter pressure may cause a substantial distortion in left atrial anatomy. While catheter position on the mid to low posterior wall, the ridge between the left atrial appendage and the left pulmonary veins, the septum and the pulmonary vein ostia was within the 3D ultrasound-derived contour, the catheter reproducibly appeared beyond the atrial silhouette on the high posterior wall, roof and high anterior wall, suggesting that these areas were more prone to catheter deformation.

It took on average 234 +/- 78 min to perform each procedure. Total fluoroscopy time averaged 65 +/- 12 minutes. Radiofrequency energy was delivered for 89 +/- 46 minutes. Ten of the patients had adjuvant CFAE ablation and two had ablation for atrial flutter following AF ablation. Seven had SVC isolation. Atrial fibrillation could be terminated with radiofrequency energy delivery in all five patients who presented for ablation in AF. There were no intra or post-procedural complications. At 10 +/- 1 months of follow-up 11 patients (73%) remain free of recurrent AF following the initial three months blanking period.

Discussion

Integration of intracardiac echocardiography and 3D electroanatomic mapping was used to guide ablation of atrial fibrillation refractory to medical therapy in fifteen patients with both paroxysmal and chronic substrates. This approach allowed rapid acquisition of real time cross sectional images of the left atrium without having to enter this chamber. The images were then integrated into a registered three-dimensional model of the left atrium without the need for pre-procedural imaging. CartoMerge was not used during this experience. Ablation guided using this technique was successful in eliminating atrial fibrillation in 73% of the patients. Ablation points distorted the left atrial anatomy generated using ICE, demonstrating that the wall of the left atrium can easily deform under the pressure applied by the relatively stiff standard ablation catheter. This needs to be accounted for during point-by-point mapping of the left atrium.

In a recently published experience precision of navigation using the CARTOSOUND system was evaluated. In 12 dogs, clips were percutaneously implanted in each cardiac chamber. Three-dimensional maps of the cardiac chambers were then constructed using this system from a family of two-dimensional echocardiographic images. Clip sites were identified on 3D images derived from ultrasound and CartoMerge CT reconstruction images. Precision of navigation to the clip sites was then evaluated using identification of the clip sites using real-time 2D intracardiac echocardiography as the gold standard. The authors found a substantially smaller point-source error when navigating using an ultrasound-derived geometry compared to CartoMerge for both atria and ventricles.

The tip of the ICE catheter as well as the projected ultrasound fan was monitored in 3D CARTO space during ablation. This allowed scanning through the tip of the ablation catheter to monitor and verify tip position using feedback from the navigation sensor. Important anatomical structures such as the esophagus were readily identified.

Point-by-point mapping alone has been the
standard for AF ablation in some electrophysiology laboratories. Unfortunately, this procedure is time consuming and may be imprecise. While integration of pre-acquired images may help solve this shortcoming of the point-by-point technique, pre-acquired images have obvious limitations and may not accurately represent the real-time cardiac anatomy. Intracardiac echo on the other hand has been shown effective in guiding a variety of electrophysiology procedures by providing real-time information necessary to improve the accuracy of ablation, to monitor and prevent complications.

This is a small study providing a very preliminary assessment of this new technology. Some operators proficient in AF ablation but unfamiliar with ICE may have a rather steep learning curve with this approach. Automation of ICE image acquisition in the future may help address this issue. While we generally do not practice electroanatomically guided circumferential pulmonary vein ablation, operators using this approach with or without ensuring pulmonary vein isolation would derive a greater benefit from the CartoSound system than we could demonstrate. Ablation approach used during this experience did not rely on 3D reconstruction of the LA anatomy and is typically guided by 2D intracardiac echocardiography and a circular mapping catheter. An ideal AF ablation toolkit would include real-time anatomical mapping using intracardiac echocardiography, 3D electroanatomical imaging system, which could accurately visualize both the ablation and the circular mapping catheter, and catheters that would not deform the left atrial wall. Further studies assessing utility of real-time registered integration of ICE and 3D electroanatomical imaging are necessary to define its place in cardiac electrophysiology.

Limitations

CARTOSOUND technology relies on 3D reconstruction based on 2D images, a non-linear transformation that may introduce some error into 3D modeling. A similar transformation is applied to CT slices used to reconstruct CartoMerge images. CartoMerge images were not used to verify 3D ultrasound-derived anatomy in this study.

We found a significant distortion of the left atrial anatomy involving primarily the roof of the LA with ablation points tagged beyond the ultrasound-derived 3D silhouette of the LA. Another group applied this technology to a group of 15 patients undergoing ablation for atrial fibrillation producing somewhat smaller reconstructed left atrial volumes using this technology compared to conventional point-by-point 3D electroanatomical mapping. The authors hypothesized that the difference in size of the geometries stems from the distortion of the left atrial anatomy by a conventional mapping catheter, a finding that matches ours.

Unfortunately, while the circular mapping catheter could be monitored by ICE and fluoroscopy, it could not be tracked by the CARTO system, making it difficult to cut down on the high fluoroscopy exposure typical of the PV antrum isolation procedures.

Conclusions

A mapping system combining ICE and 3D electroanatomical mapping can feasibly reconstruct a 3D shell of the left atrium and the esophagus. Ablation guided using this approach appears safe and effective in a small group of patients with a variety of AF substrates. A broader investigation of this novel approach to AF ablation may be warranted.

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Skin Burn at the Site of Indifferent Electrode after Radiofrequency Catheter Ablation of AV Node for Atrial Fibrillation.

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Abstract

Radiofrequency Ablation of AV node with permanent pacemaker has been used to achieve rate control in persistent symptomatic atrial fibrillation. Although RF Ablation is safe, complications may occur in up to 3% of the procedures. A rare complication of 2nd degree skin burn at indifferent electrode site has been described here. This report highlights the rare but possible complication in patients undergoing such a procedure and help in preventing by taking appropriate measures.

Introduction

Radiofrequency (RF) energy is a low voltage high frequency electrical energy which produces controlled focal tissue ablation. It has revolutionised the treatment of refractory supraventricular tachycardias. Although radiofrequency catheter ablation (RFCA) is a safe procedure, application of RF energy is not without complications. Major complications may occur in up to 3% of patients undergoing RFCA which includes AV block, Cardiac tamponade, Coronary artery spasm, thrombosis, Pericarditis, Vascular Injury, Thromboembolism, Transient ischemic attack and or stroke, Pulmonary hypertension secondary to pulmonary vein stenosis, Pneumothorax, Left atrial-esophageal fistula and Phrenic nerve paralysis. Most of the complications of RF ablation of supraventricular arrhythmias are limited to the site of RF energy application and skin burn at the indifferent electrode site was described in only case secondary to maladhesion of the electrode pads. We present a case of skin burn at the site of indifferent electrode after an elective RF ablation for recurrent AF.

Case Report

A 54 year old white obese woman (BMI 43) with 8 year history of symptomatic paroxysmal atrial fibrillation was referred for AV nodal ablation and permanent pacemaker insertion. Her past medical history is significant for hypertension and aortic valve replacement (#19 St. Jude Prosthetic valve) for congenital bicuspid aortic valve 9 years ago. She had multiple cardioversions and was treated with multiple antiarrhythmic drugs to achieve rhythm restoration. But AF remained unresponsive and she was symptomatic with fatigue, dys-
pnea and congestive heart failure secondary to rapid ventricular response. She underwent radiofrequency catheter ablation and pulmonary vein isolation without any complications. But her AF recurred and was thought to be due to severely dilated left atrium with extensive scarring from both Aortic Valve replacement and RF ablation. She was recommended RF ablation of AV node with permanent pacemaker placement. She underwent the AV Nodal ablation under sedation, using the 8.0 mm Biosense Webster Celsius catheter (50 Watt and 50 C Temp). The bundle of His was successfully mapped and AV node was ablated with no ventricular escape. The total time of RF energy delivery during the ablation was about 6 minutes. No impedance raise was noticed during the procedure. After successful ablation, skin, under the indifferent electrode pad on the lower abdominal wall, was noted erythematous with second degree thermal burn (Fig. 1) at the leading edge of the pad. The adhesion between the pad and skin was checked thoroughly and was in good contact. There was no fluid around or in between the pad and skin. The patient did not complain any pain during the procedure. The skin lesion became necrotic with scabbing and turned out to be a third degree burn over next few days requiring wound care and plastic surgery consultation.

The wound required well over 3 months to heal with a scar.

**Discussion**

Radiofrequency ablation has been proved to be safe and effective procedure in the management of tachyarrhythmias. Radiofrequency energy is a low voltage high frequency (30 KHz to 1.5 MHz) electrical energy. It was first tested safely in animal models to create AV nodal block by Huang et al.\(^3\) The ability of usage of catheter to deliver the RF energy coupled with the ability to create controlled focal tissue destruction resulted in increasing use of RF energy. Ability to use higher levels of RF energy in non-arrhythmic conditions such as in the management of tumours has led to identify new

**Figure 1:** Skin burn at the leading edge of the indifferent electrode pad over the abdominal pannus.
Skin burns at the indifferent electrode have been identified and reported in electrosurgical procedures where the procedure typically lasts longer and requires higher energies. The electrical current passing through the body produces heat energy and increases the temperature of the tissues. According to Ohm’s Law, the raise of temperature depends on the amount of electrical energy, density of the energy per attachment area, and the resistance to the flow of energy at the attachment site.

The biggest raise of temperature occurs at the tip of the catheter, where the electrical density is highest. This ability to raise the temperature which results in local tissue destruction makes the basic principle of ablation. Although similar amount of electrical current flows through the indifferent electrode, which completes the circuit, the temperature rise is much less because of the use of the dispersive pads. Dispersive pad reduces the electrical density by their size and wider area in contact with body and does not result in “exit wounds” as seen in electrical injuries. It was postulated that the temperature rise to 45-47°C at the indifferent electrode site can cause skin burn. The modern RF ablation catheters typically use higher energies. Faulty indifferent pads with cracks or loose connections may cause excess resistance in the circuit. Skin burn at indifferent electrode sites have described in the management of solid tumour ablations which typically require higher energies and long duration of energy application than a typical electrophysiology ablation.

It is also known that the characteristics of the current flow towards a contact depend on the shape of the contact. The typical shape of the pad at the skin contact is acute or convex and the current density tends to be higher at such edges or sharp angles. It probably resulted in differential temperature raise at the pad contact site making the edges more vulnerable to burns. This might explain the ‘leading edge phenomenon’ described by Stenkie et al. Electrical conductive media such as normal saline or other body fluids which contain inorganic salts, when present at the pad site can change the path of circuit and may result in unwanted outcomes.

The rise in the temperature also depends on the ability of the human body to disperse the heat generated which in turn depends on the amount of blood flow, amount of the subdermal fat which acts as an insulator. When the surrounding room temperature is very low, it can result in vasoconstriction of cutaneous blood vessels further resulting in poor heat dissipation. The deep sedation of the patients during the procedure may result in ignoring the discomfort and pain caused by the raise in temperature.

We believe that, in this patient, multifactorial causes including obesity, excessive fat at the pad attachment site, deep sedation and environmental conditions resulted in the generation of excess heat at the pad site resulting in thermal injury.

Conclusions

Although rare, risk of skin burn at indifferent electrode site should be considered especially in obese patients undergoing RF catheter ablation. We believe that the poor blood circulation and excess fat at the site of pad attachment resulted in poor dissipation of heat resulting in the thermal burn in this patient. Using larger pads with wider area of contact, choosing a site with better cutaneous perfusion, rotation of the pads or using multiple ground pads with sequential activation, reducing the time of RF energy delivery, choosing less energy settings and avoiding deep sedation during the procedure may help in reducing such a complication.

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Atrial fibrillation and heart failure are epidemics of contemporary cardiovascular medicine. In the US, more than 2 million people are suffering from atrial fibrillation and more than 5 million have heart failure.1-3 Atrial fibrillation and heart failure often coexist, and patients with one condition, who subsequently develop the other, have an increased mortality.[4] Heart failure is associated with a 4.5 to 5.9-fold risk for atrial fibrillation.5 The prevalence of atrial fibrillation increases with the severity of heart failure from ≤ 5% in patients with functional class NYHA I to nearly 50% in patients with functional class NYHA IV.6 Approximately 40-50% of heart failure patients have preserved left ventricular function, which is often associated with older age, female gender and a history of hypertension.7,9 In these patients, atrial fibrillation is even more prevalent than in patents with reduced ejection fraction.7,9,10 Atrial fibrillation may lead to further hemodynamic deterioration in heart failure patients. An inappropriately fast or slow ventricular response, ventricular rhythm irregularity and loss of mechanical atrial function can have negative hemodynamic consequences and may elicit an increase in sympathetic tone.6,11,12 A chronic fast ventricular response may lead to tachycardia-induced cardiomyopathy causing exacerbation or aggravation of heart failure.13

This article focuses on clinical management of atrial fibrillation in heart failure patients. Treatment options to prevent thromboembolism, control heart rate and maintain sinus rhythm will be discussed.
Anticoagulation

Data from the National Registry for Atrial Fibrillation suggest an overall stroke risk of 4.4% per year in patients with non-rheumatic atrial fibrillation aged 65 to 95 years. The annual stroke risk ranges from 1.9% in the absence of, to 18.2% per year in the presence of all of the following risk factors, recent congestive heart failure, history of hypertension, age ≥ 75 years, diabetes mellitus and prior stroke or history of prior thromboembolism. Data from the Framingham Heart Study suggest that the risk of stroke is increased by 4.8-fold in atrial fibrillation and by 4.3-fold in heart failure. The presence of atrial fibrillation in patients with heart failure almost doubles the risk of stroke in men and triples the risk of stroke in women. Recent meta-analyses showed, that dose-adjusted warfarin reduces the risk of stroke by 64% to 67%, but antiplatelet agents (i.e. aspirin and dipyridamole) are less effective, reducing stroke by only by 22%. Heart failure and left ventricular ejection fraction ≤ 35% are both considered moderate risk factors for thromboembolic events in patients with atrial fibrillation. Anticoagulation with dose-adjusted warfarin should be maintained in all patients with heart failure and a history of atrial fibrillation unless contraindicated.

Data from the AFFIRM trial shows that major bleeding during anticoagulation with warfarin in patients at risk of stroke occurs in approximately 2% of patients per year. Congestive heart failure increases the risk of major bleeding by 43%. However, the rate of major bleeding in patients with atrial fibrillation at risk of stroke is usually lower than the expected rate of a thromboembolic event. Thus, anticoagulation is still favored.

Pharmacologic Approach to Maintain Sinus Rhythm

In prior randomized trials (AFFIRM, RACE and STAF) comparing rhythm control and rate control with antiarrhythmic drugs, neither strategy demonstrated a survival benefit over the other. The recently completed AF-CHF study addressed this issue specifically in heart failure patients. A total of 1,376 patients with heart failure symptoms, a left ventricular ejection fraction of ≤ 35% and at least one episode of atrial fibrillation within 6 months preceding enrollment were included. Mean left-ventricular ejection fraction was 27%; 31% of patients were in functional class NYHA III to IV and atrial fibrillation was persistent in 69% of patients. After a mean follow-up of 37 months, there was no difference between rate and rhythm control groups in the primary endpoint of cardiovascular mortality. Secondary outcomes including total mortality, worsening heart failure and stroke were also not different between groups.

Patients included in these studies are likely different from those usually considered for catheter ablation of atrial fibrillation. It is conceivable, that patients with severe symptomatic episodes of atrial fibrillation would not have been considered as optimal participants. In the AFFIRM study, only patients of at least 65 years of age or with other risk factors for stroke or death could be enrolled. The mean age of the participants in the AFFIRM, RACE, STAF and AF-CHF studies was 66 to 70 years.

In contrast, the mean age of patients undergoing catheter ablation for atrial fibrillation was 60 years in a recent large multicenter registry. The AFFIRM, RACE and other studies have shown that maintenance of sinus rhythm is associated with improved survival and less hospitalizations, but in AFFIRM, antiarrhythmic drug use was associated with a worse outcome. Thus, whether sinus rhythm is only a marker of less severe illness or causative for a better outcome remains controversial.

In the absence of data clearly favoring one strategy over the other, therapy has to be individualized. Our practice is to consider rhythm control in patients with a first episode of persistent atrial fibrillation, for symptomatic paroxysms of atrial fibrillation, and when adequate rate control is difficult to achieve.

Amiodarone or dofetilide, both class III antiarrhythmic drugs, are the major pharmacologic considerations for attempted maintenance of sinus rhythm in patients with heart failure. Amiodarone was shown to be safe in heart failure patients in the CHF-STAT trial with a trend to a better survival in patients with non-ischemic cardiomyopathy. In the SCD-HeFT trial, amiodarone did not significantly influence overall mortality, but subgroup analysis showed an increased mortality in patients with NYHA III heart failure. Whether this
Dofetilide was shown to be relatively safe in heart failure patients, provided that several precautions are taken in its use. In this patient group, it has efficacy in converting atrial fibrillation to sinus rhythm and maintaining sinus rhythm. As an IKr blocker, dofetilide prolongs the QT interval. It caused torsade de pointes in approximately 3% of patients in the DIAMOND trial, even after dose-adjustment according to renal function and attention to following the QT interval. The peak increase in the QT interval was seen within the first 2 days, and 76% of cases of torsades de pointes occurred within the first 3 days of dofetilide therapy. In-hospital monitored initiation of dofetilide for 3 days is warranted. ICDs may provide protection from death due to this arrhythmia. There is no head-to-head comparison of amiodarone and dofetilide in heart failure patients.

Sotalol is another class III antiarrhythmic drug that is an IKr blocker and also a non-selective beta-blocker. It may be considered as a therapeutic alternative. Data from the CTAF and SAFE-T trials show, that amiodarone is superior to sotalol in maintenance of sinus rhythm, but sotalol is still superior to placebo. In patients with coronary artery disease, sotalol and amiodarone are similarly efficacious. Of note, the minority of patients in both trials had abnormal left ventricular function. Sotalol has a proarrhythmic potential similar to that of dofetilide. This effect may have been the cause of excess mortality that led to premature termination of the SWORD trial in which the d-isomer of sotalol was administered to patients with a history of prior myocardial infarction and an ejection fraction ≤ 40%.

Excess in total mortality was driven by arrhythmic cardiac deaths. However, torsade de pointes were reported in only 0.2% of patients receiving sotalol. The proarrrhythmic effect of sotalol warrants in-hospital initiation of the drug.

The CAST trial showed an excess of mortality with use of class I antiarrhythmic drugs (sodium channel blockers, including flecainide) in patients with structural heart disease. Heart failure patients may be prone to suffer from arrhythmogenic and cardiodepressant side effects of class I antiarrhythmic drugs. Accordingly, these drugs should be avoided in heart failure patients.

Non-Pharmacologic Approach to Maintain Sinus Rhythm

Over the last 20 years, surgical and catheter ablation techniques for treatment of atrial fibrillation have been developed and improved, with most of the trials in populations with no or little heart failure. The Cox maze III procedure, which was introduced into surgical treatment in 1988, is regarded as the gold standard for surgical treatment of atrial fibrillation. Long-term success in over 90% of patients, most of them off drugs, has been reported. A review of recent publications on radiofrequency catheter ablation for atrial fibrillation shows consistently success rates in approximately 80% of patients, most of them off drugs, although more than one procedure is required in a significant number. It is difficult to extrapolate these results for heart failure patients, since patients in these trials are selected to be reasonable ablation candidates, often with no or minimal structural heart disease. As for most therapies, lower success rates would be anticipated in patients with heart failure. Left atrial scarring, decreased left ventricular function, persistent atrial fibrillation and age were identified as predictors of procedural failure in catheter ablation for atrial fibrillation.

Surgical and catheter ablation procedures in patients with depressed left ventricular function were investigated in several recent studies. In a retrospective study of 37 patients with a left ventricular ejection fraction < 55% (mean, 44%), who underwent a Cox maze procedure for paroxysmal and chronic atrial fibrillation and flutter, there was no perioperative mortality, and 3 patients required placement of a permanent pacemaker. During a
median follow-up of 48 months, atrial arrhythmias recurred in 4 patients. Mean left ventricular ejection fraction improved significantly to 54%. Improvement in functional capacity was noted in 56% of patients, deterioration of functional capacity was not observed. Surgical risks are an important consideration. A recent review of 48 studies on surgical treatment of atrial fibrillation including the classical Cox maze III procedure, most performed with concomitant valve or bypass procedures, reported a 30-day mortality of 2 to 4%, major complications in 8% and the need for pacemaker implantation in 5 to 6% of cases.

Hsu and coworkers studied 58 patients with congestive heart failure and a left ventricular ejection fraction < 45% (mean, 35%), who underwent radiofrequency catheter ablation for atrial fibrillation. One patient died 3 months after the procedure of heart failure. After a follow-up period of 12 months, 78% of patients remained in sinus rhythm, 69% off antiarrhythmic drugs. To achieve this result, a second procedure was required in 50% of patients. Success rates in a control group were 84% and 71%, respectively. Mean left ventricular ejection fraction improved to 56%, and left ventricular dimensions decreased. This translated into better functional capacity and quality of life. Similar results were seen in another study on catheter ablation for atrial fibrillation, which included 90 patients with a reduced left ventricular ejection fraction of < 40% (mean, 36%). After a follow-up of 14 months, 73% of patients were free of atrial fibrillation, compared to 87% of patients in a control group. The increase in left ventricular ejection fraction to 41% was not significant, but quality of life improved significantly. In 22% of patients a second procedure was successful. Major complications of catheter ablation for atrial fibrillation occur in 4 to 6% of patients, and it can be anticipated that heart failure patients will generally be at greater risk.

These reports from highly experienced centers with selected patients are promising, but controlled data confirming a prognostic benefit for patients undergoing these procedures are still lacking. The ongoing CABANA trial, which compares catheter ablation for atrial fibrillation with current state-of-the-art medical therapy, addresses this issue with a primary outcome measure of total mortality, but does not focus solely on a heart failure population. At present, catheter ablation for atrial fibrillation in heart failure is warranted in selected symptomatic patients with atrial fibrillation refractory to at least one antiarrhythmic drug. Surgical ablation for atrial fibrillation is usually considered for symptomatic patients undergoing other cardiac surgery, such as mitral valve repair. Patients may also be considered for surgical ablation, when they prefer a surgical approach, have failed one or more catheter ablation procedures or are not candidates for catheter ablation.

Pharmacologic Control of Heart Rate

Atrial fibrillation with a fast ventricular response may have immediate adverse hemodynamic effects and places the patient at risk for tachycardia-mediated cardiomyopathy, particularly if the chronic heart rate exceeds 100 beats per minute. Digoxin is recommended for rate control in patients with heart failure, but it slows atrioventricular conduction more effective at rest than during exercise. Beta-blockers are usually indicated in all symptomatic patients with systolic heart failure, but in heart failure initiation should be at a low dose followed by a gradual increase, because negative inotropic effects may cause fluid retention and worsening of heart failure. Combination of beta-blockers and digoxin may be more effective than beta-blockers alone. Amiodarone is an alternative for pharmacologic rate control in patients, where the abovementioned medications are contraindicated or fail, but it has a considerable potential of adverse drug effects and is usually avoided for rate control alone. Non-dihydropyridine calcium channel blockers verapamil and diltiazem slow heart rate during exercise, but should be avoided due to their negative inotropic effect, which increases the risk of exacerbation of heart failure.

Pharmacologic rate control with atroventricular nodal blocking agents is chosen either as first line strategy or when attempts to establish and maintain sinus rhythm fail. Heart rate goals are 60 to 80 beats per minute at rest and 90 to 115 beats per minute during moderate exercise, but may vary according to patient age.

Non-pharmacologic Control of Heart Rate

Radiofrequency catheter ablation of the atrioven-
tricular junction and pacemaker placement may be warranted in medically refractory atrial fibrillation where sinus rhythm cannot be maintained and adequate rate control is not possible. Limitations of this approach include the persistent need for anticoagulation, loss of atrioventricular synchrony and pacemaker dependency.\textsuperscript{18}

A meta-analysis of 21 studies showed, that ablation and pacing reduces symptoms and healthcare use and improves left ventricular function, exercise duration and quality of life, with a one year total and sudden death mortality of 6.3\% and 2.0\%, respectively.\textsuperscript{51}

However, right ventricular apical pacing may be detrimental by worsening heart failure and increasing mortality.\textsuperscript{52} Right ventricular pacing induces electrical and mechanical dyssynchrony, which can adversely influence contraction and relaxation, ultimately causing unfavorable ventricular remodeling. It may be less well tolerated in patients with pre-existing systolic heart failure and mitral regurgitation.\textsuperscript{53, 54} Consistent with this consideration is the observation that atrioventricular node ablation and permanent pacing for refractory atrial fibrillation leads to hemodynamic deterioration in certain patients. Ozcan and coworkers studied this approach in patients with left ventricular dysfunction with a mean left ventricular ejection fraction of 26\% before the procedure.\textsuperscript{55} Mean ejection fraction increased to 34\% after ablation. The twenty-nine percent of patients with near normalization of the left ventricular ejection fraction to ≥ 45\% had a survival comparable to that of normal subjects. However, the majority of patients had a persistent low ejection fraction and a poor prognosis with a mortality of 48\% during a mean follow-up of 40 months.\textsuperscript{55} In some patients with heart failure, ablation and pacing is followed by aggravation of mitral regurgitation.\textsuperscript{56} Vanderheyden and coworkers found hemodynamic deterioration in 7\% of patients undergoing ablation and pacing therapy, which was related to worsening mitral regurgitation. Of note, baseline echocardiograms in patients with hemodynamic deterioration showed left ventricular dilation and subnormal fractional shortening.\textsuperscript{57}

The PAVE study compared conventional right ventricular with biventricular pacing in patients undergoing atrioventricular node ablation for the management of atrial fibrillation.\textsuperscript{58} Biventricular pacing was associated with improvement in functional capacity at 6 months. Left ventricular ejection fraction remained unchanged after implantation of a biventricular system in contrast to right ventricular pacing, where a slight but significant decline in ejection fraction was observed. Patients with a baseline ejection fraction of ≤ 45\% or NYHA functional class II / III symptoms had a greater improvement in functional capacity than patients with normal left ventricular function or class I symptoms.\textsuperscript{58} In another study of patients with severe heart failure after atrioventricular node ablation and right ventricular pacing for management of chronic atrial fibrillation, upgrade to a biventricular system was followed by improvement in left ventricular dimensions and function, and quality of life and a decrease in hospitalizations.\textsuperscript{59} The HOBIPACE study compared bi-ventricular to right ventricular pacing for 3 months in a randomized cross-over design trial in 30 patients. Biventricular pacing was superior to conventional right ventricular pacing with regard to left ventricular function, exercise capacity and quality of life in patients with left ventricular dysfunction and standard indication for pacemaker implantation.\textsuperscript{60}

Accordingly, implantation of a biventricular pacemaker is a reasonable consideration for patients who are undergoing atrioventricular node ablation for drug-refractory atrial fibrillation with heart failure or depressed left ventricular function. An upgrade to a biventricular system should be contemplated in patients with persistent heart failure, who have undergone atrioventricular junctional ablation and have only right ventricular pacing.\textsuperscript{18}

Polymorphic ventricular tachycardia, ventricular fibrillation and sudden death were not uncommonly observed early after ablation of the atrioventricular junction and pacemaker implantation. These complications occurred in 6\% of cases in a larger study of Geelen and coworkers. Ventricular arrhythmias mostly occurred during slow ventricular escape rhythms or slow pacing rates of ≤ 60 beats per minute. Bradycardia and pacing-related prolongation of repolarization, change in ventricular activation, increased dispersion of re-
polarization, increased sympathetic tone and individual factors like heart failure, hypokalemia and female gender may increase the vulnerability to these arrhythmias. Pacing at 90 beats per minute for 1 to 3 months after the procedure appears to prevent this complication.61, 62

The recently completed PABA CHF trial compared catheter ablation for atrial fibrillation with atrioventricular node ablation and biventricular pacing. Preliminary results showed a significantly greater ejection fraction in the catheter ablation group at 6 months post procedure.63

Prevention of Atrial Fibrillation in Heart Failure

Perhaps the best way to deal with atrial fibrillation and its negative consequences is through prevention. Angiotensin converting enzyme inhibitors, angiotensin receptor blockers and beta-blockers belong to the standard pharmacologic armamentarium for treatment of heart failure.19 There is strong evidence of participation of the renin-angiotensin system in electrical and structural atrial remodeling, involved in the pathogenesis of atrial fibrillation.64 Both angiotensin converting enzyme inhibitors and angiotensin receptor blockers reduce atrial fibrillation in patients with heart failure or hypertension, as supported by meta-analysis.65 The benefit was similar between these two classes of drugs and greatest in patients with heart failure with a 44% relative risk reduction.66 A recent meta-analysis on the efficacy of beta-blockers in heart failure trials showed a significant prevention of atrial fibrillation by use of beta-blockers with a 27% relative risk reduction.67

The protective effect of cardiac resynchronization therapy is still unclear. Although a small study showed a significantly lower incidence of atrial fibrillation in patients with cardiac resynchronization therapy, data from the CARE-HF study did not support this hypothesis.67, 68

Conclusions

Atrial fibrillation is common in heart failure. Patients with one condition who subsequent develop the other have an increased mortality. Treatment has to be individualized in these complex patients and the risks and benefits of the different therapeutic options carefully considered. Anticoagulation and rate control are crucial in all patients with atrial fibrillation and heart failure. Pharmacologic rhythm control offers no survival benefit over rate control, and may be used in selected symptomatic patients. Catheter ablation of atrial fibrillation in selected patients can be successful, but also has risks. Atrioventricular node ablation and placement of a biventricular pacemaker for drug-refractory atrial fibrillation is an option when rate control and sinus rhythm can not be maintained. The important question, of whether catheter ablation for atrial fibrillation has the potential to prolong life, is still unresolved. The answer may have substantial impact on our approach to treat atrial fibrillation in the future.

Disclosures

None to disclose in context of current subject matter.

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How Do Atrial-Selective Drugs Differ From Antiarrhythmic Drugs Currently Used in the Treatment of Atrial Fibrillation?

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Abstract

Current pharmacologic strategies for the management of atrial fibrillation (AF) include use of 1) sodium channel blockers, which are contraindicated in patients with coronary artery or structural heart disease because of their potent effect to slow conduction in the ventricles, 2) potassium channel blockers, which predispose to acquired long QT and Torsade de Pointes arrhythmias because of their potent effect to prolong ventricular repolarization, and 3) mixed ion channel blockers such as amiodarone, which are associated with multi-organ toxicity. Accordingly, recent studies have focused on agents that selectively affect the atria but not the ventricles. Several atrial-selective approaches have been proposed for the management of AF, including inhibition of the atrial-specific ultrarapid delayed rectified potassium current (IKur), acetylcholine-regulated inward rectifying potassium current (IK-ACh), or connexin-40 (Cx40). All three are largely exclusive to atria. Recent studies have proposed that an atrial-selective depression of sodium channel-dependent parameters with agents such as ranolazine may be an alternative approach capable of effectively suppressing AF without increasing susceptibility to ventricular arrhythmias. Clinical evidence for Cx40 modulation or IK-ACh inhibition are lacking at this time. The available data suggest that atrial-selective approaches involving a combination of INa, IKur, IKr, and, perhaps, Ito block may be more effective in the management of AF than pure IKur or INa block. The anti-AF efficacy of the atrial-selective/predominant agents appears to be similar to that of conventionally used anti-AF agents, with the major apparent difference being that the latter are associated with ventricular arrhythmogenesis and extracardiac toxicity.

Introduction

The development of atrial-selective antiarrhythmic agents was necessitated by the proclivity for induction of life-threatening ventricular arrhythmias and/or extra-cardiac toxicity of currently available anti-atrial fibrillation (AF) agents. This review is an attempt to briefly summarize currently current knowledge relative to this effort.

It has been more that decade since Wang et al first described the ultrarapid delayed rectified potassium current (IKur, carried by Kv 1.5 channels encoded by the KCNA5 gene) which is present only in atria, but not ventricles. Block of IKur affects only atrial electrical parameters, which...
makes this current a potential target for chamber-specific management of atrial arrhythmias.2 Among other atrial specific targets suggested to be used for the suppression of atrial arrhythmias is the acetylcholine (ACh)-regulated inward rectifying potassium current (IK-ACh), encoded by Kir3.1/3.4 alpha-subunits) and, to a certain degree, connexin 40 (Cx40, encoded by Gja5 and).2-4

Most recently, another approach has been proposed for the management of AF, consisting of atrial-selective/predominant depression of sodium channel current (INa)-dependent parameters. INa blockers, such as ranolazine, which predominantly or selectively, depresses INa-dependent parameters in atria vs. ventricles.5 Ranolazine has been shown to be effective in suppressing AF in a variety of experimental models5 as well as reducing supraventricular arrhythmias (p<0.001) and new onset AF (p=0.08) in patients with non-ST segment elevation acute coronary syndrome.6 Block of IKr has also been shown to cause a preferential prolongation of atrial vs. ventricular repolarization.7-13

Figure 1: Block of IKur with 4-aminopyridine (4-AP, 50 μM)

Atrial-Specific Antiarrhythmic Approaches for AF

Atrial-specific targets are those that are present exclusively or almost exclusively in atria. Atrial-specific agents include those that inhibit IKur and IK(ACh). Agents that modulate Cx40, found in atrial but not ventricular myocardium, are commonly included in this category with the caveat that Cx40 is present in the conduction system of the ventricles.2,4 While it is conceivable that an effect on Cx40 may suppress some forms of AF, there are no specific Cx40 inhibitors available yet, so that the hypothesis remains to be tested.

Vagally-mediated AF is the most likely form of AF to be suppressed by IK-ACh inhibition. A vagal component may also contribute to the initiation of paroxysmal AF.14,15 Normally, IK-ACh is activated through the muscarinic receptors in response to release of ACh, leading to an abbreviation of atrial repolarization and, thereby, promoting AF. In the atria of human patients with chronic AF, ACh-activated IK-ACh is reported to be either increased16 or decreased.3 There is another form of IK-ACh that abbreviates APD90 in “healthy” (plateau-shaped action potential), but prolongs it in “acutely remodeled” (triangular-shaped action potential) canine coronary-per fused Atrial preparations (pectinate muscles). Low flow ischemia was used to generate the “acutely remodeled” atria. Left panel is from Burashnikov et al.,24 with permission.
does not require vagal influences or muscarinic receptors for activation, i.e., the constitutively active IK-ACh. This current is present in normal human atria and is significantly increased in atria of chronic AF patients. In canine atria, a corresponding constitutively active IK-ACh is also present under baseline conditions and this current is up-regulated in tachycardia-remodeled atria. The constitutively active IK-ACh is likely to contribute to abbreviation of atrial APD and AF vulnerability. Selective block of IK-ACh with tertiapin prolongs atrial APD and suppresses AF in experimental AF models. Block of IK-ACh, however, may be pro-arrhythmic in post-operative AF cases, since the preservation of the anterior fat pad (containing mostly parasympathetic nerves endings) decreases the incidence of postoperative AF. There are no clinically available selective IK-ACh blockers at the present time. An important caveat in the development of clinically safe IK-ACh blockers is that these agents should not produce significant vagolytic influences in other organs. Thus, the clinical feasibility of an “IKA-Ch approach” is yet to be established.

Among atrial-specific targets, IKur is the most investigated and is considered by many as the most promising target at the present time. The pharmacological response of “healthy” and “remodeled” atria (displaying a plateau-shaped and triangular-shaped AP morphology, respectively) to IKur block is very different (Fig. 1). Block of IKur in “healthy” atria prolongs only the early repolarization phase but abbreviates the late repolarization phase (APD70 or APD90) and the effective refractory period (ERP). In contrast, in remodeled atria, a reduction of IKur prolongs APD70-90. Interestingly, loss-of-function mutations in KCNA5, the gene that encodes the Kv1.5 channel protein, have been associated with familial AF, suggesting that a reduction in IKur may predispose to the development of AF. In support of this hypothesis, block of IKur with 10-50 μM of 4-AP was shown to promote the induction of non-sustained AF in “healthy” canine arterially-perfused atrial prepa-

**Figure 2:** Ranolazine specifically induces prolongation of the effective refractory period (ERP) and development of post-repolarization refractoriness in atria

(PRR, the difference between ERP and APD75 in atria and between ERP and APD90 in ventricles; ERP corresponds to APD75 in atria and APD90 in ventricles). CL = 500 ms. C – control. The arrows in panel A illustrate the position on the action potential corresponding to the end of the ERP in atria and ventricles and the effect of ranolazine to shift the end of the ERP in atria but not ventricles. * p<0.05 vs. control. † = p<0.05 vs. APD75 values in atria and APD90 in ventricles; (n=5-18). From Burashnikov et al with permission.
rations, secondary to the development of an abbreviation of APD90 and ERP.\(^{25}\)

A number of studies have demonstrated that agents capable of blocking IKur (AVE0118, AVE1231, S9947, S20951, ISQ-1, DPO-1, vernakalant; AZD7009; NIP141, NIP-142) selectively prolong atrial ERP both in electrically-remodeled and non-remodeled (i.e., “healthy”) atria in vivo and in vitro.\(^{27-34}\) Because ERP prolongation in “healthy” atria is not consistent with APD70-90 abbreviation recorded in “healthy” atrial preparations in vitro,\(^{23-25}\) the ERP prolongation observed in response to these agents may be related to their action to also depress INa. Prolongation of ERP in the absence of APD90 prolongation is a well-known feature of sodium, but not potassium, channel blockade. This is the result of post-repolarization refractoriness (PRR), which develops more readily in atria than in the ventricles (Fig. 2).\(^{3,35,36}\) Consistent with this line of thinking, IKur blockers such as AZD7009 and vernakalant have been also shown to be capable of potently block INa.\(^{32,37,38}\) AZD7009 has been shown to behave as an atrial selective INa blocker in the canine heart in vivo, slowing conduction velocity and increasing diastolic threshold of excitation in atria, but not ventricles.\(^{32}\) ISQ-1 may also block INa, since this agent slows down conduction velocity in atria in vivo.\(^{39}\) AVE0118 prolongs ERP but not APD90 and reduces VMax in canine coronary-perfused atrial preparations (Burashnikov et al, unpublished). Note that with the exception of AZD7009 (see above), comparison of the effects of IKur blockers on INa or sodium channel-dependent parameters in atria and ventricles has not been conducted.

IKur blockers that have been shown to be experimentally and clinically effective in terminating AF (i.e., AZD7009 and vernakalant) have also proven to exert potent block of INa and IKr.\(^{37,38}\) It is not clear whether IKur or INa plays the greater role in producing atrial-selective prolongation of ERP and suppression of AF. Perhaps the most investigated IKur blocker, AVE0118, suppresses AF in goats and pigs, but at concentrations that inhibit Ito and IK-ACh.\(^{27,40}\) Another IKur blocker ISQ-1 can terminate AF in in vivo dogs at the concentrations that block IKr and possibly INa, since conduction time is significantly increased in atria.\(^{39}\) Low concentrations of 4-AP (10-50 μM, which selectively inhibit IKur) do not prevent the initiation of AF or terminate persistent ACh-mediated AF in canine coronary-perfused atrial

**Figure 3:** Ranolazine produces a much greater rate-dependent inhibition of the maximal action potential upstroke velocity (Vmax) in atria than in ventricles.
preparations.25

Thus, available experimental and clinical data suggest that “pure” IKur inhibition alone is incapable of effectively suppressing AF and that the antiarrhythmic effects of most IKur blockers under development are attributable to associated inhibition of other ion channels including INa, Ito, and/or IKr). The relative contribution of IKur reduction is not clear at this time.

Atrial Predominant Antiarrhythmic Approaches for AF.

We refer to atrial selective or predominant targets as to those that are present in both chambers of the heart, but inhibition of these targets produces greater effects in atria vs. ventricles. “Atrial-predominant” refers to a lesser degree of atrial selectivity. The results of recent experimental studies indicate that some INa blockers (such as ranolazine and chronic amiodarone) depress sodium channel-dependent parameters in an atrial selective or predominant manner.5,35,36 While not well appreciated, IKr blockers are also atrial-predominant in that they preferentially prolong atrial repolarization at normal heart rates.7-13

Atrial Predominant Effects of IKr Block on Cardiac Repolarization

In direct comparisons, selective IKr blockers such as E-4031, sotalol, d-sotalol, dofetilide, WAY-123,398, ibutilide, MK499, and almokalant preferentially prolong atrial vs. ventricular ERP and APD at normal pacing rates.7-13 At slow pacing/heart rates, however, ventricles, but not atria commonly develop exaggerated APD prolongation, early afterdepolarizations, and Torsade de Pointes in response to a reduction of IKr.41,42

Does Ito Block Preferentially Alter Atrial vs. Ventricular Repolarization?

The IC50 of 4-AP’s action to block atrial Ito is one third of that of ventricular Ito in human and canine myocytes.43,44 If this proves to be the case with other Ito blockers, then Ito block might be expected to produce a greater effect on atrial vs. ventricular repolarization. Because most IKur blockers also reduced Ito, inhibition of Ito may contribute to the atrial-selectivity of IKur blockers, both with respect to their antiarrhythmic and proarrhythmic actions.

Atrial Predominant Sodium Channel Block

In recent studies, we examined atrioventricular differences of the effects of ranolazine, chronic amiodarone, lidocaine and propafenone on sodium channel-dependent parameters, such as the maximum rate of rise of the action potential upstroke (Vmax), diastolic threshold of excitation (DTE), conduction velocity (CV), and PRR.5,35,36,45 Using canine isolated coronary-perfused atrial and ventricular preparations, we evaluated therapeutically-relevant concentrations of these agents. Ranolazine, a recently marketed antianginal agent, was found to depress Vmax, DTE, CV, and induce PRR exclusively or predominantly in atrial preparations.5 Thus, when studied in beating multicellular preparations, ranolazine proved to be an atrial-selective/predominant sodium channel blocker (“an atrial selective Class I agent”).

Chronic amiodarone was found to depress sodium-channel dependent parameters in both atrial and ventricular preparations, but much more effectively in atria.35,36 Lidocaine was also atrial-predominant, but far less atrial-selective than ranolazine or amiodarone.5 Propafenone showed no chamber selectivity for INa block at a normal pacing rate (CL = 500 ms), but some atrial predominance at rapid pacing rates, likely due to atrial specific APD prolongation (see later).45 As previously mentioned, AZD7009 also behaves as an atrial-selective INa blocker.32

Ranolazine, propafenone, and chronic amiodarone all produce prolongation of APD90 in the canine atria, likely to due to their actions to inhibit IKr. This effect of these agents potentiate their effects to reduce INa and depress INa-dependent parameters, thus contributing to their atrial-selective effects, particularly at rapid activation rates (Fig. 3C).

The atrial-selective action of these agents is thought to be due to important distinctions in action potential characteristics as well as biophysical properties of sodium channels of atrial and
ventricular myocytes. The half inactivation voltage (V0.5) in canine atrial myocytes is 12-16 mV more negative than that of ventricular myocytes and resting membrane potential (RMP) in atria is less negative than ventricles (approx. – 83 vs. -87 mV). These factors indicate that there is a larger fraction of inactivated sodium channels at RMP in atria vs. ventricles and a smaller fraction of resting sodium channels at RMP in atria vs. ventricles. This is expected to slow the unbinding of the drug and recovery of the sodium channel from pharmacologic block in atria, since this recovery occurs principally during the resting state.

Anti-AF Potential of Atrial Selective vs. Conventional Agents

We compared the effectiveness of therapeutically-relevant concentrations of ranolazine, propafenone, and lidocaine in suppressing and preventing the re-induction of AF in isolated canine coronary-perfused right atrial preparations. The effectiveness of chronic amiodarone in preventing induction of AF was examined as well. Ranolazine prevented the initiation acetylcholine-mediated AF, terminated persistent AF, and prevented its re-induction in coronary-perfused atrial preparations (Fig. 6). This anti-AF efficacy of ranolazine (10 μM) was greater than that of lidocaine (21 μM) and similar to that of propafenone (1.5 μM). In atria isolated from chronic amiodarone-treated dogs (40 mg/Kg for 6 weeks), persistent ACh-mediated AF could be induced only in 1 out of 6 atria (vs. 10/10 atria isolated form untreated controls). These anti-arrhythmic effects of ranolazine, amiodarone, and propafenone were associated with both APD prolongation (in the presence of ACh) and the development of a significant PRR, with the duration of the latter being much longer than the extent of APD prolongation, suggesting that sodium-channel block plays a more predominant role in the anti-AF actions of these agents.

Ranolazine and propafenone both suppress AF but ranolazine, unlike propafenone, does it without prominent effects on ventricular myocardium. These findings suggest that atrial-selective/pre-dominant sodium channel block, perhaps with additional IKr block, may be a promising new atrial-selective approach for the management of AF. Interestingly, all clinically effective anti-AF INa blockers also inhibit IKr. Pure INa blockers, such as lidocaine, are not very effective in suppression of AF in the clinic.

Clinical efficacy has been reported for only three atrial-selective agents: AZD7009, vernakalant (agents that block IKur, INa, and IKr) and ranolazine, which blocks INa and IKr. There is therefore little basis for a comparison of atrial-selective agents with conventional anti-AF agents. In a study that was not designed to test the anti-AF efficacy of ranolazine, this agent was found to reduce the incidence of new onset AF onset by 30% in acute coronary syndrome patients (p=0.08). AZD7009 was reported to successfully convert up to 70% of patients with an average AF duration of 43 days to sinus rhythm whereas vernakalant was successful in converting 52-56% of patients with recent AF onset (< 7 days) but only 8% of patients with long-duration AF (< 45 days). These findings are not very different from those of conventionally used anti-AF agents, such as flecainide, propafenone, dofetilide, amiodarone, ibutilide, etc. The benefit of the atrial selective agents is that they do not produce significant electrophysiological changes in the ventricles. It appears that amiodarone can also be categorized as atrial-selective. It is noteworthy that direct comparisons of the effects of most clinically-used anti-AF agents in atria and ventricles are not available either in vivo or in coronary-perfused preparation studies.

Current pharmacologic strategies for the management of AF include sodium channel blockers such as propafenone and flecainide, potassium channel blockers such as sotalol and dofetilide and mixed ion channel blockers such as amiodarone. All have demonstrated efficacy but distinct indications based on their proclivity to promote ventricular arrhythmogenesis under different conditions. These adverse effects distinguish these agents from the newer atrial-selective agents. The sodium channel blockers are contraindicated in patients with coronary artery or structural heart disease because of their potent effect on conduction in the ventricles, potassium channel blockers predispose to the development of acquired long QT and torsades de pointe arrhythmias because of their potent effect to prolong ventricular repolarization, and mixed ion channel blockers such as...
Atrial Selectivity and Atrial Remodeling.

It is important to recognize that the atrial selective/predominant effects of some INa as well as IKr blockers have been tested in relatively “healthy” atria and ventricles. Clinical AF commonly occurs in conjunction with a number of conditions (congestive heart failure, hypothyroid, dilatation, hypertension, etc) associated with electrical and/or structural remodeling of the atria. These pathophysiologic changes can importantly modify the response to sodium and potassium channel blockers, and thus modify the atrial selectivity of these agents.

Conclusions

There is no robust evidence in support of the hypothesis that “pure” inhibition of IKur may effectively suppress AF. No clinical data are available relative to the anti-AF efficacy and safety of IKACH or Cx40 as atrial-specific approaches. The available data suggest that atrial-selective approaches involving a combination of INa, IKur, IKr, and, perhaps, Ito blockade, may be more effective in the management of AF than pure IKur or INa block. The anti-AF efficacy of the atrial-selective/predominant agents appears to be similar to that of conventionally used anti-AF agents, with the major difference being that the latter are associated with ventricular arrhythmogenesis as well as extracardiac toxicity. It is noteworthy, however, that the long-term toxicity of the atrial-selective drugs, with the exception of ranolazine, is not known.

Disclosures

Dr. Antzelevitch consults for CV Therapeutics, AstraZeneca. Dr. Antzelevitch received lecture fees from CV Therapeutics, Cardiome, Solvay, Pfizer, Aventis. Dr. Dr. Antzelevitch received grant support from CV Therapeutics, AstraZeneca, Cardiome, Epix, Solvay, Genzyme

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Introduction

Radiofrequency ablation of atrial fibrillation (AF) has emerged as a very effective technique for the treatment of this common arrhythmia. When AF ablation was first described by Haissaguerre et al nearly ten years ago, the technique was focused on the elimination of focal triggers for AF, emanating largely from the pulmonary veins (PVs). For patients with predominantly paroxysmal AF and little structural heart disease, this paradigm remained successful, with evidence confirming that elimination of all possible triggers via pulmonary vein isolation (PVI) would successfully prevent AF recurrence. However, in populations with more persistent and permanent AF, the high success rates of PVI procedures were not replicated. In these patients, it is believed that additional targets may be required to maximize success. In particular, there has been interest in identifying the critical elements of the atrial substrate required for maintaining AF. By targeting this so-called “substrate,” it is hoped that AF ablation may achieve better cure rates in a wider spectrum of AF patients. While markers of the AF substrate have been proposed as potential targets of ablation, the efficacy of using such targets is not well known. Furthermore, whether such targets should be eliminated alone, or in conjunction with known triggers is also not well understood.

Trigger-Based Ablation

The goal of most present-day AF ablation techniques is to electrically isolate the PVs from the rest of the atrium by ablating around the origin of the veins. In their original article, Haissaguerre et al showed that in the majority of paroxysmal, lone AF patients (94%), focal triggers for AF were found in one or more of the PVs. Although non-PV sites may also trigger AF, this is less common, occurring in no more than 6-10% of paroxysmal AF patients. Thus, most present-day techniques are focused on ablating around the PVs. Initially,
operators ablated early activation sites around the ostium of the veins—a technique often referred to as segmental, ostial isolation. However, as the understanding of the anatomy of the PV-left atrium (LA) interface increased, it was realized that the veins merge into the LA as a funnel-shaped structure, sometimes referred to as the “antrum”. To effectively isolate the PVs from the LA, it is necessary to isolate the entire antral region with the goal of achieving complete electrical disconnection between PVs and LA. Although this technique has many names and variations, including “pulmonary vein antrum isolation,” “circumferential PV ablation,” or “extraostial isolation,” the lesion sets produced by the procedures are all very similar (Figure 1). Success rates are also similar, with recent pooled analyses showing success in the 80% range.

Evidence has also suggested that the success of such ablation procedures is directly related to eliminating conduction between the PVs and the LA. Verma et al studied patients post-PV antrum isolation and found that those with successful outcomes had significantly more PVs isolated compared to those who failed. Furthermore, patients who were responsive to antiarrhythmic medications had more conduction delay between the LA and PVs versus those who were not responsive. Ouyang et al also found that recurrent LA-PV conduction was the predominant finding in patients with recurrent arrhythmia post-PV antrum isolation. In both studies, patients were successfully cured by re-isolating all of the PV antra. The majority of patients in these studies had paroxysmal, lone AF. These results are not necessarily appli-

Figure 1: Panels depicting the similarity in location of the radiofrequency lesions produced by various groups’ approaches to atrial fibrillation ablation.

The upper left panel shows the location of lesions produced using a CARTO-guided approach described by Morady and colleagues. The lower left panel shows the location of lesions produced using another CARTO-guided approach described by Pappone and colleagues. In all three cases, the location of the lesion sets is similar, encompassing the anterior and posterior borders of all four pulmonary venous antra. LSPV=left superior pulmonary vein, LIPV=left inferior pulmonary vein, RSPV=right superior pulmonary vein, RIPV=right inferior pulmonary vein. (Reproduced from Verma et al, Circulation 2005, 112:1214-22 with permission from publisher Lippincott Williams &Wilkins)
cable to more persistent AF populations. Furthermore, wide PV antral isolation requires very extensive lesion sets, which presents risks including perforation and stroke. In particular, PV antral isolation requires a lot of ablation along the posterior LA wall, which presents a risk of collateral damage to the esophagus. All of these reasons have prompted investigators to search out alternative or adjuvant lesion sets that may be required to modify the atrial substrate for AF maintenance beyond trigger-based ablation.

Substrate-Based Ablation

There is no general consensus on what exactly constitutes the “substrate” in clinical AF, making the use of this term somewhat problematic. It seems that when most clinicians talk about targeting the substrate for AF, they are referring to critical regions or components of the left atrial anatomy/eletrophysiology that are responsible for allowing AF to perpetuate. Investigators have proposed different ablation targets to try and identify these critical regions including complex fractionated electrograms (CFEs), dominant frequencies (DFs), and autonomic ganglionated plexi (GPs).

Complex Fractionated Electrograms

From early animal and human experiments, it was found that atrial regions exhibiting very rapid activation may represent critical rotors responsible for maintaining AF. Furthermore, regions demonstrating very fragmented potentials, to the point of almost continuous baseline activity, may represent pivot points or regions of very slow conduction responsible for continued fibrillatory conduction. Nademanee et al first described targeting these types of electrograms (EGMs) exclusively to ablate AF. He defined so-called “complex fractionated atrial electrograms” as either EGMs with (1) two deflections or more and/or have a perturbation of the baseline with continuous deflections from a prolonged activation complex or (2) very short cycle length (<120 ms) with or without multiple potentials. These EGMs also typically have very low voltages of 0.06-0.25 mV. By ablating these targets, Nademanee described a 76% success rate after one procedure (91% after two). Others have also shown that by adding complex atrial electrograms to ablation, success rates may be increased. However, targeting CFE either as a stand-alone or adjuvant technique is still subject to controversy. One reason is the subjectivity in identifying CFEs. Published articles have not been consistent in their definitions of CFE. For example, some define any EGM with more than 2 components a “CFE” regardless of the cycle length or continuity of the signal (Figure 2). While an EGM with 2 or more components may technically be “fractionated,” only low-voltage EGMs with rapid or continuous activity have been described as ablation targets or true complex fractionated electrograms (CFE). To this end, automated mapping algorithms have been developed to automati-
cally identify CFEs and the early results have been promising (Figure 3). Verma et al\textsuperscript{11} reported on the use of an automated CFE mapping algorithm in a prospective, multicenter study. The study found that the algorithm accurately identified CFE when compared to independent, experienced investigators and that CFE ablation resulted in high rates of AF regularization and termination. Finally, as an adjuvant strategy, CFE ablation combined with PVI resulted in a significantly better outcome compared to PVI alone.

However, reliable, consistent identification is not the only potential limitation to the use of CFE. There is debate as to the temporal and spatial stability of CFE and whether these EGMs represent transient regions of wavefront collision as opposed to critical, stable regions of AF perpetuation.\textsuperscript{12} These complex electrograms have been reported by some to be spatially stable and their elimination results in AF cycle length prolongation, regularization, and possibly long-term AF reduction.\textsuperscript{9,13} Moreover, Lin et al demonstrated that with an adequate sampling time of more than 5 seconds, the consistency in CFE sites both spatially and temporally is very high.\textsuperscript{21} Some have also reported looking for such complex activity sites during sinus rhythm by examining the Fourier transform of sinus EGMs and looking for multiple late, rightward shifted frequencies or so-called “fibrillar” myocardium.\textsuperscript{14}

**Dominant Frequency**

Trying to identify and interpret complex signals can be very challenging during AF. Therefore, some investigators have tried to use DF sites to identify regions of high frequency atrial activity. Sanders et al, for example, reported that AF termination or AF cycle length prolongation during ablation was usually seen while ablating over a DF site.\textsuperscript{15} They also showed that the distribution of DF may vary from paroxysmal to permanent patients, with DFs less likely to be associated with the PVs in non-paroxysmal patients. However, like CFE, there is some question as to the temporal and spatial stability of DFs. Ng et al showed that DF values were significantly impacted by local EGM factors such as amplitude variation, frequency fluctuation, and EGM ordering or phase.\textsuperscript{16} Thus, DF sites may not necessarily correlate with atrial regions exhibiting the most rapid or complex atrial activity. There have not yet been any studies validating the approach of targeting DF

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**Figure 3:** Example of a three-dimensional representation of the left atrium (AP view) with color-coded regions indicating areas of complex fractionated activity using an automated mapping algorithm (Ensite NavX, St Jude Medical, St Paul, MN).
sites for AF ablation.

Autonomic Ganglionated Plexi

It has been suggested that autonomic inputs from ganglionated plexi surrounding the heart may contribute to both the initiation and maintenance of atrial fibrillation (AF). High-frequency stimulation of epicardial autonomic plexi can induce triggered activity from the pulmonary veins and also affect atrial refractory periods so as to provide a substrate for the conversion of PV firing into sustained AF. Elimination of vagal inputs may prevent AF recurrence in both animal and patient models of vagal AF. In human AF patients, recent data has suggested that identification and ablation of autonomic ganglia during PV isolation may improve long-term success. However, in another report, use of ganglionated plexus ablation alone in vagal AF patients had a success rate of less than 30%. The location of these plexi has been correlated with the presence and location of CFE, but whether targeting plexi alone will ultimately prove effective remains unclear.

The Need For Clinical Trials

Ultimately, several targets have been proposed for AF ablation, each with their own supporting evidence and limitations. It is also quite likely that for any given approach, there will be overlap in the targets that are ablated. Performing circumferential lesions around the PVs may not only isolate them, but may also eliminate some sites of CFE and some autonomic inputs. However, whether we need to systematically add other targets to PVI or whether we need to move beyond PVI as a whole remains a somewhat controversial issue. The only way to definitively determine the efficacy and utility of different approaches is to subject them to the rigor of randomized clinical trials. One such trial, Substrate versus Trigger Ablation for Reduction of Atrial Fibrillation (STAR-AF) will specifically look at the utility of targeting CFE versus PVI. In this randomized, three-arm, multicenter comparison, PVI will be compared to CFE alone as well as a hybrid procedure combining PVI and CFE in a largely persistent AF population. The primary outcome will be freedom from AF at one year. Canadian and European centers are now actively enrolling in the pilot phase of this trial and results should be available within the next year.

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Pre-Procedural Imaging to Direct Catheter Ablation of Atrial Fibrillation: Anatomy and Ablation Strategy

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Abstract

Successful catheter ablation of atrial fibrillation (AF) requires a detailed understanding of left atrial anatomy in order to maximize the safety and efficacy of the procedure. Common and rare variants of left atrial and pulmonary venous anatomy have been described which can affect the optimal ablation strategy for each individual patient. These variants include the presence of a right or left middle pulmonary vein, a left or right common pulmonary vein, a common inferior pulmonary vein, a right top pulmonary vein, and other rare forms of anomalous pulmonary venous drainage. There are also important patient-specific differences in pulmonary venous ridges and left atrial roof morphology. Pre-procedural CT or MR imaging can define these anatomic variants in exquisite detail and be used with image-integration strategies to direct the ablation procedure. In this review, we describe common and uncommon variants that can be identified by pre-procedural imaging, and suggest ablation strategies tailored to these anatomic variants.

Introduction

Catheter-based pulmonary vein isolation has become an accepted treatment for atrial fibrillation (AF),1 based on the observation that electrical activity in the pulmonary veins may serve to trigger AF.2 To perform this procedure successfully and safely requires knowledge of the anatomy of the left atrium (LA) and pulmonary veins (PVs). Early ablation procedures utilized fluoroscopy (at times aided by contrast injection), providing limited anatomical detail in regard to the anatomy of relevant structures. As catheter ablation for AF has evolved, it has become increasingly clear that a detailed understanding of a patients’ LA and PV anatomy can facilitate the ablation procedure and reduce the potential for complications such as pulmonary vein stenosis. Magnetic Resonance Angiography (MRA) and Computed Tomography (CT) can produce highly precise images delineating the anatomy of the LA, PVs and surrounding structures. Recent advances in image integration have allowed the merging of LA/PV images from pre-procedural MRA or CT with real-time electroanatomic maps, allowing for direct visualization of catheter position within the MRA or CT images.3 Anatomical variants of the LA and PVs have been identified by these imaging studies that have implications for the catheter ablation procedure. In this review, we summarize common and uncom-
mon LA and PV anatomy, and also describe ablation strategies that can be utilized when these anatomic variants are encountered.

**Typical PV Anatomy**

**Typical PV Structure**

The most common PV anatomy involves 4 pulmonary veins: 2 left and 2 right. (Figure 1) This pattern has been reported in various series in: 56% of 105 patients with AF imaged by MRA, 62% of 55 patients (approximately 1/2 with AF) imaged by MRA, and 81% of 58 patients with AF imaged by CT. Typically the superior pulmonary veins (both left and right) are more anteriorly directed compared to the inferior pulmonary veins.

**Size and Shape of Typical PVs**

Most studies of PV size have reported ostial diameters ranging from approximately 7-25 mm in the setting of typical PV anatomy. Some studies have reported that the superior veins have a larger ostial diameter than the inferior veins, while other studies have reported similar ostial size for the superior versus inferior vein ostia. When the PV anatomy is typical, the right vein ostia have been reported to be slightly larger than the left in most studies, and comparable in another study, although rigorous statistical comparison was not performed between left and right vein ostial diameters in all studies. Some of the discrepancies might be explained by the finding that there is substantial ovality to the pulmonary vein ostia, which could affect the measurement of ostial diameter depending on the axis utilized for measurement. It was also found that there is greater ovality to the left veins compared to the right, with ovality ratios of 1.4-1.5 on the left versus 1.2 on the right, possibly related to a “compressive” effect of the ridge separating the left pulmonary veins from the left atrial appendage (LAA), and also to compression of the left pulmonary veins (particularly the left inferior pulmonary vein) by the aorta.

There is also substantial variation in the distance between the right and left pulmonary veins. (Figure 2) The distance from the os of the RSPV to the LSPV averages 33 + 11 mm, but with great variation between AF patients, ranging from 10 to 66 mm. The distance from the os of the RIPV to LIPV is similar (39 + 12 mm), and also shows great inter-patient variability, ranging from 17 to 71 mm.

**Ablation Strategies**

With typical PV anatomy, encirclements are typically made around the antra of each set of pulmonary veins (Figure 1), with the goal of achieving electrical isolation of the veins. If the ridges separating the superior and inferior pulmonary veins are sufficiently wide, further linear ablation may be performed along these ridges to electrically...
separate the superior and inferior veins on either the left and/or the right side. Alternatively, a “box lesion” can be performed around all 4 pulmonary veins, isolating them en-bloc from the remainder of the left atrium (Figure 3). This “box” lesion has potential advantages in that a larger region of the posterior left atrium is isolated compared to the traditional lesion set, and fewer ablation lesions are delivered along the posterior left atrium in regions which may be adjacent to the esophagus. The box lesion may be particularly desirable when there is a relatively small distance separating the right and left pulmonary veins, whereas it may be more difficult to achieve electrical isolation using the box lesion when this distance is very large.

Common Pulmonary Vein Variants

Right Middle Pulmonary Vein (RMPV)

A single RMPV (3 total right sided veins) is the most commonly encountered PV variant in most reported series, with incidence ranging from 9.5% to 27%. When present, this vein is nearly always smaller than typical pulmonary veins, with a reported ostial diameter ranging from 7.5 + 2.1 mm to 9.9 + 1.9 mm. The RMPV may project either anteriorly or posteriorly, depending on which segment of lung it is draining. The ridges separating the right pulmonary veins are typically quite narrow when a RMPV is encountered (<2mm in narrowest width in > 50% of patients). (Figure 4) Because these ridges are generally narrow in the presence of a RMPV, we typically avoid catheter ablation along these ridges when this variant is encountered to reduce the risk of inadvertent ablation within the pulmonary veins, as catheter stability along these narrow ridges is typically poor. Of note, a left middle pulmonary vein has been reported only rarely (0-3% in one study and not described at all in many other similar series).

Multiple Right Middle Pulmonary Veins

Multiple (>2) right middle pulmonary veins are also encountered in the LA. (Figure 5) The incidence of this variant has been reported in various series at 2%, at 4-5%, and 4%. These variants can be sub-classified based on whether there are 2 or 3+ right middle pulmonary veins and on the branching pattern, but currently reported series are too small to accurately estimate the relative frequency of these sub-variants. Although no published reports are available on dimensions of the ridges separating multiple right pulmonary veins, it is our experience that the widths of these ridges (as well as the diameters of the vein ostia) tend to be quite small. Based on concern for pulmonary vein stenosis if ablation is performed inadvertently in these small veins, we typically avoid ablation along the ridges separating multiple right middle pulmonary veins.

Figure 3: A “box” ablation lesion set is shown in this posterior MRI view of the left atrium.

4A shows an endoluminal view demonstrating the ridges between the right pulmonary veins. Note the narrowness of the ridges separating these veins, which could potentially impair catheter stability if ablation was performed along these ridges. 4B shows a left posterior view, demonstrating the ablation lesions required to isolate the left and right pulmonary veins. Note that ablation was performed between the LSPV and LIPV, but that all of the right pulmonary veins were isolated en-bloc in the presence of a RMPV.
pulmonary veins.

**Left Common Pulmonary Vein (LCPV)**

The second most common pulmonary vein variant reported in most studies is a LCPV, which has a single ostium from the LA, and then typically divides distally into superior and inferior branches. (Figure 6) The incidence of LCPV has been reported to be as rare as 3.4% of patients whereas another study reported this variant in 32% of patients with AF. Other studies have reported a LCPV incidence of 9.5%, 14%, 17%, and 6% in patients with AF and 20% in patients without AF. Of note, in the study describing a 32% incidence of LCPV in AF patients, 7% were described as a LCPV with a “long trunk” and the remaining 25% with a “short trunk”. It is possible that some investigators might describe a particular anatomy as comprising separate left superior and inferior pulmonary veins, while others might classify this same anatomy as a LCPV with a “short trunk”, and this may contribute to the reported discrepancies in the incidence of LCPV. Given that this single vein must drain the entire left lung, it is not surprising that it generally has an ostium that is substantially larger than the ostia of typical pulmonary veins. The average ostial diameter of the LCPV has been reported at 19.4 ± 5.3 mm, 26.0 ± 4.0 mm, and 32.5 ± 0.5 mm. Studies which measured the LCPV ostia in 2 dimensions have noted it to have significantly greater ovality than other pulmonary veins, and so axis of measurement may explain the discrepancies in reported diameter of this vein.

Typically we attempt to isolate a LCPV by encirclement around the entire antrum of the common vein. Of note, commercially available “lasso” catheters are often smaller than the os of a typical LCPV, and will often slide deep into this vein (Figure 6). Effective imaging of this vein, with pre-procedural CT/MR and/or intra-procedural ICE, can help to prevent inadvertent ablation within a LCPV. Ablation within the LCPV (along the ridge between superior and inferior branches) is generally avoided given the risk of pulmonary vein stenosis when ablating within a vein. It is our experience that it is generally more difficult to isolate a LCPV with this approach compared to isolation of separate LSPV and LIPV. In some cases, especially when a LCPV has a very “short trunk” before branching, limited ablation is performed carefully between superior and inferior branches in order to achieve LCPV isolation when isolation can’t be achieved by ablation around the ostium of the LCPV.

**Right Common Pulmonary Vein (RCPV)**

A RCPV (a single right pulmonary vein ostia, typically then separating into superior and inferior
branches) is less commonly encountered than a LCPV. This variant has been reported in 0-2%8 and 2%13 of patients, while other studies with similar numbers of patients have not reported this variant.4,6,9,10 As with a LCPV, there may be a certain degree of observer discretion in identifying a RCPV with a “short neck” versus typical anatomy including separate RSPV and RIPV. We typically plan an ablation strategy for a RCPV similar to a LCPV, with attempts to isolate the entire vein en bloc with antral encirclement. We reserve ablation at the ridge between the superior and inferior branches of a RCPV only for cases in which the ridge is wide, catheter stability on the ridge is good, and if ablation at this site is necessary to completely isolate the vein after full antral ablation has been performed.

Uncommon Pulmonary Vein Variants

Common Inferior Pulmonary Vein (CIPV)

A rare variant of drainage for the inferior lobes of both lungs is a CIPV, which typically empties via a common ostium into the central region of the infero-posterior LA. (Figure 7) It is not clear what the true incidence is of this rare variant, but it appears to be encountered in less than 1% of patients, relegating its description to single case reports.15,16 Like a LCPV or RCPV, it is possible to isolate an CIPV en bloc by a single encirclement around the common ostia, reducing the risk of pulmonary vein stenosis which would exist with ablation deeper into each vein.

Right “Top” Pulmonary Vein (RTPV)

Another uncommon pulmonary vein variant is the RTPV. This is characterized by a single, typically small pulmonary vein draining the upper regions of the right lung and emptying into the roof of the right atrium, superior to the typically larger RSPV. (Figure 8) Its incidence has been reported as 3 out of 91 subjects in one series17, although other similar series have not reported it, and so its true incidence is somewhat uncertain. It is important to identify this variant in pre-procedural imaging, as its ostium is superior to the antrum of the RSPV, at a region that is typically ablated when performing circumferential ablation of the right pulmonary veins. It is possible that a RTPV could be identified by electroanatomic mapping or intracardiac echocardiography (if pre-procedural imaging was not performed), but there would be far greater risk of failing to identify this vein by these modalities, especially if its presence were not being actively sought. Given the generally small size of the RTPV, the risk of PV stenosis is presumed to be high if ablation is performed inadvertently within this vein. When this variant is encountered, modifying the ablation line to avoid ablating within this vein (possibly by extending the ablation line further onto the LA roof to incorporate the RTPV into the encirclement of the other RPVs) seems to be a prudent choice.

Variant Pulmonary Vein Drainage

Partial anomalous pulmonary venous return (PAPVR) has been extensively reported in the cardiac surgical literature18, and these variants may be defined in great detail by pre-procedural CT or MR imaging.19 One example we encountered is a patient presenting for catheter ablation of paroxysmal AF with an anomalous RSPV draining directly into the SVC (Figure 9). This abnormality is often associated with the presence of sinus venosus ASD atrial septal defect. Other variants in the PAPVR category include the scimitar syndrome (drainage of right lower lobe pulmonary...
Pulmonary veins, and separating the left pulmonary veins from the left atrial appendage (LAA), are highly relevant to the ablation procedure (Fig. 10). Ablation along these ridges can facilitate isolation of the veins, and wider ridges typically allow for greater catheter stability with less risk of inadvertent catheter slippage into the pulmonary veins. It is difficult to accurately assess these ridges even with highly detailed electro-anatomic mapping alone. The dimensions of these ridges can be assessed with high accuracy with pre-procedural MR or CT imaging, however, and can also be assessed with intracardiac echocardiography. Intracardiac echocardiography (possibly used in conjunction with pre-procedural imaging) can also provide important real-time information on catheter position in relation to these pulmonary vein ridges.

The pulmonary vein ridges relevant to the ablation procedure have average minimal widths in the range of 2-8 mm. The average width of the ridges separating the RPVs (in the presence of a RMPV) are significantly less than average width of the ridges separating the LSPV from the LIPV. The width of the ridge separating the LPVs from the LAA is also significantly less than the width of the ridge separating the RPVs from the LAA.

There is, however, a paucity of published information about ablation strategies in patients with PAPVR. Without pre-procedural imaging or detailed intra-procedural ICE imaging, it seems likely that many of these variants would be missed in a typical anatomical ablation strategy. When these variants are identified during pre-procedural imaging, however, alternative ablation strategies for these patients, such as electrical isolation of the SVC (thereby electrically disconnecting the anomalous RSPV from the SVC and right atrium) in the patient shown in Figure 9, can be tailored to an individual patient's anatomy.

**Other Left Atrial Structures**

**Pulmonary Vein Ridges**

The dimensions of the ridges separating the pulmonary veins into the IVC at or below the level of the dia-phragm), and left sided PAPVR (drainage of left superior pulmonary vein into a vertical vein that connects to the left innominate vein, therefore causing a left to right shunt). A separate entity in the spectrum of pulmonary venous return abnormalities is the cor triatriatum, where all four pulmonary veins drain into a posterior receiving chamber that is separated by an abnormal septum from an anterior left atrial chamber.  

Intracardiac echocardiography (possibly used in conjunction with pre-procedural imaging) can also provide important real-time information on catheter position in relation to these pulmonary vein ridges.
the LAA tends to narrow as the ridge ascends from the LIPV to the LSPV. As a LCPV is relatively uncommon, the width of the ridge separating the LCPV from the LAA has not been described. These generalities cannot fully account for patient-specific differences in ridge dimensions, however, and so accurate imaging to delineate the ridges in each patient is useful to direct the ablation procedure.

Left Atrial Roof Morphology

A variety of morphologies of the LA roof have been described, including flat, convex and concave. Although the ablation strategy at the LA roof is not substantially different for these variants, identification of an individual patient’s LA roof morphology can facilitate catheter contact along the LA roof and minimize risk of perforation. Pouches arising from the LA roof have also been described, which may increase the difficulty of creating complete electrical isolation along a “roof line” connecting antral ablation lines from the left and right superior pulmonary veins. Of note, the right pulmonary artery often passes very close to the LA roof, and so potentially could be injured by ablation at this site. Pulmonary artery injury has not yet been reported as a complication of catheter ablation of AF, however, and this may relate to the cooling effect of high blood flow in this structure.

Esophagus

The esophagus runs in close proximity to the left atrium, and injury to the esophagus during AF ablation has resulted in the rare but potentially fatal complication of atrio-esophageal fistula formation. The relationship between the esophagus and the left atrium can be identified by pre-procedural cardiac CT scanning and by MRI, providing a potential tool to identify LA sites that are in close proximity to the esophagus. It has been noted, however, that the esophagus can migrate from a site adjacent to the left PVs to a site adjacent to the right PVs during an ablation procedure. For this reason, real-time assessment of esophageal location by methods such as esophageal temperature monitoring, barium swallow or intracardiac echocardiography may be more useful in minimizing the risk of esophageal injury than pre-procedural assessment of esophageal location.

Left Atrial Appendage (LAA)

The LAA lies in close proximity to the left pulmonary veins. It is rare to target ablation within the LAA during typical ablation procedures for AF, although atrial tachycardias have been reported which were successfully ablated within or at the antrum of the LAA. The ridge separating the LAA from the left pulmonary veins is a target for ablation during isolation of the left pulmonary veins, and catheter stability allowing effective lesion formation without inadvertent ablation within the LAA or left-sided veins can be difficult at this site (Figure 10). Pre-procedural cardiac imaging can be useful to define this ridge (including length, width, and orientation), and integration of electro-anatomic mapping with the resulting images can facilitate ablation along this ridge. Pre-procedural imaging can also define the size and dimensions of the LAA in great detail, with substantial inter-patient differences documented in LAA size, and this may prove useful in directing device occlusion of the LAA, which is currently an investigational strategy intended to reduce strokes resulting from AF.
Limitations of Pre-Procedural Imaging

There are several limitations in the ability of pre-procedural imaging to accurately direct catheter ablation of AF. It is possible for volume shifts to occur in the atria between the time of imaging and the time of ablation that may lead to differences in pre-acquired images compared to real-time mapping. Three dimensional rotational LA angiography has been described which allows for LA imaging immediately prior to catheter mapping, but this technology currently lacks the spatial resolution possible with CT or MR imaging. Concordance of cardiac cycle gating between pre-procedural CT or MR imaging and real-time mapping has not been universally performed, possibly leading to error in image registration. Additionally, cardiac deformation by catheter contact can create distortions during real-time catheter mapping which are not identified by pre-procedural imaging. Real-time imaging strategies, such as (currently available) intracardiac echocardiography or (currently investigational) interventional MR imaging during the ablation procedure can provide even more precise detail of catheter position in relation to complex LA anatomy.

Conclusions

The LA is a complex structure, with great inter-patient variability. A detailed understanding of an individual patient’s LA anatomy may improve the ability to effectively isolate the pulmonary veins and to produce other desired ablation lines and lesions within the LA. This may also reduce the risk of complications such as cardiac perforation and damage to surrounding structures, including the esophagus and the pulmonary veins. Pre-procedural cardiac CT or MR imaging can produce highly detailed representations of each individual patient’s anatomy within the LA and relative to surrounding structures. This allows an ablation strategy to be tailored for each patient to maximize both efficacy and safety.

Disclosures

Nothing to disclose.
Featured Review


Catheter Ablation for Atrial Fibrillation in Patients with Obesity

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Introduction

Obesity is a risk factor for atrial fibrillation (AF) and common comorbid conditions such as hypertension, sleep apnea, and structural heart disease. This study was designed to determine whether catheter ablation of AF can be performed safely and effectively in obese and overweight patients compared with patients with normal body weight.

Methods

A cohort of 523 patients with symptomatic AF undergoing radiofrequency ablation at a single institution was included in this study. Body weight was determined and patients were stratified by body mass index into three groups: lean (BMI < 25 kg/m2), overweight (BMI 25-29.9 kg/m2) and obese (BMI ≥ 30 kg/m2). Two techniques for atrial ablation were employed: 298 patients underwent pulmonary vein ostial ablation with a 5mm tip ablation catheter and 222 patients underwent wide-area circumferential ablation outside the pulmonary vein ostia with an 8mm tip ablation catheter. Patients in this second group also underwent creation of linear lesions and ablation of focal triggers of AF identified during isoproterenol infusion.

Patients were followed up with a 24-hour Holter monitor 3 months after the ablation. Follow-up after that time was performed by telephone, annual questionnaires, and with intermittent monitoring, though the method and timing of monitoring is not well-described. Quality of life questionnaires were administered 3 and 12 months after ablation. Outcomes are reported at 12 and 24 months after ablation but Kaplan-Meier curves are not provided.

Results

The majority of patients (58%) had paroxysmal AF. Only 18% of patients were classified as lean, while 44% were overweight and 38% were obese. Patients with higher BMI were younger, more likely to have persistent AF, hypertension, diabetes, structural heart disease, left atrial enlargement, and sleep apnea. Despite the increased prevalence of these comorbidities, no significant difference in the rate of freedom from AF was seen among the groups at the 12-month and 24-month follow up points. At the 24 months, 74% of lean, 73% of overweight, and 69% of obese patients were free of AF. Significantly more obese patients (48%) were lost to follow-up, which is a limitation of the study. All groups had a significant improvement in quality of life scores at the 12-month follow-up visit, and improvement in these scores was associated with maintenance of sinus rhythm. Obese patients had similar fluo-
roscopy times during the procedure, but radiation exposure was nearly triple in obese patients compared with lean patients (1.97 Gy vs. 0.69 Gy). Serious complication rates were moderate (5%) but similar across different BMI classes.

**Conclusion and Comment**

Many patients with AF are obese, and this retrospective cohort study suggests that radiofrequency ablation is equally efficacious for patients across different body weights. One important consideration when performing ablation in obese patients is that radiation dose is markedly increased due to the nonlinear relationship of radiation dose to body size. This must be a consideration when discussing ablation procedures with patients, particularly if repeat procedures (performed in 17% of patients in this study) may be necessary. The outcomes reported in this study are primarily based on patient-reported symptoms and routine ambulatory monitoring was not performed after 3 months. Since asymptomatic AF may be more common after ablation, the method of symptomatic outcome reporting may significantly overestimate success rates. The results are also reported on a monthly basis and cumulative success rates are not reported. It is unclear whether these factors may interact with obesity (for instance, if obese patients had more asymptomatic AF) to limit the results of this study. Further research on this topic may be required.

**Disclosures**

None to disclose in context of current subject matter
Aim

In this study the authors compared two different ablation strategies for the treatment of paroxysmal atrial fibrillation (AF): selective isolation of the pulmonary vein triggering AF (SePVI) versus empirical isolation of all the four pulmonary veins (EmPVI).

Methods and Results

Arrhythmogenic vein was identified by immediate recurrence of AF after cardioversion using infusion of isoproterenol as provocative manoeuvre. The exclusion criteria were as follows: non-paroxysmal AF, non detectable foci, non-PV foci, multiple PV foci or presence of structural heart disease. After exclusion of those, 77 patients out of 260 patients that underwent AF ablation, were enrolled in the study. After more than 3 years of follow up, 38% of patients treated with SePVI experienced AF recurrences versus 26% of patients treated with EmPVI (p = ns). Very late recurrences (later that 1 year) had a tendency to be more common in the SePVI group (19%) than in the EmPVI group (6%) (p = ns). A redo ablation was performed in most of patients that experienced recurrences. Fifty-four percent of patients in the SePVI group exhibited a reconnection of PV previously disconnected, 38% exhibited triggers arising from the ipsilateral but not ablated PV and 8% from the contralateral PV. On the other hand, a reconnection of PV was demonstrated in 37% of patients in the EmPVI group, triggers arising from ipsilateral PV in 25% of patients and from the contralateral PV in 38% of patients.

Conclusion

Given these findings authors conclude that there was non statistically significant difference in the success rate between the two ablation strategies.

Comments

Authors suggest the sharable idea that a minimal approach may be applicable to a subgroup of younger and healthier patients manifesting par-
oxysmal AF clearly initiated by limited triggers. However, the main limitation of the study is that the resulting absence of statistically significant difference in success rate is certainly due to the small size of study population. In fact, increasing the number of patients, the same 12% of absolute difference would become statistically significant. Therefore, how to select patients that can be treated appropriately with a limited strategy remain to be clarified.

**Disclosures**

None to disclose in context of current subject matter
Introduction

The population of patients with atrial fibrillation (AF) continues to expand and emerges to be the most common arrhythmia we deal with. Referrals to centers performing catheter based ablation procedures for AF also continue to grow as catheter ablation becomes an increasingly accepted therapeutic approach. In this article we will describe the infrastructure we have developed to manage our atrial fibrillation ablation population at the Richard and Annette Bloch Heart Rhythm Center at the University of Kansas Hospital. Our goal is to provide a “nuts and bolts” overview from the allied health professional perspective. For concise reviews of AF management we recommend the ACC/AHA/EFC 2006 guidelines and the HRS/EHRA/ECAS expert consensus statement on catheter and surgical ablation of atrial fibrillation.1,2

Our outpatient allied health staff consists of nurse practitioners, registered nurses, exercise specialists, medical technicians, ECG, Holter and event recorder staff at our main campus and at various outreach sites. The Bloch Heart Rhythm Center provides comprehensive care for electrophysiology patients including medical management, implant devices and complex ablation techniques.

Our facility initiated a catheter based AF ablation program in 2005. Volume increased substantially with the addition of Dr. Dhanunjaya Lakkireddy in July 2006 and has continued to increase. Currently we perform approximately 20 cases monthly. The logistics of evaluating these...
patients, completing appropriate pre-procedure diagnostic testing, and orchestrating post-procedure follow-up is complex. As our population grows, the complexity of organization continues to grow as well. Although all of our staff is expected to be familiar with this patient population, we quickly learned identification of “AF Champions” was necessary to our ongoing success as a regional referral center. We also identified the need to partner with our surgical colleagues to offer an integrated program which includes surgical as well as medical and catheter based options. Ultimately, the Center for Excellence in Atrial Fibrillation was developed.

(Figure-1) The outpatient portion of the Center needs a strong outpatient allied professional team consisting of RNs, EP technicians, EKG and holter technicians along with administrative staff. (Figure-2)

**Figure 1:** Flow chart of organization of Center for Excellence in Atrial Fibrillation
As part of ongoing training, our outpatient staff has the opportunity to observe in the EP lab to ensure familiarity with the procedure itself. The staff also has the opportunity to attend relevant meetings such as the Boston Atrial Fibrillation Symposium and the Heart Rhythm Society Scientific Sessions.

We have established basic pathways but remain flexible. No two AF patients are the same. It is important to customize our approach to accommodate patient needs. Our basic pathway continues to evolve over time.

**Pre-Procedure AF Management**

Information management is facilitated by our electronic medical record. Outside records are scanned into this system so that all pertinent information is immediately available to anyone on our staff who requires access to it.

Prior to scheduling appointments, we attempt to obtain all relevant outside records, including office notes, echocardiograms, stress tests, and laboratory work. Previous catheterization data, results of electrophysiology studies and implanted device information are also obtained. Our business office reviews insurance information for compatibility. Once pertinent records are obtained, patients are scheduled at our main campus or one of our outreach sites to see an electrophysiologist to discuss treatment options. All appropriate options are discussed with the patient and family in detail. Additional patient education is carried out by Allied Health staff and includes both print and web-based materials.

If catheter ablation is a determined to be a viable option, a detailed discussion of procedures, possible outcomes and complications, is outlined in detail verbally and again reinforced with written and web-based materials. If patients have not had an Echo Doppler completed within the past twelve months, we will update the study or request one from the referring physician if they provide echo services.

We routinely obtain a 64-slice cardiac CT to assess the left atrium and pulmonary vein anatomy for proper planning of the procedure. Also these segmented images are used for integration into our EP lab three dimensional mapping systems. Insurance reimbursements for these critical tests continue to be an issue and we try to deal with these one on one. Ruling out prior PV stenosis is important especially for people who had prior attempts at AF ablation. More than a few times we caught...
structural anomalies like intracavitary (right atrial) coronary artery, tortuous and elongated left atrial appendageal clots usually not visualized by TEE with the help of these preablation CTs. The importance of post ablation CTs could not be stressed less.

Anticoagulation management is an area of particular concern. INR’s are obtained weekly for at least one month prior to the procedure. Coumadin is typically held for two days before ablation. For patients in atrial fibrillation in the days prior to the procedure, a Lovenox bridge is utilized. (1 mg/kg subcutaneously every 12 hours with the last dose administered 12-18 hours prior to the procedure.) Although, in the recent months, we are slowly moving towards ablation while INRs are therapeutic between 2 and 3. There is increasing evidence that AF ablation can be safely performed on therapeutic INRs minimizing the risk of periprocedural stroke.

Transesophageal echocardiograms are obtained on the day prior to the procedure, or on the day of the procedure, if anticoagulation has been interrupted in the presence of atrial fibrillation. Most patients do not require a TEE. This is an area where particularly close communication between the physician performing the A-Fib ablation procedure and the nurse orchestrating pre-procedure care is important.

Routine pre-procedure labs, besides PT/INR include CBC, BMP and magnesium. These are typically obtained 7-14 days prior to procedure to allow adequate time to address any abnormalities. If a woman of childbearing potential is scheduled for ablation, a beta HCG is obtained within three days of the procedure. Membrane active antiarrhythmic medications are typically held for 48 hours before ablation. Amiodarone is typically held for at least six weeks prior to ablation. Patients are admitted on the morning of their procedure and most procedures are done on an outpatient basis, although all of our patients remain in the hospital overnight.

Post-Procedural Care

Patients are discharged on Lovenox 0.5mg/kg q 12 hours until their INR is greater than or equal 2.0. PT/INR is monitored every 2-3 days early post-procedure. Most patients are on membrane active antiarrhythmic drugs pre-procedure and most continue on these drugs for at least 8-12 weeks post-procedure.

Post-procedure rhythm monitoring requires a robust infrastructure. We do ambulatory recording on our patients for at least three months post-procedure. We typically use a “heart card” type device and request that patients make recordings whenever they are symptomatic, and at least twice a week on a random basis. Rhythm strips are reviewed by staff on a daily basis. Significant abnormalities are brought to the attention of one of our Electrophysiologists, or ARNP for further guidance and management. Otherwise, recordings are reviewed by a physician at the end of each month. We continue to evaluate new technologies to enhance post-procedure monitoring.

Patients are contacted by phone by the EP lab staff, 2-4 days post-procedure and by the office staff at 1 and 2 weeks post-procedure. The staff inquires about potential post-procedure complications, including palpitation, lightheadedness, catheterization site status, chest pain, shortness of breath, dysphagia and overall sense of well being.

Follow-up is recommended at one month with the patient’s primary provider and at two months with the ablating electrophysiologist. Not infrequently patient concerns lead to additional APRN visits. At two months, if the patient is doing well, membrane active drugs are discontinued. In those patients who have had recurrence of arrhythmia in the first two months membrane active drugs are continued. Heart rhythm monitoring is continued for another 4 weeks off of the antiarrhythmic drug. In the absence of any recurrences we discontinue the heart rhythm monitoring but continue monthly EKGs either at the primary care physician or the cardiologists office. In the event of symptoms we tend to extend the heart rhythm monitoring.

A second follow-up visit with one of our electrophysiologists is scheduled at 3-4 months post-procedure. A follow-up CT is typically obtained at 4-6 months although we are considering eliminating this as a routine, given very low incidence
of significant pulmonary vein stenosis.

The six month follow-up visit is generally the first time that we will entertain the possibility of discontinuing Coumadin in appropriate patients (CHADS score 0-1 and no evidence of AF recurrence). In conjunction with this decision, an additional 30 days of heart rhythm monitoring is typically completed. We take a conservative approach to anticoagulation and favor maintaining it if there is any question as to possible recurrence of arrhythmia.

Management of Post Ablation Atrial Tachyarrhythmias

Management of post ablation left atrial tachycardia is complex. Majority of these are reentry tachycardias that subside by the end of 8 weeks post ablation. Certainly, a small percentage (5%) of these patients have persistent atrial tachycardias that need repeat intervention. We generally take an aggressive approach to terminating any sustained arrhythmias within 24-48 hours by moving quickly to DC cardioversion. If these patients have not been on a membrane active antiarrhythmic drug, one is initiated in the hospital in association with cardioversion. We try to delay repeat ablation until at least three months, preferring up to six months, after the initial procedure.

Psychosocial Issues

Many of these patients are very knowledgeable about atrial fibrillation and have actively researched their condition. These patients often have many questions which we begin to address by phone even before they are seen for their initial evaluation. Much of what they have read and heard is accurate and helpful, but occasionally they have some misperceptions that we work hard to correct. Both pre and post-procedure patients often have significant anxiety. They require extensive counseling and reassurance. Prompt access to a well informed RN, APRN, or physician is the key to managing these patients in a constructive way.

Conclusions

A well trained, well educated, focused staff supported by their physician partners, enhances our ability to effectively manage patients pre and post-procedure. Excellent counseling skills as well as technical expertise, is necessary to maintain patients’ confidence through what can be an emotional and physical roller coaster ride for these patients. The guiding bodies like HRS should proactively consider releasing some position statements in attempt to create uniform practice guidelines.

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References