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Dear Colleagues

Welcome to the May edition of JAFIB. Hope you had a wonderful
learning time at the Heart Rhythm Society Annual Sessions in San
Francisco. It was great to see a lot of you in person. On behalf of
the journal and the entire electrophysiology community we want
to congratulate and thank Drs. Hugh Calkins (Immediate Past
President, HRS) and Richard Fogel (President, HRS) for their
service, vision and leadership. The new ACC/AHA/HRS AF
guidelines are out and it is probably worthwhile to review these.

In this issue we have several manuscripts that are thought
provoking and provide solid review of many interesting topics in
atrial fibrillation (AF). Eraldo Occhetta presented their prospective,
randomized, cross-over, double-blinded RARE PEARL study that
evaluated the role of ventricular rate stabilization feature in the
single chamber pacemaker patients with permanent AF. In patients
with permanent atrial fibrillation (AF) rate irregularity can cause
symptoms and impair the pumping function of the heart. Ventricular
pacing at a rate close to the mean spontaneous ventricular rate can
result in a more stable ventricular rate. VRS seems to be preferred
by a lot of patients however, this seems to increase the percentage
ventricular pacing and its long term impact on ventricular function is
yet to be assessed. Francesca Galati and group presented a fantastic
paper that attempts to understand the pathophysiology of AF in post-
menopausal women. This study suggests that in post-menopausal
women atrial fibrillation could be promoted by the association of
cholesteryl ester transfer protein (CETP) B2B2/AA genotype with
higher triglycerides values. In their original article Sandor Kovacs
and colleagues describe atrial stiffness as a measurable parameter to
assess the LA function and potentially evaluate it going forwards.
Andreas Goette et al have an excellent review on the role of
Calpains in the creation of atrio-myopathy that could potential lead
to AF. Anne Curtis and group have presented a great review of the
current state of AF ablation in women. Success rates for AF ablation
are seems to be higher in earlier stages of the disease process, before
atrial remodeling sets in. In order to have a comparable success rate
of AF ablation in women, early referrals for ablation before they
develop a high risk profile. This article also highlights the additional
risk of vascular complications in women than their male cohorts.

Chris Liu wrote a nice review on the evolving role of Intracardiac
echocardiography (ICE) in clinical electrophysiology. Integration of
ICE into the 3D mapping system has improved electrophysiologists’
appreciation for anatomical correlates to various arrhythmias like
VT. Potential role in Left Atrial Appendage Exclusion and Trans
Aortic Valve Replacement (TAVR). Advances in volumetric 3D ICE
imaging hopes to improve real-time visualization and potentially
reduce need for fluoroscopy further. Claudio Tondo et al discuss
the role of effective and continuous rhythm monitoring after AF
ablation. Continuous rhythm monitoring over long periods of time
is superior to intermittent recording using external monitors to
detect the presence of AF episodes and to quantify the AF burden.
With the new thinner and smaller subcutaneously implanted devices
continuous AF monitoring is a reality and has come to be an attractive
option. In particular, it is not known whether there is any critical
value of daily AF burden that has a prognostic significance. This issue
remains an area of active discussion, debate and investigation.

In his concise review Girish Nair described the role of the renin
angiotensin system (RAS) in the etiopathogenesis of AF and appraises
the current understanding of RAS antagonism, using angiotensin
converting enzyme inhibitors (ACE-I), angiotensin receptor
blockers (ARB) and aldosterone antagonists (AA), for prevention of
AF. In a nice review article, Gregory Lip and colleagues discussed
stroke prevention in AF, and the clinical impact of CKD and its
implications for management. AF is often associated with an adverse
impact on HRQOL. Improvement in HRQOL, with a secondary
reduction of disability and health-care resource utilization, is one of
the major therapeutic goals in the management of AF. Successful

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AF ablation is associated with significant long-term improvement in HRQOL irrespective of the type of AF. Jason Andrade presented a concise review of the impact of catheter ablation on HRQOL. John Clark and colleagues present their experience with catheter ablation with zero fluoroscopy approach in pediatric population. Even though it sounds like a daunting task they clearly demonstrate that effective use of other imaging modalities like transesophageal echo and 3D mapping systems should dramatically reduce or eliminate the need for fluoroscopy. I think this is a major step forwards in creating procedural environment that continues to depend less on fluoroscopy. Josef Krautzner presented a brief review of the available contact force sensing ablation catheter systems and their role in tissue ablation especially in AF. These new technologies seem to hold a lot of promise for the future of AF ablation. We have a special feature in this issue in the form of a guest editorial by Abraham Kocheril on the role of right atrium in atrial fibrillation.

We wish you a great summer and a productive mid-year!!!

With Best Regards
Catheter Ablation Without Fluoroscopy: Current Techniques And Future Direction

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Abstract
Background: Catheter ablation is the treatment of choice for most forms of SVT. Traditionally, fluoroscopy has been the primary tool for visualizing catheter position. However, newer, 3-dimensional mapping technologies offer multiple options for minimizing fluoroscopy use. We review our 8 year experience of a zero-fluoroscopy approach using the Ensite system, and discuss our current techniques.

Methods: From January 2006 to October 2013, we performed 524 catheter ablation procedures with a zero-fluoroscopy approach. The Ensite system was used exclusively. Early in the study, NavX mode was employed. In the later time period, Velocity mode was used. The Ensite system allowed easy access to all right sided arrhythmias. For left sided arrhythmias, TEE was added to aid with transseptal puncture.

Results: Reviewing 524 consecutive procedures, mean age was 14 years (range 7 weeks to 65 years). Mean weight was 60.7 kg (range 3 to 174 kg). Mean procedure time was 142 minutes (range 42 – 402 minutes). There were no complications. Twenty-five patients required the use of fluoroscopy, mostly as part of simultaneous diagnostic or interventional cath procedures. There was only one instance in which fluoroscopy was used when not anticipated at the start of the procedure. With this data available, and seeing that fluoroscopy is rarely needed unexpectedly, we hypothesized that catheter ablation no longer requires a traditional cath lab. We present our early approach to ablation outside the catheterization lab.

Conclusions: Three dimensional mapping systems can eliminate fluoroscopy use in virtually all routine ablation procedures. As technology improves, ablation procedures will shift beyond the traditional cath lab.

Introduction
Awareness of radiation exposure has changed significantly in recent years. In 1980, the most common source of radiation exposure for a US citizen was environmental. By 2006, that had been surpassed by medical radiation exposure. From 1980-2006, there was a 600% increase in medical radiation exposure.1 Although medical imaging and procedures are diagnostically and therapeutically beneficial, there are long-term risks associated with such radiation exposure, which include dermatitis, cataracts, thyroid disease, and inducing malignant transformation.1-5 According to most reports, children carry a 3 to 10-fold increased risk of malignancy compared to adults and have a longer life expectancy in which to express risk.5,6 In addition to patients, these risks also accrue to medical personnel.5,7-10

Key Words: AtrialFibrillation, Stroke, Bleeding, Risk Assessment.

Disclosures:
None.

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Furthermore, breaks in double stranded DNA are generally considered the alterations responsible for the late effects of ionizing radiation, such as cancer.11 In 2009, Beels et al. reported an elegant study, which prospectively looked at 49 children undergoing non-EP cardiac catheterizations. Peripheral blood lymphocytes were analyzed before and after the procedure and the number of DNA breaks in each cell were counted to assess how radiation contributes to DNA breaks.12 They reported a significant number of DNA breaks at almost any dose of radiation, which was 4-fold greater than what had been predicted.12 In recent years, the guiding principle has been to reduce radiation exposure to patients and medical personnel to “as low as reasonably achievable” (ALARA). This focus is especially important in the pediatric population.

As medical specialists began to focus attention on radiation reduction, the general public's awareness of medical imaging and procedural radiation risks has also grown. With this information before the public eye, the medical field is again challenged to minimize medical radiation. After mechanical barriers were developed for personnel, such as lead aprons, goggles, thyroid collars and shielding, occupational doses of radiation dramatically declined.5,13 In EP studies, there have been technological advances to reduce radiation exposure, including better beam filtering, digital image enhancement,
and fewer pulses/second. The most significant advance in radiation minimization, however, resulted from the development of three-dimensional mapping systems.

In 2002, shortly after 3-D mapping tools became available, a Journal of Cardiovascular Electrophysiology editorial questioned the value and feasibility of 3D mapping. Since then, its utility has been demonstrated in multiple reports. In 2002, Drago reported the first experience of catheter ablation without use of fluoroscopy. However, technical limitations of 3-D mapping tools at that time constrained their use. A 2006 report documented a series of adult patients in which fluoroscopy was minimized or eliminated. A year later, the first series of catheter ablation without fluoroscopy in pediatrics was reported.

In this article, we report our experience with more than 500 ablation procedures and discuss the direction we believe catheter ablation is headed in the future.

Material & Methods

All but two procedures were performed under general anesthesia. The EnSite system (St. Jude Medical Inc., St. Paul, MN, USA) was used in NavX/Velocity mode. A 5F octapolar, steerable CRD2 catheter (St Jude Medical) was placed from the right femoral vein and advanced up the inferior vena cava (IVC) to the right atrium, and confirmed by the presence of atrial electrograms. For most procedures, an initial geometry is drawn consisting of SVC, IVC, right atrium, tricuspid valve and coronary sinus. The location of the His bundle is also marked. This process takes about 5 minutes at the start of the procedure. All EP catheters can then be maneuvered within this created geometry with real-time, continuous visualization (Figure 1). For all manifest accessory pathways, as well as AVNRT ablations, two catheters are utilized. The CRD2 catheter is positioned in the coronary sinus and the ablation catheter targets the substrate. For concealed accessory pathways a third catheter is positioned in the RV apex to allow for ventricular pacing during mapping and ablation. Standard atrial and ventricular protocols were then performed. This basic geometry is adequate to allow mapping of all right-sided arrhythmias. However, left-sided arrhythmias present a different set of obstacles. In most pediatric labs, ablating left sided arrhythmias involves performing a transseptal puncture. The transseptal sheath cannot be visualized on the Ensite system. Therefore, left-sided substrates could not be reached using the 3D mapping system alone.

For left sided arrhythmias, we perform transseptal puncture utilizing TEE guidance. A guide wire is advanced up the SVC and visualized by TEE (Figure 2). The transseptal sheath is then advanced over the wire and the wire exchanged for the transseptal needle. The sheath is then positioned in the fossa ovalis. When the fossa is shown to be tenting into the left atrium with the correct orientation, the needle is advanced. Saline contrast is used to confirm that the needle tip is in the left atrium and the sheath is advanced over the needle. The ablation catheter can then be positioned in the left atrium and geometry drawn, (Figure 4). It is possible to visualize the transseptal needle on the Ensite system. If an electrical coupling is established with the proximal end of the transseptal needle, the distal tip will show up on the 3D mapping system as a single point in space. However, it will only show up after the needle has exited the tip of the dilator. Because of this, there is no practical application of visualizing the transseptal needle on the 3D mapping system, and some other means of visualization must be utilized. With the combined tools of the Ensite system and TEE, fluoroscopy can be eliminated in nearly all routine EP procedures.

For right-sided arrhythmia substrates, patients were not anticoagulated. For left-sided targets patients were anticoagulated with heparin to achieve an activated clotting time of 250 seconds.

As this study is from a pediatric lab, there were no ablations of atrial fibrillation performed.

For all arrhythmia targets in the midseptal or anteroseptal location, cryoablation was performed. For all free-wall substrates, radiofrequency was the preferred energy source.

Results

At our institution, from January 2006—to October 2013, we performed over 500 procedures with a minimal or no fluoroscopy approach. In 524 consecutive procedures, 499 of those were completed without the use of fluoroscopy. Age range was between 7 weeks and 65 years with a mean age of 14 + 7 years; and weight ranged from 3 to 174 kg with a mean weight of 60.7 + 23kg. Mean procedure time was 142 minutes with a range of 42 minutes to 402 minutes. No significant complications occurred. Fluoroscopy was used in 25 patients, most of whom were undergoing an interventional...
or diagnostic catheterization at the same time. However, in three patients, the ablation could not have been completed without the use of fluoroscopy. Of these, the first patient was a small 4-year-old with a left-sided accessory pathway. The procedure was performed early in our experience with TEE and transseptal puncture. The TEE was technically difficult and adequate images necessary to perform the transspetral puncture could not be obtained, so fluoroscopy was used. The second case was a 14-year-old patient with WPW and SVT in whom the procedure needed to be performed awake. She had a left-sided pathway and TEE could not be performed with her awake, so fluoroscopy was used for transseptal puncture. The third patient was a 23-year-old patient s/p mustard atrial switch procedure who had intraatrial re-entrant tachycardia. He also had a transvenous atrial pacemaker. The pacing lead cannot be visualized on NavX, so fluoroscopy was used to avoid entanglement or RF lesions on the pacing lead. In two of these three patients, fluoroscopy use was anticipated before the case started. Therefore, in 524 consecutive procedures, unplanned fluoroscopy was required only once.

Discussion

This report summarizes our experience with a zero fluoroscopy method for both left and right-sided ablation procedures. Three-dimensional mapping without fluoroscopy provides a number of important benefits: 1) decreased radiation exposure, with its attendant risks; 2) staff comfort, and 3) easier access to ablation for certain populations, such as during pregnancy or radiation therapy.

The initial advantage of zero fluoroscopy results from the decreased radiation risk to patients and staff. We noted a significant reduction in radiation exposure after implementing a zero fluoroscopy approach, as reflected in radiation badge readings. (Figure 5). Nearly all radiation exposure seen on radiation badge readings now comes from device implants or background environmental radiation. With this zero fluoroscopy approach, lead vests and protective shields have been virtually eliminated. For more than five years we have not needed lead aprons in our lab. This not only makes the procedure more comfortable for the staff, but may also decrease the long-term likelihood of developing spinal orthopedic problems, which are well described.19 A zero fluoroscopy approach also allows us to perform ablations on patients in whom radiation would otherwise be contraindicated.

Our institution, as well as others, has shown the feasibility of performing catheter ablation without radiation in the pregnant female.20-24 In addition, we have had two staff members become pregnant and were able to continue their job in the EP lab throughout pregnancy, without the risk of an occupational hazard such as radiation. We have also had one referral for catheter ablation of SVT in a woman who had reached her maximum dose of radiation exposure due to radiation therapy for breast cancer. In this instance, the procedure was easily performed without additional radiation exposure to the patient. Although these isolated scenarios are uncommon, the capability to prevent radiation is tremendously beneficial to the patient’s overall care.

Our institution uses the EnSite system exclusively. The alternative system most commonly used is CARTO (Biosense Webster, Diamond Bar, CA, USA). Each of these two systems functions in a unique manner. In the EnSite system, catheter electrodes are detected and displayed based on impedance measurements from three separate, orthogonal electrical fields. We find this system provides two important benefits: 1) it creates highly accurate geometry in minutes, and 2) any catheter can be visualized within the system. The system’s drawbacks include a “drift” or “shift” in geometry resulting
### Table 1: Characteristics of Patients Undergoing AF Ablation by Sex

<table>
<thead>
<tr>
<th>Study</th>
<th>Left atrial diameter (mm)</th>
<th>LVEF (%)</th>
<th>Comorbidities (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Women</td>
<td>Men</td>
<td>Women</td>
</tr>
<tr>
<td>Forleo, 2007</td>
<td>4.0±6.5</td>
<td>4.0±6.3*</td>
<td>57.4±3.4</td>
</tr>
<tr>
<td>Patel, 2009</td>
<td>43±0.5</td>
<td>46±0.3*</td>
<td>56±8</td>
</tr>
<tr>
<td>Zhang, 2013</td>
<td>45.9±0.5</td>
<td>45.5±7.7</td>
<td>59.6±4.2</td>
</tr>
<tr>
<td>Takiga wa, 2013</td>
<td>37.2±5.0</td>
<td>38.0±5.1</td>
<td>68.6±6.2</td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th></th>
<th>Type</th>
<th>Women</th>
<th>Men</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HTN</td>
<td>52.1</td>
<td>30.7*</td>
</tr>
<tr>
<td></td>
<td>Valvular disease</td>
<td>15.5</td>
<td>5.3*</td>
</tr>
<tr>
<td></td>
<td>Stroke</td>
<td>8.5</td>
<td>8.7</td>
</tr>
<tr>
<td></td>
<td>Structural heart disease</td>
<td>32.4</td>
<td>23.3</td>
</tr>
<tr>
<td></td>
<td>HTN</td>
<td>55.2</td>
<td>40*</td>
</tr>
<tr>
<td></td>
<td>Diabetes type II</td>
<td>15</td>
<td>11*</td>
</tr>
<tr>
<td></td>
<td>Stroke</td>
<td>3.8</td>
<td>1.6*</td>
</tr>
<tr>
<td></td>
<td>CAD</td>
<td>11.3</td>
<td>7*</td>
</tr>
<tr>
<td></td>
<td>HTN</td>
<td>42.5</td>
<td>40.1</td>
</tr>
<tr>
<td></td>
<td>Rheumatic heart disease</td>
<td>19.2</td>
<td>1.4*</td>
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<tr>
<td></td>
<td>Stroke</td>
<td>11.0</td>
<td>8.8</td>
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<tr>
<td></td>
<td>HTN</td>
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<td>Valvular disease</td>
<td>7.6</td>
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<td></td>
<td>Stroke</td>
<td>7.7</td>
<td>7.5</td>
</tr>
<tr>
<td></td>
<td>Structural heart disease</td>
<td>17.8</td>
<td>16.4</td>
</tr>
</tbody>
</table>

AF: atrial fibrillation; CAD: coronary artery disease; HTN: hypertension; LVEF: left ventricular ejection fraction. *P < 0.05

from impedance changes as lung volumes or total body fluid volume changes. Shift could also occur from patient perspiration resulting from the administration of isoproterenol, as well as from changes in reference electrode contact. We find the optimal way to overcome this is to position a catheter in the coronary sinus, which provides a quite stable position to follow for evidence of shift or drift. Because of the confined size, shape and location of the coronary sinus, we can identify even small amounts of drift. Another helpful maneuver is to localize and mark the His bundle. If there is a question about catheter drift during the case, the His electrogram serves as a reasonable landmark for the geometry.

The CARTO system functions by measuring magnetic fields, rather than electrical impedances. Therefore, the CARTO system geometry is less prone to shift. It typically requires physical movement of the patient on the magnets to create any shift. This appears if the patient moves or simply coughs. Requirements for proprietary catheters and a significantly longer time to draw a reasonable geometry represent drawbacks of the CARTO system. Due to rapid improvements in both systems, the deficiencies of each are quickly disappearing.

In the early stages of our experience with minimal fluoroscopy catheter ablation, the most common reason for using fluoroscopy was with transseptal puncture. We chose transesophageal echocardiography (TEE) as our solution to the issue. This has proven effective, but other options include intracardiac echocardiography (ICE), or intravascular ultrasound (IVUS). The benefits of TEE include the capability to perform the study in any size patient as well as eliminating need for additional vascular access. In the pediatric population vascular access is often a limiting factor in the procedure. The downside of TEE is that an additional physician is needed to perform it, requiring orchestrating schedules to accommodate the transseptal puncture with TEE. By contrast, ICE and IVUS can be performed by the catheterizing physician, eliminating the need to coordinate the schedules of two physicians. This makes ICE and IVUS somewhat quicker to perform. The drawback, however, is that both require additional vascular access, which may be unavailable in small patients.

As previously stated, in more than 500 consecutive catheter ablations, unanticipated fluoroscopy was needed only once. As technology and experience continues to evolve, permanently mounted fluoroscopic C arms will eventually become obsolete. We anticipate EP labs of the future will be completely portable. Convenience and flexibility will accrue when an ablation can be scheduled in any existing hospital operating room instead of exclusively in the cath lab, resulting in scheduling efficiencies. In addition, opening a portable EP lab will cost only a fraction of what is needed to construct a traditional catheterization lab.

Bringing the EP lab to some patients will also be safer than transporting the patient to the EP lab. This applies to the rare patient who presents in an incessant tachycardia with heart failure requiring ECMO support. In that instance, it will be easier and safer to take the EP lab to the patient’s bedside in the ICU, rather than attempting to transport the patient while on ECMO. Lastly, hospitals that adopt an early, aggressive approach to radiation reduction stand to see increased numbers of referrals and procedures due to today's level of public awareness and concern regarding radiation exposure.

Because of the above-mentioned factors, our hospital has adopted a protocol of performing catheter ablations outside of the traditional cath lab. Our first procedure was undertaken in October of 2013, on a 12-year-old male with AVNRT. Our decision tree is fairly simple: anyone who meets certain criteria can be scheduled for ablation in the OR instead of the EP lab. Exclusion criteria include children under the age of 5 years, complex congenital heart disease, a transvenous pacing device, or need for concomitant diagnostic or interventional cath. Schedules are verified to ensure availability of an echo physician on during the procedure. By adopting this approach, we are now routinely doing most of our ablations outside of the EP lab.

**Limitations**

Zero-fluoroscopy ablation is still early in development, and ablation outside the cath lab is brand new. Therefore, all potential limitations are not yet known. A deliberate, planned, cautious approach is
necessary to define the learning curve and to delineate the potential pitfalls that have yet to be identified, as well as the tools necessary to advance the field.

**Conclusions:**

In conclusion, catheter ablation can be routinely performed without fluoroscopy in the majority of procedures. By employing three-dimensional mapping and TEE, fluoroscopy is rarely required. The reduction and elimination of radiation has long-term benefits to both patients and staff. There are also significant cost-saving benefits to the hospital. As more demand is placed on industry to provide better tools for reducing radiation exposure, the technology will continue to evolve. Future EP labs are likely to be portable and institutions will not require a traditional catheterization lab.

**Acknowledgements**

We would like to thank the Rebecca D. Considine Research Institute for their administrative support.

**References:***


Diastolic Function In Normal Sinus Rhythm Vs. Chronic Atrial Fibrillation: Comparison By Fractionation Of E-Wave Deceleration Time Into Stiffness And Relaxation Components

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Abstract
Although the electrophysiologic derangement responsible for atrial fibrillation (AF) has been elucidated, how AF remolds the ventricular chamber and affects diastolic function (DF) has not been fully characterized. The previously validated Parametrized Diastolic Filling (PDF) formalism models suction-initiated filling kinematically and generates error-minimized fits to E-wave contours using unique load ($x_0$), relaxation ($c$), and stiffness ($k$) parameters. It predicts that E-wave deceleration time (DT) is a function of both stiffness and relaxation. Ascribing DT to stiffness and DT to relaxation such that DT = DT + DT is legitimate because of causality and their predicted and observed high correlation ($r=0.82$ and $r=0.94$) with simultaneous (diastatic) chamber stiffness (dP/dV) and isovolumic relaxation (tau), respectively.

We analyzed simultaneous echocardiography-cardiac catheterization data and compared 16 age matched, chronic AF subjects to 16, normal sinus rhythm (NSR) subjects (650 beats). All subjects had diastatic intervals. Conventional DF parameters (DT, AT, E peak, E dur, E-VTI, E/E') and E-wave derived PDF parameters (c, k, DT, DT) were compared. Total DT and DT, DT in AF were shorter than in NSR (p<0.005), chamber stiffness, (k) in AF was higher than in NSR (p<0.001). For NSR, 75% of DT was due to stiffness and 25% was due to relaxation whereas for AF 81% of DT was due to stiffness and 19% was due to relaxation (p<0.005).

We conclude that compared to NSR, increased chamber stiffness is one measurable consequence of chamber remodeling in chronic, rate controlled AF. A larger fraction of E-wave DT in AF is due to stiffness compared to NSR. By trending individual subjects, this method can elucidate and characterize the beneficial or adverse long-term effects on chamber remodeling due to alternative therapies in terms of chamber stiffness and relaxation.

Introduction

Atrial fibrillation (AF) is a known correlate of heart failure (HF) and affects millions of patients worldwide. Investigators have demonstrated that AF and HF are concordant and increase overall mortality rate. Significant progress has been made in the diagnosis, electrophysiologic mechanism, and treatment of AF. However, the mechanistic consequences of AF on left ventricular (LV) function, chamber stiffness and relaxation, and global LV diastolic function (DF) in particular, remain incompletely characterized.

Key Words:
LV Stiffness, LV Relaxation, Diastolic Function, Atrial Fibrillation, E-Wave DT.

The instantaneous slope of the left ventricular (LV) pressure-volume relation, dP/dV, defines chamber stiffness and serves as one of the two main parameters (the other is relaxation) by which global diastolic function (DF) is quantitated. Traditionally, LV chamber stiffness is determined invasively from the slope ($\Delta P/\Delta V$) of the end-diastolic pressure volume relationship (EDPVR). However, due to the lack of atrial contraction, end-diastole in AF and NSR are different physiologic states. Hence the EDPVR cannot be used to compare the chamber stiffness in AF with that in NSR. Therefore, the diastatic pressure volume relationship (D-PVR) provides the appropriate physiologic metric for AF vs. NSR chamber stiffness comparison. It has been established that (passive) diastatic chamber stiffness, i.e. the slope of D-PVR, is significantly elevated in AF compared to NSR.

Chamber stiffness ($\Delta P/\Delta V$) is a ‘relative’ index and can be determined using ‘relative’ (echo), rather than ‘absolute’ (cath) measurement methods. Little et al used physiologic modeling to predict that E-wave DT is determined by stiffness ($K_{LV}$) alone. However, for E-wave contours well fit by underdamped oscillatory kinematics, the PDF formalism parameter k is the algebraic...
Clinicians know that tall, narrow E-waves having a short DT, referred to as the ‘constrictive-restrictive’ pattern, are associated with stiff chambers. Similarly, long DT is referred to as a manifestation of the ‘delayed relaxation’ pattern. Therefore, from an intuitive clinical perspective it is self-evident that both stiffness and relaxation must be DT determinants. This intuitive role of stiffness and relaxation as DT determinants has been made physiologically precise by Shmuylovich et al who have shown that two subjects having echocardiographically indistinguishable DT can have significantly distinguishable values of chamber stiffness and relaxation (tau) on simultaneous hemodynamic analysis. Using PDF-based analysis, the derived algebraic expression for DT was shown to be a function of both stiffness (PDF parameter \(k\)) and relaxation (PDF parameter \(c\)). The aforementioned naturally justifies decomposition of E-wave DT into its stiffness (DT\(_k\)) and relaxation (DT\(_r\)) components such that \(DT = DT_k + DT_r\). The expected causal relationship between DT\(_k\), DT\(_r\), and simultaneous stiffness (\(\Delta P/\Delta V\)) and relaxation (tau) has been firmly established by the high observed correlation \((r=0.82\) and \(r=0.94\) respectively). We hypothesized that AF LVs are stiffer than NSR LVs. Consequently, decomposition of E-wave DT into stiffness (DT\(_k\)) and relaxation (DT\(_r\)) components will show that, compared to NSR, DT\(_k\) is shorter in AF and a larger percentage of E-wave DT in AF is due to stiffness than to relaxation.

Material And Methods

Subject Selection

Thirty two datasets (mean age 61, 22 men) were selected from the Cardiovascular Biophysics Laboratory database. Subjects underwent elective cardiac catheterization to determine presence of suspected coronary artery disease at the request of their referring physicians. All participants provided informed consent prior to the procedure using a protocol approved by the Washington University Human Research Protection Office (HRPO).

Sixteen datasets of subjects in NSR, were selected so they were aged matched with the 16 subjects of the chronic AF group (average duration 7.3±4.1 years). All were in AF during data acquisition. Selection criteria for the NSR group were: no acute ischemia, normal valvular function, normal LV ejection fraction \((LVEF\geq50\%)\), no history of myocardial infarction, peripheral vascular disease, or bundle branch block, and clear diastatic intervals following E-waves.

Selection criteria for the AF group were similar, with the exception that four of the 16 AF subjects had LVEF somewhat < 50%. Among the 16 NSR datasets, 9 had normal LV end-diastolic pressure \((LVEDP<14\ mmHg)\), 3 had \(15\ mmHg < LVEDP < 20\ mmHg\) and 4 had elevated LVEDP \((>21\ mmHg)\). The distribution of LVEDPs in the 15 AF group datasets were: 3 with LVEDP<14, 9 with \(15<LVEDP<20\ mmHg\) and 4 with LVEDP>21. A total of 650 cardiac cycles (20 beats/subject) of simultaneous echocardiographic–high fidelity hemodynamic (conductance catheter) data were analyzed. The clinical descriptors of the 32 subjects and their hemodynamic and echocardiographic indices are shown in Table 1 and 2.

Data Acquisition

The high fidelity, simultaneous echocardiographic transmitral flow and pressure–volume (P–V) data recording method has been previously described [17,20–24]. Briefly, immediately prior to arterial access a complete 2-D echo–Doppler study in a supine position using a Philips (Andover, MA.) iE33 system was performed according to American Society of Echocardiography (ASE) criteria. After arterial access and placement of a 64-cm, 6-Fr sheath (Arrow, Reading, PA), a 6-Fr micromanometer conductance catheter (SPC-560, SPC-562, or SSD-1034, Millar Instruments, Houston, TX) was directed across the aortic valve under fluoroscopic control. Pressure and volume signals were processed through clinical amplifier systems (Quinton Diagnostics, General Electric, CD Leycom) and recorded by a custom personal computer via a standard interface (Sigma-5). Simultaneous transmural Doppler images were obtained [25] using a clinical imaging system (Philips iE33, Andover, MA). Following data acquisition, end-systolic and end-diastolic volumes (ESV, EDV) were determined by calibrated quantitative ventriculography.

Doppler E-Wave Analysis

For each subject, approximately 1–2 minutes of continuous transmitral flow data were recorded in the pulsed-wave Doppler mode. Echocardiographic data acquisition is performed in accordance with published ASE guidelines. In accordance with convention, the apical 4-chamber view was used for Doppler E-wave recording with the sample volume located at the leaflet tips. An average of 20 beats per subject were analyzed (650 cardiac cycles total for the 32 subjects).

Doppler transmural E-wave contours were analyzed using the conventional triangle shape approximation, yielding peak E-wave velocity \((E_\text{peak})\), acceleration time \((AT)\), deceleration time \((DT)\), and simultaneous transmital Doppler images were obtained [25] using a clinical imaging system (Philips iE33, Andover, MA). Following data acquisition, end-systolic and end-diastolic volumes (ESV, EDV) were determined by calibrated quantitative ventriculography.
The classes of prescribed medications among the 16 subjects of the AF group were as follows: 14 on anticoagulants/antithrombotics, 9 on beta blockers, 7 on lipid lowering agents, 7 on ACE inhibitor or ARB, 6 on calcium channel blockers, 6 on diuretics, and 5 on digoxin.

### Statistical Analysis

For each subject, parameters were averaged for the beats selected. Comparisons of diastatic stiffness, AT, DT, E\textsubscript{dur}, PDF parameters, and other parameters between NSR and AF groups were carried out by Student’s t-test using MS-Excel (Microsoft, Redmond, WA).

### Results

#### Diastatic Stiffness And Other Invasive Measurements In NSR And AF

LV (passive) chamber stiffness measured as the slope of the D-PVR is significantly higher in the AF group than that in the NSR group (0.18±0.08 mmHg/ml vs. 0.11±0.05 mmHg/ml, p<0.01). In contrast to NSR, where diastatic pressure and volume is different than end-diastolic pressure and volume at end atrial systole), in AF, diastatic pressure and volume is the same as end-diastolic pressure and volume since there is no atrial contraction in AF. In AF diastatic pressure and volume are similar to the diastatic pressure and volume in NSR (18 ± 4 mmHg for AF vs. 17 ± 5 mmHg for NSR, p=0.48 and 167 ± 55 ml for AF vs. 159 ± 12 ml for NSR, p=0.59).

#### Triangle Method Measurements Of E-waves In NSR And AF

Figure 1 shows that E-wave DT and E-wave duration (E\textsubscript{dur}) are significantly shorter in the AF group than NSR group (DT: 153 ± 22 msec vs. 192 ± 19 msec, p<0.001, E\textsubscript{dur}: 236 ± 26 msec vs. 281 ± 27 msec, p<0.001). E-wave acceleration time (AT) is not significantly different between the two groups (84 ± 8 msec vs. 89 ± 11 msec, p=0.13).

#### PDF Measurements In NSR And AF

Results from PDF analysis show (Figure 2) that PDF stiffness parameter (k) in AF group is higher (stiffer) than NSR group (274 ± 70 1/sec\textsuperscript{2} vs. 191 ± 41 1/sec\textsuperscript{2}, p<0.001). PDF parameters c, x\textsubscript{o} are not significantly different between AF and NSR groups (c: 15.7±3.0 1/sec vs. 16.3±3.5 1/sec, p=0.65 and x\textsubscript{o}: 10.2±2.5 cm vs. 10.1±2.9 cm, p=0.93).

#### Fractionation Of Deceleration Time Into Stiffness And Relaxation Components In NSR And AF

Figure 3 shows the stiffness and relaxation components in both groups and their contribution to DT. The relaxation (DT\textsubscript{r}) component

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**Figure 1:**

- **A)** Comparison of stiffness (DT\textsubscript{s}) and relaxation (DT\textsubscript{r}) components of total DT according to group. Asterisk (*) indicates DT\textsubscript{s} and DT\textsubscript{r} are both significantly shorter in AF than in NSR.

- **B)** Comparison of total DT between groups indicates significant difference (*). When DT is decomposed into its DT\textsubscript{s} DT\textsubscript{r} components in NSR and AF groups, significant intergroup differences in components persist as shown in Panel A. See text for details.

**Figure 2:**

- **A)** Least mean square determined linear fit of stiffness component of DT (DT\textsubscript{s}) vs. diastatic stiffness (K) in 16 NSR subjects, B) 16 AF subjects. See text for details.

**Figure 3:**

- **A)** Comparison of stiffness (DT\textsubscript{s}) and relaxation (DT\textsubscript{r}) components of total DT according to group. Asterisk (*) indicates DT\textsubscript{s} and DT\textsubscript{r} are both significantly shorter in AF than in NSR.

- **B)** Comparison of total DT between groups indicates significant difference (*). When DT is decomposed into its DT\textsubscript{s} DT\textsubscript{r} components in NSR and AF groups, significant intergroup differences in components persist as shown in Panel A. See text for details.

**Figure 4:**

- **A)** Least mean square determined linear fit of stiffness component of DT (DT\textsubscript{s}) vs. diastatic stiffness (K) in 16 NSR subjects, B) 16 AF subjects. See text for details.

**Figure 5:**

- **A)** Least mean square determined linear fit of relaxation component of DT (DT\textsubscript{r}) vs. time constant of isovolumic relaxation (\(\tau\)) in 16 NSR subjects, B) 16 AF subjects. See text for details.
Invasive And Non-Invasive Measurements Of AF Chamber Stiffness

Although multiple methods for LV chamber stiffness determination using echocardiography have been proposed, one of the most important methods for characterizing passive chamber stiffness has been the end-diastolic pressure volume relation (EDPVR), defined by the locus of points inscribed by end-diastolic pressures and volumes at varying loads. Considering the EDPVR in the setting of chronic AF raises a concern, however. Because there is no atrial contraction, end-diastole in (rate controlled) AF is the hemodynamic equivalent of diastasis. During diastasis the ventricle is in static equilibrium. End-diastole in AF is shorter than in NSR, which is inversely related to chamber stiffness, is shorter than in NSR (DT_AF=123±20 vs. DT_NSRI=142±14). The shorter DT in AF and the known inverse relation between DT and (diastatic) stiffness indicates that AF chambers are stiffer than NSR chambers. DT, and diastatic stiffness derived from P-V data (K) were highly correlated in both NSR and AF groups (NSR: DT = -0.21 K + 0.16, R²=0.57, AF: DT = -0.19 K + 0.16, R²=0.56) (Figure 4). DT, and time constant of isovolumic relaxation (τ) were highly correlated in both NSR and AF groups (NSR: DT = 1.30 τ - 0.03, R²=0.84, AF: DT = 1.11 τ - 0.03, R²=0.77) (Figure 5).

For the 16 NSR datasets 75% of total DT is due to stiffness and 25% is due to relaxation. For the 16 AF datasets 81% of DT is due to stiffness and 19% is due to relaxation (Figure 6). These differences are significant (p<0.005). If the four AF subjects with LVEF <50% are removed from the intergroup comparison, all of the conclusions remain unaltered.

Discussion

In addition to invasive approaches, the stiffness of the LV chamber can also be estimated noninvasively. The PDF parameter k obtained from echocardiographic E-wave analysis is mathematically and experimentally related to the invasively measured chamber stiffness (ΔP/ΔV) during early rapid filling. E-wave deceleration time (DT) has also been correlated with stiffness as proposed by Little et al. It was shown that an inverse square relationship exists between stiffness and E-wave DT.

Both the triangle based (DT) and PDF model based (k) noninvasive estimates of chamber stiffness showed significant difference between the AF and NSR groups, consistent with the invasive chamber stiffness findings between groups at diastasis. The significantly shorter DT in the AF group is not likely to be explained by the higher average HR of the AF group since it is known that in the presence of a diastatic interval, E-wave DT remains essentially unchanged when HR increases.

Deceleration Time Of E-wave Correlation With Chamber Stiffness And Relaxation

Average left ventricular (LV) chamber stiffness, ΔP/ΔV, is an important diastolic function (DF) metric. An E-wave based determination of ΔP/ΔV by Little et al predicted that deceleration time (DT) is related to stiffness according to ΔP/ΔV = A/(DT)². This implies that if the DTs of two LVs are indistinguishable, their stiffness should be similarly indistinguishable. Shmylovich et al. have shown that two subjects with indistinguishable E-wave determined DTs can have distinguishable catheterization-determined values of chamber stiffness, because of differences in relaxation, i.e. the viscoelastic parameter (PDF parameter c) in the two subjects. We found E-wave DT and its stiffness component are significantly shorter in the AF group (DT: p<0.001, DT: 0.005) shorter in the AF group (DT=153±22 msec, DT=123±20) than NSR group (DT=192±19 msec, DT=142±14). The shorter DT in AF group is primarily an effect of stiffness because the relaxation parameter c is similar in the two groups (p=0.65).
Decomposition Of E-wave Deceleration Time To Stiffness And Relaxation Components

Because E-wave DT depends on both stiffness (k) and relaxation (c) we have previously proposed a method by which E-wave DT can be decomposed to stiffness (DT \_s) and relaxation (DT \_r) components. We have shown that DT \_s was highly correlated (r=0.82) with (simultaneous) invasively determined (passive) diastatic chamber stiffness, and DT \_r, and the time-constant of IVR (\tau) from simultaneous high fidelity pressure data and IVRT determined by echocardiography were highly correlated (r=0.94, r=0.89).

In the current study we analyzed simultaneous LV P-V and transmitial flow (echo) data and decomposed E-wave DT in to stiffness (DT \_s) and relaxation (DT \_r) components in NSR and AF groups. As expected diastatic stiffness and PDF stiffness parameter k were higher in AF group compared to NSR group and AF E-wave DT was shorter than in NSR. Figure 6 shows the fraction of DT accounted for by stiffness (S) in the AF group is significantly higher than in the NSR group (p<0.005), and the fraction of DT due to the relaxation (R) in the AF group is significantly lower than in the NSR group (p<0.005). Although the numerical value of the PDF relaxation parameter c is similar in NSR and AF, the fraction of the total DT due to relaxation (R = DT \_r / DT \_r) is less in AF than in NSR because DT and DT \_r in AF group is shorter (Figure 3) than in NSR. This is underscored by the difference in stiffness parameter k, being higher (stiffer) in AF versus NSR. This method is totally general. It fractionates total DT into its stiffness and relaxation components and thereby reflects actual chamber properties. As such, the method allows for longitudinal assessment and trending of beneficial vs. adverse effects of alternative treatment strategies on chamber properties of stiffness and relaxation in clinical settings where echocardiography is utilized.

Limitations

Conductance Volume

The conductance catheter method of volume determination has known limitations related to noise, saturation and calibration that we have previously acknowledged. In this study, the channels which provided physiologically consistent P-V loops were selected and averaged. However, since there was no significant volume signal drift during recording, any systematic offset related to calibration of the volume channels did not affect the result when the limits of conductance volume were calibrated via quantitative ventriculography.

HR Limitation

The D-PVR is defined by a linear, least mean-squared error fit to the load varying loci of points at which diastasis is achieved. At elevated heart rates diastasis is usually eliminated. In this study datasets were selected such that for every analyzed cardiac cycle in AF or NSR a clear, diastatic interval was present after E-wave termination, prior to the onset of the next systole in AF, or prior to the onset of the Doppler A-wave in NSR.

Sample Size

Although the number of subjects (n=32) is modest, and may be viewed as a minor limitation regarding statistics, the total number of cardiac cycles analyzed (n=650) mitigates the sample size limitation to an acceptable degree.

Conclusions

We used the PDF formalism to decompose E-wave deceleration time into its stiffness and relaxation components in NSR and AF groups where E-waves were always followed by a diastatic interval. We found that AF chambers have increased (diastatic) stiffness compared to NSR chambers at diastasis. In addition, a larger percentage of

Table 1: The clinical descriptors of NSR and AF groups.

<table>
<thead>
<tr>
<th>Clinical Descriptors</th>
<th>NSR Group</th>
<th>AF Group</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>16</td>
<td>16</td>
<td>N.A.</td>
</tr>
<tr>
<td>Age (y)</td>
<td>61±8</td>
<td>61±9</td>
<td>0.92</td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>10/6</td>
<td>12/4</td>
<td>N.A.</td>
</tr>
<tr>
<td>Heart Rate (bpm)</td>
<td>62±9</td>
<td>76±9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ejection Fraction (%)</td>
<td>73±8</td>
<td>55±17</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>172±10</td>
<td>178±10</td>
<td>N.S.</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>89±14</td>
<td>99±18</td>
<td>N.S.</td>
</tr>
<tr>
<td>CHA2DS2-VASc factors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female gender</td>
<td>6</td>
<td>4</td>
<td>N.A.</td>
</tr>
<tr>
<td>Heart failure</td>
<td>0</td>
<td>4</td>
<td>N.A.</td>
</tr>
<tr>
<td>Hypertension</td>
<td>7</td>
<td>13</td>
<td>N.A.</td>
</tr>
<tr>
<td>Age 65 to &lt; 74 years</td>
<td>4</td>
<td>5</td>
<td>N.A.</td>
</tr>
<tr>
<td>Age &gt; 75</td>
<td>2</td>
<td>1</td>
<td>N.A.</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>0</td>
<td>0</td>
<td>N.A.</td>
</tr>
<tr>
<td>Stroke</td>
<td>0</td>
<td>0</td>
<td>N.A.</td>
</tr>
<tr>
<td>Vascular disease</td>
<td>0</td>
<td>0</td>
<td>N.A.</td>
</tr>
</tbody>
</table>

Data are presented as mean ± standard deviation.

Table 2: Hemodynamic and echocardiographic data in NSR and AF groups

<table>
<thead>
<tr>
<th>Hemodynamic Parameters</th>
<th>NSR</th>
<th>AF</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEDP (mmHg)</td>
<td>17±5</td>
<td>18±4</td>
<td>0.48</td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>10/6</td>
<td>12/4</td>
<td>N.A.</td>
</tr>
<tr>
<td>LVEDV (ml)</td>
<td>159±12</td>
<td>167±55</td>
<td>0.59</td>
</tr>
<tr>
<td>Diastatic stiffness (mmHg/ml)</td>
<td>0.11±0.05</td>
<td>0.18±0.08</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>( \tau ) (msec)</td>
<td>59±7</td>
<td>50±10</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

Echocardiographic Parameters

| Peak E-wave velocity (Epeak) (cm/s) | 71±15 | 89±26 | <0.05 |
| E-wave acceleration time (AT) (ms) | 89±11 | 84±8  | 0.13  |
| E-wave deceleration time (DT) (ms) | 192±19| 153±22| <0.001|
| E-wave duration time (Edur) (ms)  | 281±27| 236±26| <0.001|
| E/E’ (dimensionless)              | 4.7±1.8| 6.0±1.9| <0.05 |
| \( k \) (1/sec)                  | 10.2±2.5| 10.1±2.9| 0.93  |
| \( c \) (1/sec²)                 | 19.1±4.1| 27±4.7| <0.001|
| DT \_r (msec)                    | 15.7±3.0| 16.3±3.5| 0.65  |
| DT \_s (msec)                    | 50±10  | 30±12  | <0.001|
| DT \_r / DT \_s (%)              | 142±14| 123±20| <0.005|
| R = DT / DT \_r (%)              | 25±3  | 19±7   | <0.005|
| S = DT \_s / DT \_r (%)          | 75±3  | 81±7   | <0.005|

Data are presented as mean ± standard deviation.

LVEDP = left ventricular end-diastolic pressure
LVEDV = left ventricular end-diastolic volume
\( \tau \) = time constant of isovolumic relaxation
E/E’ = ratio of Epeak and E’peak
E-VTI = E-wave velocity-time integral
k = PDF stiffness parameter
\( c \) = PDF relaxation parameter
DT \_r = relaxation component of DT
DT \_s = stiffness component of DT
E-wave DT in AF is due to stiffness than to relaxation compared to NSR. This novel method allows clinicians to track and trend the effect of alternative pharmacologic therapies in terms of DT, and DT, not only as DF determinants, but as metrics of beneficial vs. adverse remodeling and as determinants of prognosis and rehospitalization in clinical settings where echocardiography is employed.

Acknowledgments

This work was supported in part by the Alan A. and Edith L Wolff Charitable Trust, St. Louis, and the Barnes-Jewish Hospital Foundation. Sina Mossahebi was supported in part by a teaching assistantship from the Physics Department, Washington University College of Arts and Sciences. We thank sonographer Peggy Brown for expert echocardiographic data acquisition, and the staff of Barnes Jewish Hospital Cardiovascular Procedure Center’s Cardiac Catheterization Laboratory for their assistance.

Appendix 1

The PDF Formalism

The kinematics of filling is modeled using the Parameterized Diastolic Filling (PDF) formalism which uses a linear, bi-directional spring to approximate early filling in accordance with the velocity of a damped SHO. In accordance with Newton’s second law, the equation of motion is:

$$\frac{d^2x}{dt^2} + c \frac{dx}{dt} + kx = 0 \quad [A.1]$$

Because the E-wave has zero initial velocity, the model’s initial velocity is zero (v(0)=0). However, the SHO has a non-zero initial spring displacement, x₀. Systole stores elastic strain in tissue, which at mitral valve opening, is available to power mechanical recoil and the ventricular suction process. Equation 1 allows calculation of parameters c and k per unit mass. The predicted contour of the clinical E-wave is obtained from the solution for the SHO velocity. The underdamped solution is:

$$v(t) = -\frac{x_k}{\omega} \exp(-ct/2) \sin(\omega t) \quad [A.2]$$

where . The determination of PDF parameters from each E-wave solves the ‘inverse problem’ of diastole and generates a unique set of x₀, c, and k values for each contour. The three parameters x₀, c, and k encompass the (lumped) physiologic determinants of all E-wave contours. The initial oscillator displacement x₀ (cm) is linearly related to the velocity-time integral (VTI) of the E-wave. Chamber stiffness (dP/dV) is linearly related to the spring constant k (g/s²). While the chamber viscoelasticity/relaxation index c (g/s) characterizes the resistance of the process. E-waves with long concave up deceleration portions (‘delayed relaxation pattern’) are fit by the overdamped solution and have higher c values, while E-waves that approximate nearly symmetric sine waves are fit by the underdamped solution and have lower c values.

Briefly, echocardiographic images are cropped, the mitral E-wave maximum velocity envelopes are identified and fit by the PDF generated solution using the Levenberg–Marquardt algorithm to yield the best-fit PDF parameter x₀, c, and k, values. The process is achieved using a custom LabVIEW (National Instruments, Austin, TX) interface. In addition to providing parameter values the algorithm also provides a simultaneous measure of goodness of fit. Additional PDF-derived indexes include the stored elastic strain energy available for ventricular suction (1/2kx₀²) at the onset of filling, and the peak atrio-ventricular pressure gradient (kx₀).21,24

As in previous work, interobserver variability in applying the PDF formalism for E-wave analysis was ≤ 8%.

Appendix 2

Determination of stiffness and relaxation components of E-wave deceleration time

PDF model predicts that E-wave deceleration time (DT) is a function of both stiffness and relaxation. PDF-based E-wave analysis provides a method for fractionating total DT into its stiffness (DT₁) and relaxation (DT₂) components such that DT=DT₁+DT₂. The fractionation method has been previously validated with DT₁ and DT₂, correlating with simultaneous stiffness (dP/dV) and relaxation (τ) with r=0.82 and r=0.94 respectively.19

The duration of the E-wave, AT, and DT are measured as usual from Doppler echo images using a triangle to approximate E-wave shape (Figure 7). The effect of delayed relaxation on an ideal (generated by recoil only) E-wave is to decrease its peak amplitude and lengthen its DT. Accordingly, DT₁ is determined by using the same x₀ and k as the original E-wave but setting c=0 and thereby providing the PDF generated ideal contour. Subtracting the ideal E-wave duration from actual total duration yields DT₂ (See Figure 7). Therefore, E-wave DT is decomposed into its determinants as DT=DT₁+DT₂. It is known that DT₁, DT₂, are only weakly load and heart rate dependent.19

References:

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Ventricular Rate Stabilization In Patients With Permanent Atrial Fibrillation And Single-Chamber Ventricular Pacemaker: RARE-PEARL Study

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Abstract

Background: In patients with permanent atrial fibrillation (AF) rate irregularity can cause symptoms and impair the pumping function of the heart. Ventricular pacing at a rate close to the mean spontaneous ventricular rate can result in a more stable ventricular rate. Specific algorithms for automatic Ventricular Rate Stabilization (VRS) were designed and implemented in commercially available pacemakers. To assess this dynamic rate control we designed the RARE-PEARL study: prospective, randomized, cross-over, double-blinded.

Methods: Patients with permanent AF, symptomatic episodes of brady-tachycardia, left ventricular ejection fraction (LVEF) >40%, NYHA class I/II/III, were eligible for enrolment. Each patient (n = 67) was implanted with a single-chamber VVIR pacemaker (models C20 or T20, Vitatron BV, The Netherlands) equipped with the VRS algorithm. At the end of a four week stabilization period, patients were randomized to VRS algorithm ON or OFF (2 months) and then crossed-over for the second phase (2 months). Primary endpoint was patient’s preference.

Results: Sixty six patients ended the study: 19 (29%) had no preference; 15 (23%) preferred algorithm OFF, 32 (48%) algorithm ON (p<0.0001, algorithm ON vs OFF). In 58% of patients the algorithm ON caused an increase of ventricular pacing percentage > 10%. The ventricular pacing percentage was 82±10% with algorithm ON vs 59±26% with algorithm OFF (p<0.0001). Symptoms did not differ significantly.

Conclusions: The VRS algorithm significantly increases the ventricular pacing percentage in patients with permanent AF. This pacing function is preferred by the majority of patients implanted with a single-chamber VVIR pacemaker.

Introduction

Patients with permanent atrial fibrillation (AF) and an indication for VVI(R) stimulation account for about 16% of the total number of antibradycardia devices implanted per year in Italy.¹ It is easy to programme the lower rate of a pacemaker to prevent cardiac pauses, while it is difficult to determine the optimal pacing rate to stabilize the ventricular rhythm. To overcome this, a dynamic rate control algorithm was developed. A pacemaker equipped with this function can pace the heart so as to avoid pauses and to limit beat-to-beat variations in the cardiac cycles.²⁻⁴ AF can have detrimental hemodynamic effects: loss of atrial contribution, inappropriate increase in ventricular heart rate, and RR interval irregularity with short-long-short cycles that may for a 9%–12% reduction in cardiac output.⁵⁻⁶ It has been proven that acute AF in humans causes a limited increase in coronary flow versus a more relevant increase in myocardial oxygen demand. Irregularity of the ventricular rhythm is one of the major factors negatively impacting cardiac output.⁷

Key Words:
were enrolled in accordance with the inclusion and exclusion criteria. At the inclusion time (PM implant) all patients were on optimal drug therapy, including rate control.

Inclusion criteria
- Patient with permanent AF, standard indication for VVI(R) pacing and at least 1 symptomatic episode of high ventricular rate in the last month.
- NYHA Class I; II; III
- Patient has signed informed consent form
- Patient was able to comply with follow-up times and will comply with the protocol
  - > 18 years

Exclusion criteria
- Paroxysmal AF.
- NYHA Class IV
- LVEF < 40%
- Patients with unstable angina
- Patients who have experienced an acute Myocardial Infarction or received a surgical coronary artery revascularization (CABG) or a coronary angioplasty (PTCA) within 3 months prior to enrolment
- Patient candidate for cardiac surgery, or coronary angioplasty (PTCA)
- Patients who experienced a cardiovascular accident with permanent disability or a transitory cerebral ischemia
- Life expectancy < 12 months due to other malignant medical conditions
- Pregnancy
- The patient was enrolled in any concurrent (drug and/or device) study

Study Objectives
The impact of heart rate regularization in patients’ life was evaluated by the patient’s mode preference and by the specific symptoms scale (Table 1).\(^8\)
Secondary objectives of the study were: rate irregularity estimated by the percentage of ventricular pacing; number of patients subsequently submitted to atrio-ventricular (AV) node radio-frequency (RF) ablation; side effects of pacing algorithms.

Study Design
The enrolled patients undergone pacemaker implantation, receiving a SSIR pacemaker (model C20 or T20, Vitatron BV, The
Netherlands). After pacemaker implantation, a 45 days stabilization period was respected, to stabilize the lead and the drug therapy. During the stabilization period following the implant, the final programming was performed and sensing and pacing parameters were optimized. No additional changes have been made during the randomized phase of the study and in the drug therapy as well.

At the end of the stabilization period the patient was randomized to have Ventricular Rate Stabilization (VRS) algorithm switched either ON or OFF. The 1st Study Phase ended after 2 months. Then cross-over took place: VRS algorithm was switched respectively OFF or ON and the 2nd Study Phase was started. Also the 2nd Study Phase ended after 2 months. The randomization was centralized.

The physician (co-investigator) administering the specific symptoms scale questionnaire (Table 1) was blinded (and the patient too) about the status of the VRS algorithm setting. He did not perform the pacemaker telemetric interrogation. Only the principal investigator knew about what was programmed of the VRS algorithm. The cumulative score of symptoms was compared during baseline, stabilization period, VRS ON and VRS OFF phases for each patient.

### Pacemaker Implantation and Algorithm

The pacing system was implanted according to standard clinical procedures, usually applied by the investigator. The ventricular leads were bipolar to guarantee optimal sensing. The leads were implanted in the right ventricle in accordance with the standard of each centre. All routine measurements, such as pacing threshold, endocardial sensing and impedance were performed in accordance with the local clinical practice. All adverse events encountered during the implantation procedure were documented. At discharge lower rate was set at 10 bpm below the spontaneous rate of the patient. The spontaneous rate of the patient was evaluated through a one minute ECG recording at rest.

VRS algorithm is designed to limit variations in R-R intervals during AF. Ventricular pacing slightly above the mean ventricular rate eliminates long intervals resulting in a more stable ventricular rate. The pacemaker increases the pacing rate after two consecutive ventricular sensed events, but not above the maximum therapy rate (programmed at 120 min⁻¹ in the study). After each ventricular paced event, the pacemaker decreases the pacing rate until it detects a new ventricular sensed event or it reaches the lower rate. Figure 1 shows how the ECG of the same patient is with and without the algorithm activated.

### Post-Stabilization Follow-Up

This visit marked the end of the 6 weeks stabilization period. At this stage VRS was switched ON or OFF in accordance with the randomization assigned. If VRS was ON, the relative upper-rate limit was set at 120 bpm.

### Statistics

Results were expressed as mean values ± standard deviation (SD) or as numbers and percentages, as appropriate. The Mann–Whitney U test was used if normal distribution criteria were not met. Alternatively the Student’s T-test was used. Z-test was used for proportions. A P value <0.05 was considered statistically significant. All analyses were performed by means of the SPSS (SPSS Inc., Chicago, USA) software package.

### Results

Sixty seven patients (80 ± 6 years aged; 49 M,18 F) were enrolled and randomized at the end of the post-implant stabilization period: 34 patients to VRS ON and 33 patients to VRS OFF.

One patient with VRS ON was lost to follow-up at the end of the first phase, so 33 patients per group (66 patients in total) crossed over and ended the study. One patient was submitted to AV node RF ablation at the end of the study. No adverse effects related to the VRS algorithm were reported by the patients.

### Patient’s Preference

At the end of the study 32 patients (48%) preferred VRS ON versus 15 patients (23%) who preferred VRS OFF (p<0.001 ON versus OFF). Nineteen patients (29%) did not have any preference.

### Pacing Percentage

The ventricular pacing percentage was 82 ± 10 % with algorithm ON versus 59 ± 26 % with algorithm OFF (p<0.0001). In 58% of patients the algorithm ON caused an increase of ventricular pacing percentage > 10%.

### Symptoms

Symptoms were assessed by the Specific Symptoms Scale (Table 1): the cumulative score was significantly different at baseline compared to any phase of the study, but it did not differ significantly among VRS ON, VRS OFF and the Stabilization periods (Table 2).

The lowest value of the cumulative score was achieved with VRS ON.

### Discussion

The aim of the ventricular rate stabilization (VRS) algorithm is to prevent symptoms due to rate irregularity and this might have an impact also on the episodes of high ventricular rate. The first finding of this randomized cross-over study is that VRS algorithm significantly increases the ventricular pacing percentage in patients with permanent AF. This can impact the rate regularization since pacing intervals do not show beat to beat variations comparable with those during spontaneous heart beats in AF. Second, this pacing feature was preferred by the majority of patients implanted with a single-chamber VVIR pacemaker, but symptoms did not show statistically significant differences.

### Table 1: Specific Symptoms Scale Questionnaire for patients with AF: the patient has to quantify by means of a score scale (0=absence, 10=maximum score) each of the following symptoms that occurred during the previous month (8). The cumulative score was used for statistical analysis.

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Palpitations</td>
<td>(0 - 10)</td>
</tr>
<tr>
<td>Effort dyspnea (shortness of breath during physical activity)</td>
<td>(0 - 10)</td>
</tr>
<tr>
<td>Rest dyspnea (shortness of breath at rest)</td>
<td>(0 - 10)</td>
</tr>
<tr>
<td>Exercise intolerance (fatigue during mild physical activity)</td>
<td>(0 - 10)</td>
</tr>
<tr>
<td>Easy fatigue at rest</td>
<td>(0 - 10)</td>
</tr>
<tr>
<td>Chest discomfort</td>
<td>(0 - 10)</td>
</tr>
<tr>
<td>Cumulative Score</td>
<td>(0-60)</td>
</tr>
</tbody>
</table>

### Table 2: Symptoms were collected as cumulative score (see Table 1) for comparison.

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Stabilization Period</th>
<th>VRS ON</th>
<th>VRS OFF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms score</td>
<td>18 ± 10</td>
<td>10 ± 11</td>
<td>9 ± 9</td>
<td>10 ± 8</td>
</tr>
</tbody>
</table>

Legend: VRS = Ventricular Rate Stabilization.

Statistical evaluation: Baseline vs Stabilization Period: p<0.0001; Baseline vs OFF: p<0.0001; Baseline vs ON: p<0.0001; VRS ON vs VRS OFF: p=0.862 (ns); VRS ON vs Stabilization Period: p=0.197 (ns); VRS OFF vs Stabilization Period: p=0.484 (ns).
Other studies have addressed the topic of rate regularization with dedicated and automatic algorithms. However, this is the first study evaluating patient preference, together with objective assessment of symptoms and subjective assessment of rate regularization through pacing percentage.

Tse et al. showed that an automatic algorithm can regularize the ventricular rate during AF without increasing the mean ventricular rate, thereby reducing the severity of AF-related symptoms in patients with persistent AF. It is relevant that this pacing modality could increase rate regularity without increasing the mean heart rate, so we can assume that this pacing modality does not have a negative effect on heart rate itself. However, the same study showed that rate regularization did not improve general quality of life (Medical Outcomes Study 36-item Short-Form General Health Survey), the performance of routine activities (Duke Activity Status Index), or functional capacity (hall walk) in patients with AF.

Simpson et al. showed that ventricular rate regularization using a rate-smoothing ventricular pacing algorithm might reduce symptoms and improve the quality of life (QOL) in patients with symptomatic AF despite adequate rate control.

Ciaramitaro et al. showed that a ventricular rate regularization algorithm effectively stabilizes rate, without increasing pacing rate above spontaneous rhythm and helps achieving a more favourable autonomic balance, improving rate recovery after exercise. The rate stabilization was assessed by comparing the heart rate variability that was significantly lower with the algorithm ON.

Our study confirms that a rate regularization algorithm can increase regularity and also confirmed that it does not have an impact on symptoms, as measured with standard methods. The hypothesis is that the stabilization algorithm might also prevent high rate episodes and related symptoms: symptoms score takes it into consideration. On the other hand, the majority of patients preferred the period corresponding to the activation of the algorithm.

We can conclude that rate regularization per se does not add relevant clinical benefit in patients with permanent AF chronically paced with VVIR pacemaker. The big benefit comes from the implantation of the pacemaker itself, as demonstrated by the important improvement in symptoms during the stabilization phase compared to the pre-implant period. Subsequent phases did not add statistically significant benefit. On the other hand the preference of the patient, collected in a double-blinded way, tells us that regularization may bring something positive; but between the first and the second randomization phase was not observed a wash out period, in order to avoid residual or carryover effect, but this is a limit of our study. Probably rate regularization may add objective clinical benefit in patients with impaired left ventricular function, such as patients with permanent AF and low ejection fraction; during the study period we didn’t perform an echocardiographic evaluation finalized to monitor left ventricular function. It would make sense to check this hypothesis by implanting a CRT system in such a patients, activating the rate regularization algorithm to maximize the delivering of biventricular pacing therapy and increase rate stability and monitoring the subsequent ventricular function evolution.

Besides a very short follow-up period, the principal limitation of the study was that the real efficacy of VRS algorithm has been evaluated through a subjective assessment of the wellbeing and preference of the patient, not through an accurate analysis of objective parameters (echocardiographic, radiological and lab findings). The state of well-being being warned by patient may be the result of multiple conditions (drug therapy, the evolution of underlying heart disease, psychological factors, clinical condition at the beginning of follow-up, etc.).

**Conclusions:**

Automatic rate regularization significantly increased the ventricular pacing percentage in patients with permanent AF. This pacing function was preferred by the majority of patients implanted with a single-chamber VVIR pacemaker, but symptoms did not show significant differences.

**References:**

**CETP TaqIB Polymorphism, Serum Lipid Levels And Risk Of Atrial Fibrillation: A Case-Control Study**

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**Abstract**

The cholesteryl ester transfer protein (CETP) mediates the transfer of cholesteryl esters from high-density lipoproteins (HDL) to triglyceride (TG)-rich lipoproteins. A consistent number of investigations has suggested an association between the TaqIB polymorphism of the CETP gene, plasma HDL-C levels and the risk of cardiovascular disease, but the results are controversial.

The aim of this study was to determine if the TaqIB polymorphism might be related to the presence of atrial fibrillation (AF).

We conducted a case-control study, enrolling 109 Caucasian unrelated patients coming from Salento (Southern Italy) with documented AF and 109 controls selected from the same ward. The CETP TaqIB genotypes were determined by RFLP-PCR.

The subjects with the B2B2 genotype seem to be more susceptible to AF development (OR=2.28, 95% CI 1.06-4.89, p=0.032). The AF incidence is higher if we consider only the female subgroup (OR=5.14, 95% CI 1.57-16.82, p=0.0061). In the AF female subgroup the B2B2 patients had a statistically significant decrease of HDL-C levels (1.50 ± 0.35 vs 2.07 ± 0.42; p=0.012) and statistically higher TG levels (1.34 ± 0.46 vs 0.77 ± 0.14; p=0.027) and TG/HDL-C ratio (2.14 ± 0.80 vs 0.88 ± 0.23; p=0.007) when compared to B2B2 female control subjects.

When we analyzed the linkage between the TaqIB polymorphism and the promoter variant (-629C/A), we found that 100% of the B2 alleles of the TaqIB polymorphism were associated with the A alleles of the -629 promoter polymorphism in our subjects.

This study suggests that in post-menopausal women atrial fibrillation could be promoted by the association of CETP B2B2/AA genotype with higher triglycerides values.

**Introduction**

The cholesteryl ester transfer protein (CETP) is a major determinant of the high-density lipoprotein (HDL) variability in the general population. This protein facilitates the exchange of cholesteryl esters from HDLs to triglyceride (TG)–rich lipoproteins and low-density lipoproteins (LDLs) in exchange to TGs, decreasing the HDL plasma level. In human, CETP is expressed predominantly in the liver, spleen and adipose tissue. Detectable levels of CETP can be observed in the small intestine, adrenal glands, heart, kidneys and skeletal muscle. The human CETP gene is located on chromosome 16q21 and consists of 16 exons. Several single nucleotide polymorphisms (SNPs) in the CETP gene have been identified. The most widely studied CETP variant, denoted TaqIB (rs708272), is the silent base change affecting the 279th nucleotide in the first intron of the gene. This was the first genetic variation related to HDL-C plasma levels. The less common B2 allele (absence of the TaqI restriction site) has been associated with a lower CETP mass and with a higher HDL-C level compared to the more common B1 allele. Though this polymorphism has been shown to be consistently associated with HDL-C concentration, it does not directly influence CETP concentration or function. In Caucasian population the TaqIB polymorphism has been found to be in complete linkage with −629C/A (rs1800775), a polymorphism located in the promoter region of the CETP gene. This promoter polymorphism has been shown to influence CETP gene expression and this could account for the associations found between TaqIB polymorphism and plasma CETP mass and HDL-C concentration. The −629A allele has been associated with lower CETP mass and higher HDL-C than the −629C allele as demonstrated by 50% reduction in transcriptional activity in a reporter construct comprising the CETP promoter and a luciferase reporter. Since its first description, a consistent number of investigations has suggested an association between the TaqIB polymorphism, plasma HDL-C level and the risk of cardiovascular disease, although controversy exists on this. SNPs in the CETP gene were also investigated for their association with atrial fibrillation (AF). Using the multifactor-dimensionality reduction method Asselbergs and coworkers showed, for the first time, that the B1B1polymorphism region is linked with atrial fibrillation. The present study was therefore designed to investigate whether CETP TaqIB polymorphism and promoter polymorphism might be related to the presence of atrial fibrillation.
genotype was associated with a decreased HDL-C level and the development of AF in presence of albuminuria, elevated C-reactive protein, renal dysfunction and ischemic heart disease. On the contrary, using a total of 2145 cases with AF and 4073 controls from Germany, Sinner and coworkers could not reliably replicate this association. In both studies the promoter variant has not been investigated and the lipid profile was not considered.

The aim of the present study was to determine the prevalence of TaqIB polymorphism in a cohort coming from Salento, that is a Mediterranean country, with a racially homogeneous population of Caucasian origin and to investigate the association of the CETP /TaqIB polymorphism with plasma HDL-C level and the development of AF. We found that in our population the B2B2 genotype was associated with the risk of AF in females.

Materials and Methods

Subjects
109 Caucasian unrelated patients, coming from Salento (Southern Italy), with documented AF and 109 controls, selected from the same ward, were enrolled in this study between January 2011 and June 2012. Patients with hyperthyroidism, moderate to severe valve disease, heart failure (greater than grade NYHA II) and with lone AF were excluded. The presence of AF was determined by patient's history, serial electrocardiograms or 48 hours ambulatory ECG monitoring. Patients with palpitations without ECG documentation of the arrhythmia were excluded from both patients and control groups.

We classified AF in paroxysmal when arrhythmia is self-terminating in <7 days, persistent when an episode lasts longer than 7 days or requires termination by pharmacological or electrical cardioversion, and permanent when the presence of arrhythmia is accepted by the patient.

Transthoracic echocardiogram was performed to assess left atrial and left ventricular dimensions, left ventricular ejection fraction and to detect significant valvular heart disease (at least moderate to severe). Information regarding the use of lipid-lowering drugs and smoking was obtained using a checklist. Body mass index (BMI) was calculated as the ratio between the weight and height squared (Kg/m²). Serum levels of total cholesterol, HDL cholesterol, triglycerides, glucose, C-reactive protein, interleukin-6 and urinary albumin excretion were determined in each patient. The study was approved by the local ethics committee and conducted in accordance with the guidelines of the declaration of Helsinki. An informed consent prior to participation was obtained from all subjects.

Hypertension was defined as a systolic blood pressure ≥ 140 mmHg or a diastolic blood pressure ≥ 90 mmHg or the use of antihypertensive medications. Diabetes was defined as a fasting plasma glucose level >7.0 mmol/l or a non-fasting plasma glucose level >11.1 mmol/l or the use of antidiabetic medications. Presence of ischemic heart disease was defined as prior myocardial infarction and/or angina with hospitalization and/or an infarct and/or major ischemia patterns on the electrocardiogram. Smoking was categorized as no smoking or current smoking (current or stopped <1 year ago). Chronic obstructive pulmonary disease (COPD) diagnosis was based on the presence of a post-bronchodilator FEV1/FVC <0.70 and we classified COPD as mild (FEV1 > 80% predicted), moderate (50% < FEV1 < 80% predicted), severe (30% < FEV1 < 50% predicted) and very severe (FEV1 < 30% predicted). Kidney failure (KF) diagnosis was based on a level of GFR <15 mL/min/1.73 m² or a need for initiation of kidney replacement therapy (dialysis or transplantation) for treatment of complications caused by a decreased GFR.

Laboratory Measurements
The urinary albumin excretion rate was measured as the mean of two 24-h urine collections, and urinary albumin concentrations were determined by nephelometry. Blood samples were collected from subjects, after a 12- to 14-hour fast, into tubes containing 0.1% EDTA. High-sensitive C-reactive protein (CRP) was determined by nephelometry, interleukin-6 (IL-6) by immunochemiluminescence and all lipid parameters (total and HDL-C and TG) by colorimetric/spectrophotometric procedure. LDL-cholesterol was estimated from quantitative measurements of total and HDL-C and TG using the empirical relationship of Friedewald.

DNA Analysis
DNA extraction was carried out on total blood using Archive Pure DNA Blood Kit (5-PRIME, Hamburg, Germany) according to the manufacturer's instructions. DNA was quantified with an ultraviolet spectrophotometer (Anthos Labtech, Germany). DNA was amplified using primers of TaqIB polymorphism with primer sequences AAGAGCTT TTCGAATTTCTCAGC (F) and AAGAGCTTTTCGAATTTCTCAG (R).

Table 1: Demographic and clinical features of the study population

<table>
<thead>
<tr>
<th></th>
<th>Controls n = 109</th>
<th>AF patients n = 109</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male sex, n (%)</td>
<td>53 (48.6%)</td>
<td>47 (43.1%)</td>
<td>0.3414</td>
</tr>
<tr>
<td>Age (years)</td>
<td>74±10</td>
<td>75±10</td>
<td>0.4612</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>28±5</td>
<td>27±4</td>
<td>0.1045</td>
</tr>
<tr>
<td>Current smoking</td>
<td>36 (33.0%)</td>
<td>41 (37.6%)</td>
<td>0.4831</td>
</tr>
<tr>
<td>Clinical history</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NYHA class, n (%)</td>
<td>66 (60.5%)</td>
<td>61 (56.0%)</td>
<td>0.3717</td>
</tr>
<tr>
<td>I</td>
<td>43 (39.5%)</td>
<td>48 (44.0%)</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>34 (31.2%)</td>
<td>13 (11.9%)</td>
<td>0.0005</td>
</tr>
<tr>
<td>IHD, n (%)</td>
<td>78 (71.6%)</td>
<td>83 (76.1%)</td>
<td>0.4465</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>24 (22.0%)</td>
<td>20 (18.3%)</td>
<td>0.5060</td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>20 (18.3%)</td>
<td>23 (21.1%)</td>
<td>0.6151</td>
</tr>
<tr>
<td>COPD, n (%)</td>
<td>26 (23.9%)</td>
<td>21 (19.3%)</td>
<td>0.8155</td>
</tr>
<tr>
<td>Mild</td>
<td>65 (59.6%)</td>
<td>68 (62.4%)</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>13 (11.9%)</td>
<td>16 (14.7%)</td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>5 (4.6%)</td>
<td>4 (3.6%)</td>
<td></td>
</tr>
<tr>
<td>Very severe</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Echo</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AP left atrial diameter, mm</td>
<td>43±8±7.7</td>
<td>45±1±7.2</td>
<td>0.1690</td>
</tr>
<tr>
<td>SI left atrial diameter, mm</td>
<td>52±8±6.4</td>
<td>53±3±4.1</td>
<td>0.4929</td>
</tr>
<tr>
<td>ML left atrial diameter, mm</td>
<td>37±4±6.6</td>
<td>38±3±4.2</td>
<td>0.2310</td>
</tr>
<tr>
<td>LV EF, (%)</td>
<td>55±7</td>
<td>54±6</td>
<td>0.2587</td>
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<tr>
<td>Laboratory</td>
<td></td>
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</tr>
<tr>
<td>C-reactive protein, mg/dl</td>
<td>1.17±2.04</td>
<td>0.99±1.82</td>
<td>0.4926</td>
</tr>
<tr>
<td>Urinary albumin excretion, mg/L</td>
<td>84±2±4.04</td>
<td>75±1±6.6</td>
<td>0.7212</td>
</tr>
<tr>
<td>IL-6, pg/ml</td>
<td>15.47±25.44</td>
<td>13.39±25.41</td>
<td>0.6787</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>4.50±1.14</td>
<td>4.28±0.93</td>
<td>0.1199</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>1.37±0.68</td>
<td>1.19±0.54</td>
<td>0.0315</td>
</tr>
<tr>
<td>HDL-cholesterol, mmol/L</td>
<td>1.41±0.44</td>
<td>1.46±0.35</td>
<td>0.3542</td>
</tr>
<tr>
<td>LDL-cholesterol, mmol/L</td>
<td>2.46±1.01</td>
<td>2.25±0.79</td>
<td>0.0887</td>
</tr>
<tr>
<td>Total cholesterol/HDL-cholesterol</td>
<td>3.34±0.99</td>
<td>3.13±1.16</td>
<td>0.1520</td>
</tr>
<tr>
<td>Triglycerides /HDL-cholesterol</td>
<td>2.92±1.67</td>
<td>2.02±1.17</td>
<td>0.0111</td>
</tr>
</tbody>
</table>

Drug therapy
| Statin use, n (%) | 76 (35%) | 44 (20%) | 0.0001 |

AF, atrial fibrillation; BMI, body mass index; IHD, ischemic heart disease; KF, kidney failure; COPD, chronic obstructive pulmonary disease; AF, antero-posterior; SI, supero-inferior; ML, medio-lateral; LV EF, left ventricular ejection fraction; IL-6, interleukin-6.
The levels of IL-6, CRP as well as urinary albumin excretion were no significantly different between the two groups. HDL-C levels were similar in both case and control groups. The plasma TG levels and TG/HDL-C ratio were significantly lower in the AF group compared to the control group (p=0.0315 and p=0.0111, respectively). 76 subjects of the control group (35%) and 44 patients with AF (20%) were treated with the lipid lowering drug statins (p=0.0001). Among the 109 patients with arrhythmia, 51 (46.8%) were affected by paroxysmal AF, 39 (35.8%) by persistent AF and 19 (17.4%) by permanent AF.

### Frequency of the CETP TaqIB Polymorphism

The genotype distribution of CETP TaqIB polymorphism is shown in Table 2. B1 and B2 were respectively used to denote the presence and the absence of the restriction site for the enzyme TaqI in intron 1. In the general population, the AF group had a higher percentage of both B2B2 and B1B1 genotypes and a lower percentage of B1B2 genotype compared to the control group and these differences were significant (p=0.0342). On the contrary no significant differences in B2 allele frequency were found between the two groups. When the genotypes were stratified by gender, we found no significant differences in the male subgroup. Conversely in the female subgroup, the difference of B2B2 genotype between AF and control subjects significantly increased (p=0.0059). A post-hoc analysis with Bonferroni’s correction for pair-wise comparisons confirmed the significant differences between control subjects and AF patients for the B2B2 (p=0.015) and B1B2 genotypes (p=0.019). We also observed the increase of B2 allele frequency in AF patients with respect to control subjects but the difference was not significant.

The genotype distribution of case and control group was in the Hardy-Weinberg equilibrium.

According to these data the subjects with the B2B2 genotype seem to be more susceptible to AF development (OR=2.28, 95% CI 1.06-4.89, p=0.032). The AF incidence is higher if we consider only the female subgroup (OR=5.14, 95% CI 1.57-16.82, p=0.0061).

We then examined the distribution of CETP genotypes in relation to the different forms of atrial fibrillation (paroxysmal, persistent, permanent) without observing any statistically significant difference (p=0.0917).

### Effect of the CETP TaqIB Polymorphism on Serum Lipid Levels in Female Population

The effect of CETP TaqIB polymorphism on lipid parameters in the female population is shown in Table 3. In total female population the B2B2 individuals showed a trend towards increase in HDL-C compared to B1B1 and B1B2 subjects, although the difference was not statistically significant. The increase in HDL levels in B2B2 subjects was more evident when we considered the control subgroup. In this case we have found a difference, close to statistical significance (p=0.086), in the HDL-C levels in B2B2 subjects with respect to B1 carriers. The increased HDL-C levels were concomitant with a reduction in TG levels and TG/HDL-C ratio. For both parameters, the difference was statistically significant (p=0.005 and p=0.019 respectively). Differently in the AF subgroup the B2B2 patients had a statistically significant decrease of HDL-C levels (1.50 ± 0.35 vs 2.07 ± 0.42; p=0.044) and statistically higher TG levels (1.34 ± 0.46 vs 0.77 ± 0.14; p=0.006) and TG/HDL-C ratio (2.14 ± 0.80 vs 0.88 ± 0.23; p=0.004) when compared to B2B2 control subjects. Therefore in B2B2 females, the higher TG levels contrast the raising of HDL-C levels.

### Sequence Analysis of the CETP Promoter Region

To investigate the -629C>A polymorphism that has been found to be in complete linkage with the TaqIB variant, the DNA sequence between -827 to + 36 bp of the CETP gene was amplified in all
B2B2 females (18 AF patients and 5 controls) and in 23 B1B1 AF females randomly selected. The 909-bp PCR produced from all the typed patients was directly sequenced. The sequence analysis showed that all the B2B2 subjects exhibited the –629AA genotype, while the B1B1 subjects showed the CC genotype (16/23), the CA genotype (5/23) or the AA genotype (2/23). Therefore in our subjects the 100% of the B2 alleles of the TaqIB polymorphism was associated with the A alleles of the –629 upstream promoter polymorphism, while the 80% of the B1 alleles of the TaqIB polymorphism was associated with the C alleles. These results indicate that in our female population the –629A allele was completely concordant with the TaqIB2 variant.

### Discussion

AF is the most common arrhythmia found in everyday clinical practice. The majority of patients with AF has underlying heart disease, such as valvular heart disease, hypertension, or left ventricular dysfunction. However, some patients develop AF in absence of any known risk factor. Family studies have revealed that gene mutations with a mendelian hereditary pattern underlie rare forms of AF. In addition, numerous reports have suggested associations between genetic polymorphisms and common forms of AF, but the identified variants were not often replicated in independent populations.

The CETP TaqIB polymorphism is very common in the population and seems to play an important role in cardiovascular disease. Although HDL cholesterol levels are higher about 10% in B2B2 genotype compared to B1B1, the association of this polymorphism with cardiovascular disease has not been established unequivocally. Some studies have shown a protective effect, others have highlighted the association with adverse cardiovascular events or have found no association.

Our study reported that the TaqIB2 allele and the concordant –629A allele of the CETP gene are associated with a higher incidence of AF in general population, particularly in females with increased TG levels (OR=5.14, 95% CI 1.57-16.82, p=0.0061). The role of the CETP TaqIB polymorphism on AF has not yet been unequivocally reported. Asselbergs and coworkers showed for the first time an association between CETP B1B1 genotype, decreased HDL-C level and AF. On the contrary, a study done in 8141 subjects showed that the TaqIB polymorphism was not associated with an increased risk of AF disease.

The strength of the present study lies in the selection of the participants based on their ethnic background, recruited carefully after evaluation of AF condition by patient’s history, serial electrocardiograms or ambulatory ECG monitoring, with AF onset occurring after 65 years of age in almost all the patients. It is important to note the difference in age between our population and those recruited by Asselbergs and Sinner. More than 90% of our patients was over 65 years, while all the subjects enrolled in the other two studies were less than 65 years. We know that the prevalence and incidence of atrial fibrillation increase with age, so a potential misclassification of referent subjects that will later develop AF may bias the results of the two studies. Moreover, they didn’t stratify their population according to gender, whereas we observed the most significant data in the female subgroup. In addition, Sinner sample consisted predominantly of males (over 70%).

Although it has been recognized that inflammation may facilitate the development of AF, our cohort could represent a selected group of patients in whom AF is associated with an abnormal lipid metabolism rather than inflammation. In this case the TG/HDL-C ratio is a better indicator than other measurements as CRP and IL-6, and polymorphisms in genes involved in lipid metabolism, as CETP, may have a role in the onset of the disease.

In our general population the frequency of B2 allele and B2B2 genotype the same of other Caucasian populations but

### Table 2: TaqIB polymorphism: genotype and allele frequencies in the study population

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<tr>
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<tbody>
<tr>
<td>Total</td>
<td>n=109</td>
<td>n=109</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>n=53</td>
<td>n=47</td>
<td></td>
<td></td>
</tr>
<tr>
<td>B2B2</td>
<td>14 (12.8%)</td>
<td>25 (23.0%)</td>
<td>0.0342</td>
<td></td>
</tr>
<tr>
<td>B1B2</td>
<td>62 (56.9%)</td>
<td>44 (40.4%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>B1B1</td>
<td>33 (30.3%)</td>
<td>40 (36.6%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>B2 allele</td>
<td>90 (41.3%)</td>
<td>94 (43.1%)</td>
<td>0.4634</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>n=56</td>
<td>n=62</td>
<td></td>
<td></td>
</tr>
<tr>
<td>B2B2</td>
<td>5 (9.0%)</td>
<td>18 (29.0%)</td>
<td>0.0099</td>
<td></td>
</tr>
<tr>
<td>B1B2</td>
<td>33 (59.0%)</td>
<td>21 (33.9%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>B1B1</td>
<td>18 (32.0%)</td>
<td>23 (37.1%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>B2 allele</td>
<td>43 (38.4%)</td>
<td>57 (46.0%)</td>
<td>0.0591</td>
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</tr>
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</table>

AF, atrial fibrillation
the frequency of the B2B2 genotype (9%) in our female control subgroup was lower compared to those reported in different studies: in the Framingham Offspring study the B2B2 genotype frequency in females was 18.2%.24 Park and coworkers in their Korean cohorts discovered that the B2B2 genotype frequency was 22.7%.25

Moreover in our B2B2 females it was observed a modification of the HDL-C levels by TG. The B2B2 individuals tended to have higher HDL-C levels and significant lower TG levels and HDL-C ratio compared to B1B1 and B1B2 subjects (Table 3). Conversely in the B2B2 AF females we found significant decreased HDL-C levels and a significant higher plasma TG level and HDL-C ratio compared to B2B2 controls.

When we performed sequence analysis of the CETP promoter to identify the functional polymorphisms located 629 bp upstream to the ATG codon, we observed the presence of the -629AA genotype in all the 23 B2B2 females. Thus, the -629A allele of the promoter region and the B2 allele of the TaqIB polymorphism were concordant in our population and might account for the observed increased HDL-C level in control females and the decreased HDL-C level in AF female patients with a higher TG level.

Our idea is that in the presence of hypertriglyceridemia there is a modification of the relationship between CETP and HDL-C levels. Our findings are consistent with those of Tato26 and Foger27 who showed that among hypertriglyceridemic individuals HDL-C concentration was dependent by CETP levels, while the contribution of CETP was less in normotriglyceridemic subjects. So, while in normotriglyceridemia reverse cholesterol transport by HDL-cholesteryl-ester-selective-uptake pathway, a non-CETP pathway, is important, in the presence of hypertriglyceridemia the CETP pathway becomes more important. But lower circulating CETP levels in B2B2 subjects could reduce the generation of small pre-β-HDL particles that stimulate the cellular cholesterol efflux. Low CETP levels could therefore reduce the removal of cellular cholesterol. This protein also regulates the cholesterol traffic directly at cellular level, as macrophages present in atherosclerotic lesions produce CETP. Zheng28 has shown that voltage-dependent ion channels and lipids in close proximity form functional units and no-phospholipidic molecules, as cholesterol, can change opening/closing state of such channels.

The increase in triglyceride levels after the menopausal transition could account for the data we obtained in the female subgroup. In fact a longitudinal study reported an increase of 16% in triglyceride values.29 In NHANES the gap in triglyceride levels between men and women narrowed in the 50- to 59-year age group, and from 60 years onward women had higher levels than men.30 This was confirmed in our population, in which emerged a statistically significant difference between men and women, with higher triglyceride levels in the female subgroup (1.37±0.59 vs 1.19±0.48, p=0.0212).

The low number of our sample may represent a limitation of the study we conducted. Despite this, our work was performed on patients from a well-defined geographical area and in these association studies the genetic background is particularly important. In addition, the selection mode plays a key role. In atrial fibrillation, whose prevalence and incidence increase with age, it may be important to select patients taking into account this parameter, as an age too low can lead to a potential misclassification of enrolled subjects, which may later develop arrhythmia, distorting the results of the study. However, to better define the associations observed in our work, further studies are required in larger populations, also belonging to other geographical areas.

Conclusions:

The results of our study indicate significant association of TaqIB2 and the concordant -629A alleles of CETP gene with lower HDL-C levels, higher TG levels and TG/HDL-C ratio in a subset of postmenopausal females coming from Salento (Southern Italy).

This lipid profile, added to the negative effects caused by CETP lower plasmonic levels induced by polymorphism, such as pre-β-HDL particles reduction, reduced cellular cholesterol removal, cellular membrane fluidity modification, could have promoted the onset of the arrhythmia in our population.

Acknowledgements:

The financial support of the University of Salento (Progetti di Ricerca Scientifica d’Ateneo) is gratefully acknowledged.

References:


the Cox-Maze procedure utilizes bipolar radiofrequency ablation and cryoablation to create lesions, in addition to surgical excision of the left atrial appendage. The Cox-Maze IV lesion set is comprised of multiple lesions in both the right and left atria. The left atrial lesion set consists of: 1) right and left pulmonary vein isolation, 2) connecting lesions between the left and right superior and inferior pulmonary veins, and 3) a lesion from the excision site of the left atrial appendage to the pulmonary vein and a lesion to the mitral valve annulus. The right atrial lesion set consists of: 1) ablation lines along the superior and inferior vena cavae and 2) the free wall of the right atrium down to the tricuspid valve annulus (2). Initial studies demonstrate the success of the Cox-Maze IV procedure in AF with freedom from AF and antiarrhythmic drugs at 78-82% at 12 months even in patients with increased left atrial size. Complete elimination of AF has been shown in more than 90% of patients treated with Cox-Maze procedures, establishing these procedures as the gold standard for treatment of AF.

Additional studies have shown an added benefit of surgical ablation over catheter ablation of 15.7-33.4% with excellent overall rates of AF elimination of 74.7-88%. Surgical procedures have demonstrated increased success in termination of AF compared to percutaneous catheter ablations with one year post-procedure success rates of 65% compared to 36% in the FAST trial; however, procedural adverse event rate was also significantly higher in this group. The increased risk of procedural complications with surgical approaches has promoted continued development of catheter-based procedures using radiofrequency energy to create atrial lesions. Catheter ablation is less effective than surgical approaches, but has fewer procedural complications and is significantly more effective than anti-arrhythmic medications alone. Landmark work documenting ectopic beat origination in the pulmonary veins has served as the foundation for now-standard catheter-based approaches. Consequently, catheter-based ablations have focused on the left atrium, with a particular emphasis on pulmonary vein isolation. Conventional catheter ablation has been shown to have one year success rate (elimination of AF without anti-arrhythmic drugs) of 40-60% for one procedure with a 70-80% maximal success.
rate for three or more procedures. Although catheter-based procedures are effective and have the benefit of minimal invasiveness they remain inferior when compared to Cox-Maze procedures.

One potential explanation for the relative success of Cox-Maze procedures III and IV compared to catheter-based ablation is electrical intervention in both left and right atria, which suggests a putative role for right atrial catheter ablation. Although right atrial ablation approaches have been previously documented, more recent studies incorporating atrial mapping have further elucidated the role of the right atrium in AF. Right atrial foci in the SVC, cristra terminalis, and coronary sinus ostium have been speculated to initiate AF. Since AF predominantly originates in the left atrium some studies have shown little additional benefit of right atrial lesions particularly in patients with long-lasting persistent AF; however, studies utilizing atrial mapping have suggested a role for focal right atrial ablation. Atrial mapping, specifically of paroxysmal AF suggests that between 5-25% of AF may originate in the right atrium; once mapped, focal ablation of the right atrium can effectively treat this subset of paroxysmal AF with long-term success in maintenance of sinus rhythm without AADs of 79% of patients at 19.7 months. Right atrial foci have also been identified in idiopathic AF; mapping and right atrial linear ablations successfully eliminated or allowed AF to be medically managed in 56% of these patients. Logically, biatrial ablation mapping have been shown to have the highest success rates of catheter-based approaches, with success rates of up to 85% approaching success rates seen with Cox-Maze procedures.

The success of catheter-based ablation with specific targeted lesions is improving because of recent developments in the understanding of the generation and sustenance of AF. The critical mass hypothesis describes the tendency of fibrillation to terminate in a finite-sized tissue area -- consistent with clinical data correlating increased atrial size with persistence of AF. Recent studies have revealed that AF is typically generated by a small number of localized sources that cause disorganization in the remaining atrial tissue. The CONFIRM study examined conventional ablation with and without focal impulse and rotor ablation. Atrial mapping revealed electrical rotors and focal impulses in 97% of AF patients with a median number of 2.1+/− 1.0 sources (70% rotors and 30% focal impulses). Focal impulse and rotor modulation (FIRM) ablation was used to eliminate these foci before conventional ablation. Acutely 86% of persistent and paroxysmal either terminated or slowed AF and single procedure AF elimination rates were 82.4% in FIRM-guided compared to 44.9% in FIRM-blinded cases. In addition, this approach resulted in improvement in long-term AF elimination compared to conventional ablation strategies. These findings suggest a critical role for novel atrial mapping technologies and targeted ablation to precisely deliver lesions to treat unique patient-specific foci. In US centers using this technique, about a third of the rotors are found in the right atrium (unpublished data).

It is important to review the history of catheter ablation of atrial fibrillation, and consider the judicious addition of potentially impactful right atrial lesions, at least in select cases. Whether guided by mapping of rotors or complex fractionated atrial electrograms (CFAEs), or simply anatomic lesion sets, these additional lesions have the potential to improve success rates and deserve further investigation. Some of their benefit may derive from the proximity of the right superior pulmonary vein and other key structures, as right atrial lesions are delivered. Some of the reported benefits may be from a reduction of the critical mass of atrial myocardium available to sustain AF. Since right atrial lesions are generally safer than left atrial lesions, adding these would be associated with minimal additional risk to the patient. In our quest to improve the success rates and reduce the complications associated with catheter ablation of AF, the right atrium should not be forgotten. The future is likely to be about individualization of therapies, partly from detailed mapping and targeted ablation lesions.

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A Case Of Difficult Epicardial Access For Ablation Of Ventricular Tachycardia

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Abstract
We present a case of a 67-year-old patient with nonischemic cardiomyopathy and recurrent sustained ventricular tachycardia of epicardial origin referred for ablation. Due to two previous episodes of cardiac tamponade secondary to implantable cardioverter-defibrillator lead perforation at the time of device implant, the patient had significant pericardial adhesions making epicardial access and ablation challenging.

Case
We present a 67-year-old man with nonischemic cardiomyopathy (NICM), ejection fraction (EF) 20%, New York Heart Association class II congestive heart failure, and dual chamber implantable cardioverter-defibrillator (ICD) initially implanted for primary prevention in 2008. The previous ICD placement was complicated by lead perforation of the right ventricle (RV) with cardiac tamponade and the need for pericardiocentesis, which had been performed twice during that hospitalization.

The patient experienced recurrent ventricular tachycardia (VT) in 2009 and was referred for endocardial VT ablation at an outside hospital, which was unsuccessful. The patient continued to experience recurrent ICD shocks despite beta blockers and amiodarone therapy. He was initially referred to our institution for VT ablation after receiving three ICD shocks for monomorphic VT (cycle length (CL) 400-420ms). Only intracardiac electrograms were available for review prior to the procedure.

During the initial ablation procedure, noninvasive programmed stimulation (NIPS) was performed and the induced VT was thought to be originating from the basal infero-lateral left ventricle (LV), CL 496 ms, with a Q wave in lead I, superior axis, and positive concordance in precordium (FIGURE 1). The tachycardia met criteria suggestive of an epicardial exit based on QRS duration 253 ms, Q wave in lead I, pseudo-delta of 80 ms (>34ms) and intrinsocid deflection of 106 ms (>85 ms), although the Maximum Deflection Index (MDI) at 0.41 was <0.55,1,2

Given the previous failed endocardial ablation, the NICM substrate, and the ECG criteria consistent with an epicardial exit, the decision was made to attempt percutaneous epicardial access using techniques originally described by Sosa et al. in 1996.3 Epicardial access was difficult and there was evidence of RV perforation and possible intramyocardial hematoma formation. (FIGURE 2) The decision was made not to attempt endocardial ablation with concern that systemic heparinization could extend the possible intramyocardial hematoma and the procedure was aborted. The patient was discharged on amiodarone and beta blockers with a plan to reschedule for ablation in one month.

Due to insurance issues, the patient was unable to return for repeat procedure for an extended period of time, during which he experienced multiple ICD shocks. One year later, the patient returned after experiencing VT storm with 18 ICD shocks secondary to monomorphic VT, CL 400-410 ms. The patient was transferred back to our facility from an outside hospital and taken to the electrophysiology lab for a second attempt at VT ablation. The VT induced by NIPS again had an apparent epicardial origin, but likely from a more inferior exit (positive concordance and superior axis, QRS 296 ms, pseudo-delta 181ms (>34 ms), intrinsocid deflection 181 ms, (>85 ms) and MDI of 0.71 (>0.55)). Since the patient had known difficult epicardial access, the decision was made to attempt endocardial ablation first and then decide whether repeat percutaneous epicardial access and ablation should be attempted versus a staged approach with plan for surgical hybrid epicardial ablation.

On endocardial mapping via a transseptal approach, scar was seen in the basal inferior and basal anterior LV but no late potentials or pacemaps matches were seen. Therefore, the decision was made to reverse anticoagulation with protamine and then attempt
were observed on the basal anterior lateral and inferior left ventricle with good pacemaps with an 11 of 12 match for the targeted VT from a wide area with split and late potentials in sinus rhythm. However, not all regions of the epicardial ventricular surface could be mapped due to persistent adhesions. (FIGURE 4). The corresponding endocardial surface did not demonstrate late potentials or promising pacemaps that matched the VT further confirming that endocardial ablation would be of little benefit. The VT was then reinduced to look for mid-diastolic activity, but was not tolerated hemodynamically and DC cardioversion was required before further mapping could be performed.

Extensive substrate modification on the epicardial surface was performed for a total of over 40 minutes of radiofrequency energy delivery through an irrigated 3.5 mm ablation catheter (Thermocool, Biosense Webster, Diamond Bar, CA). All late potentials that were seen and accessible were eliminated. After substrate modification, the VT was reinduced with a longer TCL (504ms) with a slight morphologic variation from the targeted VT. Further substrate modification on the epicardium in the same regions as before was performed until the VT was no longer inducible with triple extrastimuli.

The patient had recurrent VT one week after the procedure and was referred for bilateral stellate ganglionectomy, and has been observed for over 6 months without recurrent ICD therapies. He developed amiodarone induced thyrotoxicosis approximately four months after the ablation and did not have any arrhythmia during that time, even after amiodarone was discontinued.

**Discussion**

Percutaneous pericardial access using a subxiphoid approach for electroanatomical mapping and ablation of VT was first described percutaneous epicardial access again, with hybrid surgical exposure as a backup plan.

Using a Tuohy needle (Havel's Inc, OH; BD Medical, NJ) epicardial access was attempted using a posterior approach. With the posterior approach it was difficult to determine the location of the advancing J-wire due to adhesions and therefore a decision was made to use an anterior approach instead, utilizing a micropuncture kit (Cook Medical, Bloomington, IA). After cardiac pulsations were felt and the pericardium was punctured, it remained difficult to pass the wire into the pericardium, so a contrast pericardiogram was performed via a 5 french soft-tipped dilator (FIGURE 3A and 3C). Significant adhesions were observed. Enough wire was able to be passed into the pericardium (FIGURE 3B) to allow for an 8 French SL0 sheath (St. Jude Medical, Inc., Minnetonka, MN) to be placed in the pericardium, but mobility was severely limited due to adhesions.

Therefore, double-epicardial access was obtained by double wiring the SL0 sheath. Using an exchange guidewire technique, an Agilis sheath (St. Jude Medical, Inc., Minnetonka, MN) and the SLO sheath were placed in the pericardium. A duodecapolar catheter was used to further manually disrupt adhesions, but there was not complete exposure of the entire epicardial surface (FIGURE 3D). After disrupting as many adhesions as possible, the duodecapolar catheter was used as a guide for ablation. Late potentials and scar
Epicardial late activation map in sinus rhythm demonstrating areas of late potentials and potential targets for ablation. A: Late potentials (arrow) in sinus rhythm.

Figure 4: Epicardial late activation map in sinus rhythm demonstrating areas of late potentials and potential targets for ablation. A: Late potentials (arrow) in sinus rhythm.

the Sosa and his colleagues in 1996 to treat patients with Chagas cardiomyopathy.1 Potential complications include right ventricular puncture, cardiac tamponade, intramyocardial hematoma, coronary laceration, pluoro-pericardial fistula, bowel perforation, liver laceration, phrenic injury, and diaphragm injury.5 The overall complication rate in a case series by Sacher et al. of 136 epicardial ablations was 5% for acute complications, and 2% for delayed complications, with tamponade the most common complication.6

Adhesions pose a significant risk to epicardial access and ablation. Patients with prior epicardial access, pericarditis and prior cardiothoracic surgery are at the highest risk for adhesion formation. Patients with previous cardiothoracic surgery with bypass grafts or previous valve surgery that require epicardial mapping and ablation necessitate a hybrid surgical approach for access.7 For patients with previous epicardial access and suspected adhesion, but without previous cardiac surgery, the approach is less clear.

Pericardial adhesions limit the mobility of catheter movement on the epicardial surface of the heart and unless the adhesions are broken up with direct manipulation of the catheter, some areas key for mapping and ablation may not be reached. Adhesion lysis with blunt dissection through catheter manipulation increases bleeding risk and this needs to be considered carefully. One technique used in this case was to manually disrupt the adhesions with the use of an Agilis steerable sheath in combination with a deflectable decapolar catheter. Deflectable sheaths have been demonstrated to be highly effective in mapping the epicardium in general.4 In a case series at the University of Pennsylvania, 10 patients with prior pericarditis (n=2) or non bypass graft cardiac surgery (n=8) underwent VT ablation with percutaneous epicardial access.8 Lysis of adhesions was performed by manipulating deflectable ablation catheters, deflectable sheaths, or multipolar mapping catheters using the curved surface of the catheter to lyse adhesions with direct blunt force. This is similar to the technique used in our case. In their series, only one patient required a subxiphoid window to be placed surgically to allow for appropriate epicardial access to the inferior wall of the heart. There was one right ventricular puncture, and no cases of severe bleeding, cardiac tamponade, or death. While this small study demonstrated the feasibility of such a technique in highly experienced hands, we believe it should be interpreted with caution especially with less experienced operators.

A variety of techniques are available to minimize pericardial access risk in general, however none are specific in the case of known adhesions. A fiber-optic pressure sensor on the tip of the needle is under development, but human data is limited.9 Additionally, endoscopic video-guided pericardiocentesis techniques are in development.10 Our group has described incorporation of electroanatomic mapping systems into epicardial access. In this technique the Tuohy needle is attached to an alligator clip to allow it to be sensed as a catheter on the mapping system. This technique was applied to 8 consecutive patients, all of which achieved successful epicardial access from the subxiphoid approach, but 1 of the 8 did have RV puncture.11

Indications for epicardial access for mapping and ablation of VT are expanding. Patients with prior epicardial access or prior pericarditis are increasingly being referred for epicardial mapping and ablation. A percutaneous subxiphoid approach has been used safely in experienced centers in these cases, but the overall number of cases still remains low, so it is difficult to assess the relative increased risk that adhesions may pose.

Conclusions:

In the case above, although epicardial access was achieved successful without morbidity, there was limited access to all surfaces of the heart, and the VT recurred leading to a referral for stellate ganglionectomy. Having a cardiothoracic surgery team available for possible thoracotomy and hybrid ablation is important in centers attempting such complex cases. Most importantly, higher risk cases such as those with adhesions should only be done at experienced centers well versed in pericardial interventions. Certainly, if done with minimal bleeding, percutaneous access to the epicardium offers patients a lower morbidity option to epicardial access compared to surgical thoracotomy. However, all options must be available and the case should be discussed within an experienced multidisciplinary team to give the patient the highest likelihood of a successful procedure.

References:


Effect Of Catheter Ablation On Quality Of Life In Atrial Fibrillation

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Abstract

Atrial fibrillation (AF) is the most common sustained arrhythmia seen in clinical practice, affecting approximately 1% of the overall population. While rarely life-threatening, AF is almost universally associated with increased morbidity and mortality, predominantly through an increased risk of thromboembolic events, left ventricular dysfunction, as well as significant impairments in functional capacity and health-related quality of life (HRQOL). Improvement in HRQOL, with a secondary reduction of disability and health-care resource utilization, is one of the major therapeutic goals in the management of AF.

Health-Related Quality Of Life

The Importance Of Assessing HRQOL In AF

The regular assessment of HRQOL with validated instruments has become an increasingly more common and widely accepted method for evaluating the impact of the disease and therapeutic interventions. In the case of AF traditional outcome parameters, such as arrhythmia-free survival, cardiac remodeling, and exercise tolerance are insufficient to evaluate the effects of different treatment approaches, and do not adequately correlate with the subjective assessment of the patients’ symptoms or HRQOL. Moreover, the use of symptoms alone is particularly unreliable in AF, leading to an underestimate the overall AF burden. As such, objective and valid assessment tools are necessary given the latent difficulty in determining the clinical impact of AF.

It is here where measures of HRQOL offer their greatest advantage. In considering multiple domains of wellness (i.e. pain, psychological, emotional, and physical disturbances), the HRQOL assessment tools are able to evaluate the degree of baseline disease-related impairment, as well as quantify the subjective improvements in well being (or conversely side-effects) resulting from therapeutic interventions. Specifically, these multi-dimensional HRQOL instruments are able to determine if an intervention had a beneficial effect across all domains concurrently or if a benefit in one domain (i.e. physical health) was offset by a negative effect in another (i.e. mental health). As such, objective and valid HRQOL assessment tools represent increasingly important instruments in the clinical assessment of the impact of AF and its therapy on patients’ functional status and health.

Definitions

Quality of life (QOL) is a subjective phenomenon and is defined as an “individuals’ perception of their position in life in the context of the culture in which they live and in relation to their goals, expectations, standards and concerns.” While QOL is a global construct that includes domains such as job satisfaction and quality of housing, health-related quality of life (HRQOL) is narrower in scope, and can be conceptualized as a combination of symptoms, functional status and the patient’s personal perception of health, which is in turn influenced by their beliefs, experiences, and expectations. However, it is important to note that while there is a significant interplay between each of these HRQOL factors the relationship between symptoms, disease recurrence, and HRQOL is not absolute. For example, while an intense symptom burden would be expected to adversely affect HRQOL, the absence of symptoms does not automatically correspond to an optimal HRQOL state. Likewise, a reduction in AF frequency and duration may not improve symptoms and HRQOL. Therefore, it is critically important to consider the individual contribution of each of these factors when assessing HRQOL, particularly in the face of the highly personal and multifaceted nature of AF.

Disclosures:

None.

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Measuring HRQOL

To date a large number of instruments have been used in published research to evaluate HRQOL. In broad terms, these instruments can be classified into generic and disease specific questionnaires. Generic instruments assess valuations of health and functioning across a predefined set of health-related domains. A widely used generic instrument is the Medical Outcome Survey Short Form (SF-36), which assesses eight different health domains: physical functioning, role limitations due to physical health, bodily pain, and general health perception, which collectively comprise “Physical Health,” and vitality (energy and fatigue), social functioning, role limitations due to emotional health, and general mental health (psychological distress and well-being), which collectively comprise “Mental Health.” In addition to these eight subscales, the SF-36 also generates the physical health weighted composite score (PCS), and the mental health weighted composite scores (MCS). Other generic instruments include the Health Utilities Index Mark 2 and 3 (HUI2 and HUI3), the EuroQol-5D (EQ-5D). Generic instruments have the advantages of extensive validation across a wide range of populations and conditions, ease of use, and generalizability. Moreover the generic instruments are extremely useful for health economic evaluations. Through the use of a HRQOL weight (i.e. utility score) a Quality Adjusted Life Years (QALYs) score can be used as a summary measure of health outcome and to inform subsequent healthcare resource allocation decisions. Contrariwise, the main drawback of generic instruments being a disproportionate focus on general physical health and functioning, which may render it insensitive for measuring AF-specific HRQOL (i.e. the scores being more influenced by patient demographics and comorbidities rather than the impact of the disease or intervention itself). In response to these criticisms disease-specific instruments have been developed and validated. These instruments include symptom specific scales (the most widely used are the University of Toronto Atrial Fibrillation Severity Scale [AFSS] and the Symptom Checklist–Frequency and Severity Scale), and Atrial fibrillation-specific QOL symptom scales (i.e. the Atrial Fibrillation Effect on Quality of Life questionnaire [AFEQT]). These instruments, while lacking the ability to compare between disease states (i.e. the HRQOL of AF patients to CHF patients), are more precise in measuring HRQOL domains directly-related to AF and therefore are more sensitive to changes in patients’ health status (either spontaneous or as a result of intervention). However, in comparison to the wealth of data behind the generic instruments, the use of disease-specific instruments is limited by lack of validation and generalizability. As such, a combination of both types of instruments represents the ideal method to balance the generalizability and extensive validation that comes with generic HRQOL measures with the relatively high sensitivity and precision associated with disease-specific HRQOL questionnaires.

HRQOL In Atrial Fibrillation

An understanding of the overall impact of AF on HRQOL is problematic owing to that the literature-base being derived from interventional studies (i.e. examining the impact of cardioversion, various pharmacotherapies, pacemaker implantation and programming, and surgical or catheter-based ablation procedures), thus potentially biasing the assessment towards highly symptomatic patients. Within the context of these limitations the presence of AF is associated with significantly impaired functional capacity and HRQOL across areas of physical and social functioning, mental and general health, and metrics of illness intrusiveness.14-19 These impairments are marked when compared to population norms, with a degree of impairment that is comparable or worse than in patients with heart failure or coronary disease (post-infarction or post-angioplasty), and as intrusive in their daily lives as chronic hemodialysis.14 In general older patients, women, and those with comorbidities (obesity, valvular heart disease, and chronic pulmonary disease) report lower HRQOL in relationship to AF.19,20 Interestingly, outside of the psychological dimension the subtype of AF (persistent, paroxysmal, or permanent AF) did not seem to have any relationship to HRQOL. This is postulated to relate to anxiety surrounding recurrences as the deterioration in HRQOL has been noted to parallel the number of symptomatic episodes, emergency department visits, and healthcare utilization.21,22 Lastly, it is important to note that patients with purported asymptomatic AF still express a lower HRQOL and reduced global life satisfaction compared to healthy controls in sinus rhythm.14

HRQOL With Medical Pharmacotherapy

In recent years a number of randomized, controlled studies have investigated the effect of ventricular rate control vs. a strategy of maintenance of sinus rhythm (rhythm control).21-27 While not a primary outcome, an improvement in HRQOL was observed in most of these studies over the early follow-up period (~12 month). Importantly, while similar improvements in HRQOL were observed between the both the rate, and rhythm control arms at no point were significant differences observed between the randomized groups in any of the studies. As a result these studies have been interpreted to indicate that a strategy of rate control can be at least as effective as efforts to control rhythm with respect to HRQOL outcomes. However, there are several important limitations to consider. Firstly, with the exception of AFFIRM and AF-CHF, these studies were not powered to detect HRQOL differences. Second, it is possible that the antiarrhythmic drugs (AAD) utilized may have adversely impacted HRQOL due to side-effects or intolerance. In this regard the SAFE-T trial, which included a placebo group in addition to amiodarone and sotalol arms, did not note any significant difference in HRQOL between treatment groups.16,20 Likewise, the CTAf trial, which randomized patients to amiodarone, sotalol, or propafenone, reported improvements in all HRQOL measures from baseline to 3 months across all patients, however the magnitude of benefit was substantially lower than that observed post ablation (see below).29 Lastly, it is important to note that none of these studies were comparisons of successful sinus rhythm maintenance versus permanent AF with ventricular rate control. This is particularly relevant as the ability to understand the true benefit of medical sinus rhythm maintenance on HRQOL is severely limited by the modest efficacy of AADs at maintaining sinus rhythm in these trials (9-58% 1 year success freedom from recurrent AF).30-39 Unfortunately attempts to examine the effect of “achieved rhythm” on HRQOL through post-hoc analyses is made even more difficult by the observation that the relationship between rhythm and HRQOL may be non-linear – i.e. HRQOL being influenced by severe but infrequent symptoms or drug side-effects. As such the results of these post-hoc analyses are somewhat contentious. In PIAF and AFFIRM there was no difference in HRQOL when patients were compared based on rhythm status.23,40 Conversely, RACE, SAFE-T and CTAf demonstrated that patients who remained in
sinus rhythm had an improved HRQOL compared to those with arrhythmia recurrence. Likewise AF-CHF demonstrated that a higher proportion of time spent in sinus rhythm was associated with a modestly greater improvement in HRQOL scores.

**HRQOL After An AF Ablation**

Though AADs remain the first-line therapy for the maintenance of sinus rhythm, their use can be disappointingly ineffective and associated with significant cardiac and non-cardiac toxicities, the combination of which may limit the anticipated HRQOL benefit associated with sinus rhythm maintenance. Conversely, left atrial catheter ablation has been shown to be universally superior to AADs for the maintenance of sinus rhythm in multiple randomized controlled trials. Given this superior efficacy several studies have examined the effect of catheter ablation on quality of life (TABLE).

In general these studies included highly symptomatic patients who had previously failed one or more antiarrhythmic drugs, and thus preselected a fairly symptomatic subset of the AF population. Moreover the studies themselves are fairly heterogeneous in terms of: 1) the inclusion populations (varying degrees of both paroxysmal and persistent AF), 2) the ablation techniques and technologies, and 3) the HRQOL measure utilized (while almost all of the used the SF-36 questionnaire, many used a symptom checklist, with or without other HRQOL measures). However, despite these differences positive changes were near universally observed in almost all SF-36 subscales after catheter ablation (15-40 point improvement in individual SF-36 subscales; scored up to 100). Moreover, the extent of improvement in the Physical Health weighted composite score and the Mental Health weighted composite score were consistently in the range of 10-20 points (scored up to 50). In some cases the SF-36 PCS and MCS composite scores reached normative levels after an ablation procedure, while these scores remained impaired in the medical therapy group throughout the year of follow-up.

In an elegant study Gerstenfeld et al. described 71 patients undergoing attempted ablation of focal PV ablation of AF triggers, with HRQOL prospectively assessed 1 month before and 6 months after the procedure. While ablation was the intention for all patients, 23 patients underwent exclusive mapping due to insufficient or multifocal ectopy. When HRQOL was assessed 6 months post ablation a significant improvement was observed only in the subset of patients undergoing ablation (58 patients), with a significant improvement in all six HRQOL measures in the long-term successful ablation group, compared to four of the six measures in those undergoing ablation with AF recurrence.

Three randomized trials of a pulmonary vein isolation (PVI) procedure vs. AADs for patients with paroxysmal AF have likewise showed significantly greater improvements in HRQOL following catheter ablation. Wasnì et al. randomized 70 patients to PV ablation (33) vs. AADs (37). On follow-up the HRQOL was significantly improved in 5 subclasses of the SF-36 (general health, physical functioning, social functioning, role physical, and pain) in the ablation group, when compared to the AAD group. Jais et al. similarly randomized 112 patients to PV ablation (53) vs. AADs (59). Significant improvements in symptom severity, physical composite scores, and mental health composite scores were observed in both groups, however the extent of benefit was more marked in the ablation group. Moreover, while, the largest magnitude of improvement was observed between baseline and day 91, the benefit was maintained at day 365 where the physical and mental component summary scores remained significantly higher in the ablation group when compared to the AAD group. Wilber et al. randomized 167 patients to PV ablation (106) vs. AADs (61). Similar to Jais et al., the SF-36 PCS and MCS were significant higher in the ablation group at 3 months post ablation, a difference that persisted without significant change at 6- and 9-months post ablation.

Similarly, significant changes in HRQOL have been observed after ablation of more persistent forms of AF. Oral et al. randomized 146 patients to amiodarone plus cardioversion (69 patients) versus catheter ablation (77 patients). Due to arrhythmia recurrence a significant proportion (77%) of the amiodarone group crossed over and underwent catheter ablation at a mean of 128±57 days after cardioversion, which limited the utility comparisons between groups. However, when all patients undergoing ablation were combined a significant improvement in the symptom severity score was observed at 12 months after ablation. While patients who remained in sinus rhythm had a greater improvement in the symptom severity score (10±5 vs. 5±7 in those with arrhythmia recurrence, P=0.002), significant improvements were noted at 12 months irrespective of arrhythmia recurrence. Fiala et al. prospectively examined 160 patients who were undergoing ablation of long-standing persistent AF (median AF duration of 28 months). Quality of life was assessed using the European Quality of Life Group instrument. Compared with the baseline both HRQOL indices improved significantly at 1 year (EQ-5D: 68.8±12.5 to 75.4±14.4; EQ-VAS: 62.8±13.2 to 70.6±13.8) with a further slight increase at 2 years post ablation (EQ-5D: 71.1±15.5; EQ-VAS: 70.9±14.0). Similar to previous, the benefits in HRQOL were largely restricted to patients achieving sinus rhythm, as those who accepted permanent AF did not obtain any substantial benefit in HRQOL at 2 years. Further, restoration of sinus rhythm was associated with beneficial improvements in left atrial appendage outflow velocity, left ventricular ejection fraction, peak oxygen consumption, and NT-proBNP.

Hunter et al. examined the effect of a catheter ablation strategy geared towards sinus rhythm maintenance, with that of a medical rate control strategy in patients with persistent AF, symptomatic heart failure (HF), and an LVEF of ≤50%. In total 50 patients were randomized to catheter ablation (26 patients) or medical rate control (24 patients). At 6 months post ablation freedom from AF was achieved in 21/26 (81%). Ablation was associated with an improved peak oxygen consumption (22±6 vs. 18±6 mL/kg/minute; P=0.01), improved LVEF (40±12% vs. 31±13%; P=0.015), and an improved HRQOL as measured by the Minnesota living with HF questionnaire score (10±5 vs. 5±7 in those with arrhythmia recurrence, PS=0.002), significant improvements were noted at 12 months irrespective of arrhythmia recurrence. Fiala et al. prospectively examined 160 patients who were undergoing ablation of long-standing persistent AF (median AF duration of 28 months). Quality of life was assessed using the European Quality of Life Group instrument. Compared with the baseline both HRQOL indices improved significantly at 1 year (EQ-5D: 68.8±12.5 to 75.4±14.4; EQ-VAS: 62.8±13.2 to 70.6±13.8) with a further slight increase at 2 years post ablation (EQ-5D: 71.1±15.5; EQ-VAS: 70.9±14.0). Similar to previous, the benefits in HRQOL were largely restricted to patients achieving sinus rhythm, as those who accepted permanent AF did not obtain any substantial benefit in HRQOL at 2 years. Further, restoration of sinus rhythm was associated with beneficial improvements in left atrial appendage outflow velocity, left ventricular ejection fraction, peak oxygen consumption, and NT-proBNP.
### Table 1: Studies of AF ablation and HRQOL

<table>
<thead>
<tr>
<th>Type of Study</th>
<th>Population</th>
<th>Number of patients</th>
<th>Classification of AF</th>
<th>Male Gender %</th>
<th>Age</th>
<th>Ablation strategy</th>
<th>Follow-up</th>
<th>QOL tool</th>
<th>Time of QOL assessment</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pappone et al.</td>
<td>Observational</td>
<td>1,171 patients. 589 patients in the ablation group were compared to 582 in the antiarrhythmic group. But only 211 completed the SF-36 (109 and 102 respectively).</td>
<td>1,171</td>
<td>Paroxysmal 70%</td>
<td>59%</td>
<td>65 ± 10</td>
<td>PV isolation</td>
<td>900 days</td>
<td>SF-36</td>
<td>Every 3 m for 1 y</td>
</tr>
<tr>
<td>Hsu et al.</td>
<td>Observational</td>
<td>58 patients with LVEF &lt;45% (45% with structural heart disease) and 58 matched age, gender and type AF with normal LVEF.</td>
<td>116</td>
<td>Paroxysmal 9%</td>
<td>88%</td>
<td>56±10</td>
<td>PV isolation ± roof line or mitral isthmus</td>
<td>12 ± 7 months</td>
<td>SF-36, Symptom Checklist–Frequency and Severity Scale</td>
<td>At 3 and 12 months</td>
</tr>
<tr>
<td>Oral et al.</td>
<td>Randomized</td>
<td>146 patients randomized in two groups, 69 to amiodarone + CVE the first 3 months VS 77 to a circumferential pulmonary vein ablation.</td>
<td>146</td>
<td>“Chronic” 100%</td>
<td>88%</td>
<td>57±9</td>
<td>PV isolation ± roof line or mitral isthmus</td>
<td>1 y</td>
<td>Symptom Severity Questionnaire</td>
<td>At 12 months</td>
</tr>
<tr>
<td>Wazni et al.</td>
<td>Randomized</td>
<td>70 patients randomized in two groups, 37 to antiarrhythmic drugs treatment VS 33 to PV isolation. The patients had not been treated with AAD.</td>
<td>70</td>
<td>Paroxysmal 96%</td>
<td>NA</td>
<td>53±8</td>
<td>PV isolation</td>
<td>1 y</td>
<td>SF-36</td>
<td>At 6 months</td>
</tr>
<tr>
<td>Tondo et al.</td>
<td>Observational</td>
<td>40 patients with LVEF &lt; 40% (55% with structural heart disease) and 65 control patients with normal LVEF.</td>
<td>105</td>
<td>Paroxysmal 24%</td>
<td>82%</td>
<td>57</td>
<td>PV isolation ± mitral isthmus + cavotricuspid isthmus</td>
<td>14 ± 2 months</td>
<td>SF-36</td>
<td>At 6 months</td>
</tr>
<tr>
<td>Chen et al.</td>
<td>Observational</td>
<td>94 patients with LVEF &lt; 40% (96% with structural heart disease) and 283 patients with normal LVEF. But only 193 completed the SF-36 questionnaire (43 in LVEF &lt; 40% group, and 150 in the control group).</td>
<td>377</td>
<td>Paroxysmal 51%</td>
<td>80%</td>
<td>55</td>
<td>PV isolation</td>
<td>14 ± 5 months</td>
<td>SF-36</td>
<td>At 6 months</td>
</tr>
<tr>
<td>Jais et al.</td>
<td>Randomized</td>
<td>112 patients randomized in two groups, 53 to PV ablation VS 59 to antiarrhythmic drugs.</td>
<td>112</td>
<td>Paroxysmal 100%</td>
<td>84%</td>
<td>51.1 ± 11</td>
<td>PV isolation ± roof line, mitral isthmus or cavotricuspid isthmus</td>
<td>1 y</td>
<td>SF-36, Symptom Checklist–Frequency and Severity Scale</td>
<td>At 3, 6 and 12 months</td>
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<tr>
<td>Study</td>
<td>Type of Study</td>
<td>Population</td>
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<td>Follow-up</td>
<td>QOL tool</td>
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<tr>
<td>Wokhu et al.</td>
<td>Observational</td>
<td>502 patients prospectively followed post AF ablation. No control group.</td>
<td>502</td>
<td>Paroxysmal 51%</td>
<td>82%</td>
<td>55.9±10.3</td>
<td>PV isolation + roof line, mitral isthmus and cavotricuspid isthmus</td>
<td>3.1 y</td>
<td>SF- 36 in all the patients MAFSI in 103 patients</td>
<td>At 3 months and 1, 2 and 3 years</td>
</tr>
<tr>
<td>Hunter et al.</td>
<td>Randomized</td>
<td>50 patients with symptomatic HF and LVEF &lt; 50%. Randomized to AF ablation (26) VS rate control (24).</td>
<td>50</td>
<td>Persistent 100%</td>
<td>96%</td>
<td>55±12</td>
<td>PV isolation ± CFEs, mitral isthmus, roof line, and cavotricuspid isthmus</td>
<td>1 y</td>
<td>SF- 36 Minnesota Living with Heart Failure questionnaire (MLWHF)</td>
<td>6 months</td>
</tr>
<tr>
<td>Wilber et al.</td>
<td>Randomized</td>
<td>167 patients randomized (2:1) to AF ablation (106) VS antiarrhythmic drugs (51)</td>
<td>167</td>
<td>Paroxysmal 100%</td>
<td>66.8%</td>
<td>55.7</td>
<td>PV isolation ± CFEs, mitral isthmus, roof line, cavotricuspid isthmus</td>
<td>12.5 months</td>
<td>SF- 36, Symptom Checklist-Frequency and Severity Scale</td>
<td>At 3, 6 and 9 months</td>
</tr>
<tr>
<td>Mantoan et al.</td>
<td>Randomized</td>
<td>100 patients randomized 1:1:1 in 3 groups: 32 to PV isolation; 34 to CFEs; and 34 to PV isolation and CFEs.</td>
<td>100</td>
<td>“High burden” paroxysmal 64% Persistent 36%</td>
<td>74%</td>
<td>57 ±10</td>
<td>PV isolation or CFEs or both</td>
<td>1 y</td>
<td>SF-36</td>
<td>At 6 and 12 months</td>
</tr>
<tr>
<td>Fichtner et al.</td>
<td>Observational</td>
<td>133 patients prospectively followed post AF ablation. No control group. Evaluated by 7 different QOL questionnaires</td>
<td>133</td>
<td>Paroxysmal 65%</td>
<td>74%</td>
<td>57 ±10</td>
<td>PV isolation ± CFEs ± roof line ± mitral isthmus</td>
<td>4.3±0.5 y</td>
<td>WHO-5-Well-Being-Index, Major Depression Inventory, Vital Exhaustion, Sleep and Vegetative Disorder, AF Severity Scale, AF Symptom Checklist and Illness Intros sinusness</td>
<td>At 3, 6 and 12 months, and yearly thereafter</td>
</tr>
<tr>
<td>Pontoppidan et al.</td>
<td>Observational</td>
<td>149 patients prospectively followed post AF ablation. End point relation QoL and asymptomatic AF recurrences</td>
<td>149</td>
<td>Paroxysmal 54%</td>
<td>71%</td>
<td>56±8</td>
<td>PV isolation ± roof line, mitral isthmus</td>
<td>12 months</td>
<td>SF-36</td>
<td>At 12 months</td>
</tr>
<tr>
<td>Weera soorya et al.</td>
<td>Observational</td>
<td>63 patients prospectively followed post AF ablation. No control group</td>
<td>63</td>
<td>Paroxysmal 100%</td>
<td>78%</td>
<td>56±7</td>
<td>PV isolation + mitral isthmus + cavotricuspid isthmus</td>
<td>12 months</td>
<td>SF- 36, Symptom Checklist-Frequency and Severity Scale</td>
<td>At 3 and 12 months</td>
</tr>
</tbody>
</table>
Arrhythmia Recurrence

Similar to studies of medical rhythm control the beneficial effect of ablation has been linked to arrhythmia recurrence, although there is some suggestion that an ablation procedure independently results in a significant improvement in HRQOL during short- and long-term follow-up irrespective of outcome. The reasons for the perceived disconnect between measured HRQOL improvement and objective arrhythmia recurrence is likely multifactorial, reflecting in part: 1) The difficulty in establishing a relationship between arrhythmia recurrence and HRQOL, as outlined above; 2) A relative transition from proportionally more symptomatic to proportionally more asymptomatic paroxysms of AF, which is known to occur after ablation; 3) Placebo/nocebo effects surrounding ablation/AAD use, which given the lack of blinding may affect the results of short-term HRQOL questionnaires (although the effects should be minimal over long-term follow-up); and 4) An imprecise or inaccurate tool to measure HRQOL. Specifically, despite its widespread use, the generic SF-36 may not be sensitive enough to evaluate changes in HRQOL after catheter ablation, especially when arrhythmia recurrence needs to be considered. This was elegantly demonstrated by Wokhu et al. who observed betterment in HRQOL, as assessed by SF-36, was not dependent on ablation efficacy. Specifically when assessed by SF-36 catheter ablation produced a sustained improvement in HRQOL at 2 years irrespective of arrhythmia outcome. However, when they utilized a disease-specific symptom questionnaire (Mayo AF-specific Symptom Inventory - MAFSI), the HRQOL differed significantly among ablation efficacy outcomes suggesting that arrhythmia recurrence likely plays a larger role in HRQOL than is appreciated on generic questionnaires. Similar results utilizing a disease-specific questionnaire have been observed in studies by Erdogan et al., Miyasaki et al., and Fichter et al. As such, while catheter ablation may improve HRQOL irrespective of outcome, the degree of improvement appears to be linked to arrhythmia burden.

HRQOL After AV Node Ablation

Multiple large randomised controlled trials have demonstrated that a strategy of ventricular rate control is not inferior to restoration of sinus rhythm in appropriately selected patients. For those who are unable to achieve adequate control of ventricular rate with pharmacologic agents, a strategy of AV junction ablation followed by permanent right ventricular pacing is an established therapeutic strategy. While preformed less frequently than previous, there is a wealth of evidence demonstrating that AV junction ablation is a safe and highly efficient means to control ventricular rate, with consequent improvements in symptoms, exercise capacity, quality of life, and healthcare resource utilization. One of the largest prospective studies, the Ablate and Pace Trial (APT) evaluated the effect of AV junction ablation and permanent pacemaker implantation on quality of life, and exercise capacity in 156 patients with symptomatic AF. At twelve months of follow-up they demonstrated a significant improvement in HRQOL scores: 1) all 8 subscales of the Health Status Questionnaire (HSQ), 2) the overall rating of the Quality of Life Index, and 3) the Health and Function subscales. Additionally there was a significant reduction (>30%) in arrhythmia-related symptoms (Symptom Checklist: Frequency and Severity scale). Interestingly, this was despite no significant changes in treadmill exercise duration (10.4+4.3 min at baseline and 11.6+3.6 min at 12 months) or VO2 max (1467±681 ml O2 min baseline and 1629±739 ml O2 min at 12 months). The AIRCRAFT study randomized 99 patients with permanent AF and mild to moderate symptoms to AV junction ablation and permanent pacemaker implantation vs. pharmacologic rate control. Using a disease-specific instrument (CAST QOL) they demonstrated an 18% relative improvement in QOL, however no difference was observed with generic QOL instruments. To evaluate the effect of placebo Natale et al. divided patients into three treatment groups: Group 1 undergoing AV junction ablation and pacemaker implantation as well as discontinuation of rate-control medications, Group 2 undergoing AV node ablation and pacemaker implantation without discontinuation of rate-control medications, and Group 3 undergoing pacemaker implantation with continued rate-control medical therapy but without AV node ablation. At 6 months of follow-up they observed a significant improvement in HRQOL and activity scores in the groups undergoing AV junction ablation, an effect that was most marked in the group that concomitantly withdrew rate-limiting pharmacotherapy. Similar to previous, the improvement in HRQOL was independent of exercise duration and the maximal VO2 consumption, which did not change significantly. Moreover, the effects of AV junction ablation appear to be long-lasting. Tan et al demonstrated that AV junction ablation and permanent right ventricular pacing, after a mean follow-up of 4.3±3.3 years, resulted in comparable quality of life scores in seven of the eight scales of the SF-36 questionnaire when compared to age- and sex-matched healthy controls. While in agreement with previous studies of AV junction ablation this is in stark contrast to a pharmacologic approach of ventricular rate-control, which is...
unable to improve HRQOL of patients with permanent AF to the level of healthy controls. 26

Conclusions:
Atrial Fibrillation is associated with an adverse impact on HRQOL. Improvement in HRQOL, with a secondary reduction of disability and health-care resource utilization, is one of the major therapeutic goals in the management of AF. Successful AF ablation is associated with significant long-term improvement in HRQOL irrespective of the type of AF, however those with lower baseline HRQOL derive a greater and more robust improvement in HRQOL after catheter ablation.

References:


Contact Force Assessment In Catheter Ablation Of Atrial Fibrillation

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Abstract
The efficacy of catheter ablation of atrial fibrillation (AF) remains limited. Increase of success would require more durable lesions without increased risk steam pop and cardiac perforation. Recently, novel technologies have been developed to estimate real-time catheter-tissue contact force (CF). This paper reviews three available tools for assessment of CF and data on experimental or clinical experience. Experimental data with open-irrigated catheter showed that lesion size was greater with applications of lower power (like 30 W) and greater CF (e.g. 30 to 40 g) than with high power and low CF. Impedance drop in the first 5 seconds was significantly correlated to catheter CF. Perforation was achieved more rapidly with the ablation catheter in a sheath despite the same CF because the sheath prevents catheter buckling. Clinical experience confirmed poor relationship between CF and either unipolar amplitude, bipolar amplitude, or impedance. Within the left atrium, the most common high CF site was found at the anterior/rightward LA roof, directly beneath the ascending aorta. Importantly, several studies showed that the use of CF leads to shorter procedure with less fluoroscopy time and less RF applications. CF assessment was also found to be associated with higher proportion of durable lesions. Finally, pilot studies showed that CF measurement could be associated with better clinical efficacy AF ablation.

Introduction
During the last decade, pulmonary vein isolation (PVI) has been accepted as a method of choice for management of atrial fibrillation (AF) resistant to antiarrhythmic drug therapy.1,2 In addition, this technique could be offered in selected cases as the first line therapy of AF.3 According to recent European registry, the vast majority of PVI procedures are performed using radiofrequency current.4 However, long-term clinical efficacy is limited and arrhythmia recurrences are frequent (from 20% to 55%).5,6 Although the mechanisms of recurrences are not fully understood, most patients have documented conduction gaps within the previous isolation line.

The problem of current technologies for RF ablation is that we are balancing between lower efficacy and risk of complications. To be effective, catheter electrode should be in a good contact with the tissue. Low electrode contact with the tissue is likely to increase probability of being ineffective. High electrode contact may increase substantially risk of steam pop and cardiac perforation. Recently, several technologies have been developed to estimate real-time catheter-tissue contact force (CF). This paper reviews current experience with the use of CF assessment in catheter ablation of AF.

Technology
Currently, three novel technologies are available to assess real-time catheter-tissue CF. The first one, called Intellisense, is implemented in electromechanic robotic system Sensei (Hansen Medical, inc., Mountain View, CA).7 In principle, it uses indirect assessment of catheter tip-tissue contact while measuring friction in the proximal part of catheter shaft. Small dithering movement of the catheter inside the robotic sheath Artisan is induced and the amount of friction is then proportional to the level of catheter contact with the tissue. Small dithering movement of the catheter inside the robotic sheath Artisan is induced and the amount of friction is then proportional to the level of catheter contact with the tissue.

The second type of catheter uses a small spring connecting the ablation tip electrode to the catheter shaft with a magnetic transmitter and sensors to measure small deflections of the spring (Thermocool SmartTouch; Biosense Webster, Inc) (Figure 2).8,9 Both latter systems have CF resolution <1 g in bench testing.

Key Words:
Catheter Ablation, Atrial Fibrillation, Contact Force, Pulmonary Vein Isolation.
Correlation of the Intellisense system with direct CF measurement has been studies less extensively. In our pilot study, we compared Intellisense with TactiCath catheter in 3 patients undergoing AF ablation guided by robotic system. Importantly, the TactiCath was fully compatible with Artisan robotic sheath and performed similar as to manual operation. Direct comparison between both CF systems was performed showing a mean difference of 10±8 g (Table 1, unpublished data).

Group from Charlottesville did similar comparison using in vitro model of the left atrium. After a total of 151 min of robotic manipulation, 33 episodes of excessive CF were detected with mean CF of 153 g. While all episodes of excessive CF on the posterior wall were detected by both techniques; only 10/15 of excessive CF on the roof were detected by Intellisense. Overall CF and lateral CF measured by TactiCath correlated poorly with CF measured by Intellisense (Spearman’s correlation coefficient: 0.36, -0.44, respectively). These studies suggest that for accurate assessment of CF in electromechanic robotic system, direct sensor catheter could be preferable.

**Experimental Studies**

Several experimental studies suggested that electrode-tissue CF is a major determinant of lesion size. Novel CF catheter allowed for the first time to determine the relationship between CF and tissue temperatures, lesion size, steam pop, and thrombus during RF ablation using a canine thigh muscle preparation. RF was applied at 20 or 30 W for 60 seconds in low (0.1 m/s) or high (0.5 m/s) pulsatile blood flow. Temperatures were measured in the electrode, electrode-tissue interface, and within the tissue at 3- and 7-mm depths. With closed loop catheter, interface temperature and thrombus incidence were greater at 30 W and low blood flow. With open irrigation, interface temperature remained low (less than 71°C) with no difference between 20 and 30 W or between low and high blood flow. Steam pop occurred at 20 W in 4 of 35 closed loop and 0 of 30 open irrigation and at 30 W in 15 of 28 closed loop and 4 of 28 open irrigation applications (P<0.05). In another study with similar experimental setup, RF was delivered at 30 or 50 W (irrigation 17 or 30 mL/min), using different CF values from 2-40 g. Tissue temperature (3 and 7 mm depths), lesion size, thrombus, and steam pop increased significantly with increasing CF at each RF power. Lesion size was greater with applications of lower power (30 W) and greater CF (30 to 40 g) than at high power (50 W) with lower CF (2 to 10 g).

Further experience with direct CF assessment described the area under the CF curve and expressed as the force time integral (FTI). Measured FTI was highest in constant contact, intermediate during variable contact and lowest during intermittent level of catheter contact. Importantly, FTI correlated linearly with lesion volume (P < 0.0001 for 20 and 40 W). Constant contact produced the largest and intermittent contact the smallest lesions despite constant RF power and identical peak contact forces. The other study with ex vivo model of freshly excised hearts from pigs showed that the impedance drop in the first 5 seconds was significantly correlated to catheter CF. Of a total 101 ablations, no thrombus formation was noted but popping was seen in 17 lesions.

Another important experimental evidence was obtained by Shah et al who studied right atrial free wall lesions in pigs. The intact heart was removed and the CF sensor-equipped catheter was used to mechanically perforate (without RF delivery) the free walls of both atria and ventricles. Perforation was also performed through epicardially visible RA lesions and adjacent unablated tissue.
Importantly, perforation force through transmural RA lesions was lower than through unblated RA tissue (172.4±79.1 vs. 300.6±116.8 g, P=0.0002). Perforation was achieved more rapidly with the ablation catheter in a sheath despite the same CF because the sheath prevents catheter buckling.

**Clinical Experience**

The first clinical experience with indirect CF measurement was assessed in non-randomized comparison of conventional and robotically assisted AF ablation. A robotic catheter control system was used for remote navigation-supported PVI in 22 patients (mean age = 55 +/- 9 years, 16 males, study group). An irrigated-tip catheter with estimate of CF on the tissue was used. This was compared in nonrandomized fashion with conventional hand-controlled catheter ablation in 16 patients (mean age = 55 +/- 9 years, 13 males, control group). The procedures were performed under guidance of Ensite NavX navigation system (St. Jude Medical, St. Paul, MN, USA) and intracardiac echocardiography. Robotic navigation with CF measurement was associated with significantly shorter overall duration of radiofrequency delivery (1,641 +/- 609 vs 2,188 +/- 865 seconds, P < 0.01), shorter total procedural time (207 +/- 29 vs 250 +/- 62 minutes, P = 0.007), fluoroscopy exposure (15 +/- 5 vs 27 +/- 9 minutes, P < 0.001), and lower radiation dose (1,119 +/- 596 vs 3,048 +/- 2,029 uGy•m2, P < 0.001). No complication was observed in either the study or the control group.

In another study from our lab, 100 patients with paroxysmal AF (29 women, age 56.5 ± 10 years) were ablated using electromechanical robotic system and Intellisense CF assessment. CF assessment allowed safe catheter manipulation and resulted in low fluoroscopic time (mean 11.9 ± 7.8 minutes). There were no major procedure-related complications. After a median follow-up of 15 months (range 3-28 months), 63% of the patients were free from any atrial arrhythmias ≥ 30 seconds after the single procedure. Success rate increased to 86% after 1.2 procedures.

Several clinical studies used Endosense catheter Tacticath with direct CF assessment. The first multicenter study, the Tocatta clinical trial, showed a significant inter-investigator variability (P < .0001) in CF values with mean CF values during mapping ranging from 8 ± 8 to 60 ± 35 g and from 12 ± 10 to 39 ± 29 g in the supraventricular tachycardia group and the AF group, respectively. Interestingly, high transient CFs (>100 g) were noted in 27 patients (79%) of the AF group with one device-related complication (tamponade, 3%). Subsequent analysis of Tocatta trial data revealed that besides average CF above 20 g, the number of RF applications with low CF (<10 g) was a predictor of clinical outcome at 12 months in patients with paroxysmal AF. Low CF applications appeared to be related to incomplete, non-transmural lesions resulting in gaps and long-term treatment failure. Finally, the study showed correlation between FTI and patient outcome at 12 months.

EFFICAS I was the subsequent study with the objective to correlate occurrence of PVI conduction gaps with CF parameters used during ablation while the operator was blinded to information on CF. The study population comprised 46 patients with paroxysmal AF. At follow-up, remapping of the pulmonary veins was performed to assess gap location and correlate with the index procedure ablation parameters. Altogether, 26/40 of patients presented with ≥1 gaps. Analysis of procedural parameters revealed that RF applications with minimum Force-Time Integral (FTI) <400 gs were associated with increased likelihood for reconnection (P<0.001). Gap occurrence showed a strong trend with lower average CF and average FTI.

The above CF guidelines were prospectively applied in EFFICAS II to evaluate effective reduction of PVI gap rates. Application of CF guidelines resulted in less variability in both CF and FTI in EFFICAS II compared to EFFICAS I. Continuity of each PV lesion was quantified using a “jump index” that calculates how often the catheter moved to different segments of circumferential ablation line. Each jump to a non/adjacent site increases the value of jump index. There was significant reduction of PV lines with gaps during remapping study at 3 months from 29_ in EFFICAS I to 0 in EFFICAS II for PV lines with low jump index. For PV lines with high jump index, the gap rate was unchanged. This suggests that CF guidance is effective to ensure transmurality of lesions, however continuity is needed to minimize gap occurrence. The overall durability of PVI reached 72 % in EFFICAS I as compared to 85 % in EFFICAS II.

The first human experience with the Smart Touch catheter was obtained in our lab in Prague. A high-density map of the left atrium and pulmonary veins (median 328 sites) was obtained in 18 patients undergoing AF ablation. Average CF was displayed on the 3D map. For 5682 mapped sites, CF ranged 1-144 g (median 8.2 g). High CF (>35 g) was observed at only 118/5682 (2%) sites, clustering in 6 LA regions. The most common high CF site (48/113 sites in 17/18 patients) was located at the anterior/rightward LA roof, directly beneath the ascending aorta (confirmed by merging the CT image and map). Poor relationship between CF and either unipolar amplitude, bipolar amplitude, or impedance was observed. During ablation, RF power was modulated based on CF. In this pilot trial of RF adaptation according to CF, all pulmonary veins were isolated without steam pop, impedance rise, or pericardial effusion.

The first multicenter prospective study using Smart Touch CF catheter evaluated the effect of direct CF measurement on acute procedural parameters during catheter ablation of AF. All the patients underwent the first ablation procedure for paroxysmal AF with antral PVI, aiming at entry and exit conduction block in all PVS.

Ninety-five patients were enrolled in nine centers. Overall procedure time, fluoroscopy time, and ablation time were 138.0 ± 67.0, 14.3 ± 11.2, and 33.8 ± 19.4 min, respectively. The mean CF value during ablation was 12.2 ± 3.9 g. Force time integral (FTI) analysis showed that patients achieving a value below the median of 543.0gs required longer procedural (158.0 ± 74.0 vs. 117.0 ± 52.0 min, P = 0.004) and fluoroscopy (17.5 ± 13.0 vs. 11.0 ± 7.7 min, P = 0.007) times as compared with those in whom FTI was above this value. Patients in whom the mean CF during ablation was >20 g required shorter procedural time (92.0 ± 23.0 vs. 160.0 ± 67.0 min, P = 0.01) as compared with patients in whom this value was <10 g.

The first prospective comparison of Smart Touch catheter with a non-CF open-irrigated catheter (EZ Steer Thermocool, Biosense Webster) (control group) was published more recently. Overall, 30 patients were enrolled in each group, with a standardized 12-month follow-up, free of antiarrhythmic therapy. Demographic, cardiovascular and anatomic characteristics were similar in both groups. Though complete PVI was eventually achieved in all cases in both groups, success using an exclusive anatomic approach was 80.0% in CF group versus 36.7% in control group (P < 0.0001). CF use was associated with significant reductions in fluoroscopy exposure (P < 0.01) and RF time (P = 0.01). The incidence rates of AF recurrence...
were 10.5% (95% CI, 1.38-22.4) in the CF group, and 35.9% (95% CI, 12.4-59.4) in the control group (log rank test, \( P = 0.04 \)). After adjustment on potential confounders, the use of CF catheter was found to be associated with a lower AF recurrence (OR 0.18, 95% CI 0.04-0.94, \( P = 0.04 \)).

**Conclusions:**

Current technologies of CF assessment have allowed improvement of our knowledge regarding RF lesion creation. Lesion size was greater with applications of lower power and greater CF than vice versa. CF appears to be more important than impedance or temperature. In terms of safety, perforation force through transmural atrial wall lesions was approximately half of the CF needed for perforation of unablated tissue. The use of CF in clinical practice leads to lower variability of contact with the tissue. Clinical experience with CF assessment suggests that the use of CF results in faster procedure, shorter fluoroscopic time and less RF energy needed to perform PVI. The use of CF guiding appears to be associated with higher success rate of catheter ablation for AF. However, more robust data are needed.

**References:**

Stroke And Bleeding Risk Assessment: Where Are We Now?

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Abstract

Atrial fibrillation (AF) is one of major problems of the contemporary cardiology. Ischaemic stroke is a common complication of the AF, and effective prophylaxis requires treatment with oral anticoagulants. The purpose of this current review article is to provide an overview of the various stroke and bleeding risk assessment scores that help decision making with respect to thromboprophylaxis.

Particular focus is made on the currently guideline-recommended stroke and bleeding risk scores, such as CHA2DS2-VASc (congestive heart failure or left ventricular dysfunction, hypertension, age ≥75, diabetes, stroke, vascular disease, age 65–74 and sex category [female]) and HAS-BLED (uncontrolled hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio, elderly [e.g. age >65, frail condition], drugs [e.g. aspirin, nonsteroidal anti-inflammatory drugs]/excessive alcohol) is made. Future directions for improvement of predictive ability of risk assessment with clinical factors and biomarkers are also discussed.

Introduction

Atrial fibrillation (AF) is one of commonest cardiovascular conditions we deal with. The prevalence of AF is approximately 1-2% in the general population.1 In a recent study population-bases study, the prevalence of AF was 3.2% in subjects age ≥20 years old.2 Ischaemic stroke is one of the major complications of AF, which has a high mortality and disability when strokes occur in association with AF.3

Effective thromboprophylaxis requires treatment with oral anticoagulants. Currently, two options, either the vitamin K antagonists (VKAs, eg. warfarin), or the non-VKA (previously referred to as novel or new) oral anticoagulants such as the oral direct thrombin inhibitor (dabigatran) or the oral factor Xa blockers [rivaroxaban, apixaban, edoxaban]).4 Whilst effective in reducing stroke and all cause mortality, oral anticoagulants result in an elevated risk of bleeding that can sometimes be life-threatening.5 Intracranial bleeding is the most devastating example of major bleeding events, but is up to 9 times less common than ischaemic strokes.2 Thus, the net clinical benefit of oral anticoagulation (balancing ischaemic stroke versus major bleeding) was generally positive in AF with one or more stroke risk factors.6,7

The purpose of the current review article is to provide an overview of the various stroke and bleeding risk assessment tools. These are validated instruments which provide help in making decisions with respect to antithrombotic prophylaxis. Particular focus will be on the currently recommended risk scores as CHA2DS2-VASc (congestive heart failure or left ventricular dysfunction, hypertension, age ≥75, diabetes, stroke/transient ischaemic attack [TIA], vascular disease, age 65–74 and sex category [female]), and HAS-BLED (uncontrolled hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile INR, elderly [e.g. age >65, frail condition], drugs [e.g., antiplatelet, nonsteroidal anti-inflammatory drugs]/excessive alcohol). Future directions for improvement of predictive ability of risk assessment with clinical factors and biomarkers are also discussed.

Stroke Risk Assessment In Atrial Fibrillation

There are various published stroke risk stratification schemes, amongst which the CHADS2 score (congestive heart failure, hypertension, age ≥75, diabetes mellitus, stroke/TIA) and the CHA2DS2-VASc scores are most commonly used, having been validated and compared in numerous clinical trial populations and ‘real world’ cohorts.8,9

Previous stroke risk scores from older guidelines10-12 as well as the Framingham score,13 and ‘classical’ CHADS2 score14 have all focused on stroke risk assessment by (artificially) categorizing patients into three risk categories: low, moderate and high. This was explained from the practical point of view, because thromboprophylaxis was
down to an inconvenient drug, warfarin – and if not, aspirin. Thus, old guidelines had focused on the identification of ‘high risk’ patients who could be targeted for warfarin.

First, such artificial categorization leads to more crude estimation and overall reduced discriminative ability of the risk stratification tools, that is, potential misclassification of patient’s stroke risk and following inappropriate treatment.\textsuperscript{15-17} Second, risk assessment schemes are strongly dependent on the cohorts, from which they were derived and validated. These cohorts, particularly those from older clinical trials and epidemiological studies, can be extensively variable in terms of documentation of stroke risk factors and differences in definitions of stroke risk factors between cohorts. For example, ‘hypertension’ may stand for ‘history of hypertension’ [irrespective of stage or clinical course] or ‘uncontrolled hypertension’ [systolic blood pressure >160 mmHg].\textsuperscript{8,9} Third, freedom to choose between drugs for antithrombotic prophylaxis is likely to be cause of undertreatment of patients with AF. Indeed, aspirin was erroneously perceived to be safer with lower rates of bleeding, and sufficiently effective to prevent thromboembolic events; also, aspirin more convenient as it did not require regular monitoring of the quality of anticoagulation.\textsuperscript{18,19}

In the EuroHeart survey, patients with AF were often prescribed oral anticoagulation irrespectively of stroke risk both in low (up to half of patients) and high risk strata, thus underscoring their low directive impact on the decision-making when prescribing oral anticoagulants.\textsuperscript{20} Anticoagulation was also more commonly used in such circumstances as the first episode of AF, absence of significant comorbidity, and the availability of facilities for regular INR control. On the contrary, well known components of the CHADS\textsubscript{2} score (history of stroke/TIA, hypertension, age >75 years) were associated with the administration of aspirin.\textsuperscript{20} Moreover, separate risk categories overlapped when different risk stratification schemes were applied.\textsuperscript{20} Indeed, the relative complexity of the compared risk assessment tools (apart from the CHADS\textsubscript{2} and inconsistence between guidelines were acknowledged as one of the reason for such ‘unexpected’ results.\textsuperscript{20}

We now recognize that aspirin was is neither effective nor safe for stroke prevention. In the meta-analysis of antithrombotic therapy in patients with non-valvular A, warfarin was superior to antiplatelet therapy (39% relative risk reduction, 95% confidence interval [CI] 22-52%) and aspirin monotherapy did not significantly reduce the incidence of stroke.\textsuperscript{21} Furthermore, this aspirin was ineffective with increasing age.\textsuperscript{22}

In the ‘real world’ Danish nationwide cohort study, significant reductions of stroke risk with warfarin in comparison with aspirin, as well as similarity of bleeding risk with warfarin and aspirin were confirmed.\textsuperscript{7} Also, the significant value of warfarin was seen in patients with one stroke risk factor eg. CHADS\textsubscript{2} score=1.\textsuperscript{23,24}

Clearly things may be improving, over the last decade, with about 80% of AF patients with ≥1 stroke risk factors now being prescribed oral anticoagulants, although the rate of administration of antiplatelet agents still remains high, particularly in patients with elevated bleeding risk.\textsuperscript{25}

Basically, various stroke risk stratification schemes are based on various permutations of stroke risk predictors in AF. These include such independent risk factors as stroke/TIA, increasing age, history of hypertension, and diabetes mellitus. The predictive role of the female gender, heart failure, and vascular disease are supported by more recently available data.\textsuperscript{26,27}

The CHADS\textsubscript{2} Score

The CHADS\textsubscript{2} score is one of the simplest risk stratification schemes, and was derived by the combination of 2 stroke risk classification schemes from non-anticoagulated arms of AF Investigators (AFI) and Stroke Prevention and Atrial fibrillation (SPAF) datasets, including: prior cerebral ischemia, history of hypertension, diabetes mellitus, congestive heart failure and age ≥75 years.\textsuperscript{14} Two points were assigned to a history of prior cerebral ischemia and 1 point was assigned for the presence of other risk factors.\textsuperscript{14} One validation of CHADS\textsubscript{2} score was performed on an independent sample of National Registry of Atrial Fibrillation, participants and was highly correlated with the stroke rate: 1.9 (95% CI 1.2–3.0) for a score of 0; 2.8 (95% CI 2.0–3.8) for 1; 4.0 (95% CI 3.1–5.1) for 2; 5.9 (95% CI 4.6–7.3) for 3; 8.5 (95% CI 6.3–11.1) for 4; 12.5 (95% CI 8.2–17.5) for 5; and 18.2 (95% CI 10.5–27.4) for 6.\textsuperscript{14}

The CHADS\textsubscript{2} score was further tested in 2580 participants with nonvalvular AF taking aspirin from several randomized trials (Atrial fibrillation, Aspirin, Anticoagulation I Study [AFASAK-1], AFASAK-2, European Atrial Fibrillation Trial, Primary Prevention of Arterial Thromboembolism in patients with nonrheumatic AF in primary care study and SPAF III) in comparison with the AFI, SPAF, ACCP and Framingham stratification criteria.\textsuperscript{28,29} In this study, the CHADS\textsubscript{2} scheme identified successfully and better than other stratification schemes primary prevention patients who were at high-risk of stroke as well as low risk patients were identified equally by all schemes.\textsuperscript{28} However, in the ATRIA (Anticoagulation and Risk Factors In Atrial Fibrillation) cohort of 13559 adults with AF and 685 validated thromboembolic events during median follow-up of 6.0 years the CHADS\textsubscript{2} score was not superior to other stratification schemes (AFI, SPAF, Framingham, 7th ACCP) in prediction of stroke or other thromboembolic events, which all had c-statistics ranging from 0.56 to 0.62.\textsuperscript{29}

There was a concern as for appropriateness of stratification with the CHADS\textsubscript{2} scheme, particularly in its ‘classical’ interpretation. As many as >60% AF patients could be categorized into the ‘moderate or intermediate risk’ stratum with the CHADS\textsubscript{2} scheme, where guidelines recommended ‘warfarin or aspirin’ which made decision-making difficult.\textsuperscript{29} The most obvious example is a history of stroke or TIA in the absence of other CHADS\textsubscript{2} risk factor, where the CHADS\textsubscript{2}

<p>| Table 1: Stroke and bleeding risk stratification with the CHA\textsubscript{DS}\textsubscript{2}-VAS\textsubscript{c} and HAS-BLED\textsuperscript{26} scores |
|----------------------------------|-------------------|-------------------|</p>
<table>
<thead>
<tr>
<th>CHA\textsubscript{DS}\textsubscript{2}-VAS\textsubscript{c}</th>
<th>HAS-BLED</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congestive heart failure/LV dysfunction</td>
<td>1</td>
<td>Hypertension (systolic blood pressure &gt;160 mmHg)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1</td>
<td>Abnormal renal or liver function</td>
</tr>
<tr>
<td>Age ≥75 years</td>
<td>2</td>
<td>Stroke</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1</td>
<td>Bleeding tendency or predisposition</td>
</tr>
<tr>
<td>Stroke/TIA/TE</td>
<td>2</td>
<td>Labile INRs (if on warfarin)</td>
</tr>
<tr>
<td>Vascular disease (prior MI, PAD, or aortic plaque)</td>
<td>1</td>
<td>Age (e.g. &gt;65, frail condition)</td>
</tr>
<tr>
<td>Aged 65–74 years</td>
<td>1</td>
<td>Drugs (e.g., concomitant antiplatelet or NSAIDs) or alcohol excess/abuse</td>
</tr>
<tr>
<td>Sex category (i.e. female gender)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Maximum score</td>
<td>9</td>
<td>9</td>
</tr>
</tbody>
</table>

INR, international normalized ratio; LV, left ventricular; MI, myocardial infarction; NSAIDs, non-steroidal anti-inflammatory drugs; TIA/TE, transient ischemic attack/thromboembolism; PAD, peripheral artery disease
score will be equal to 2, which will define patient’s risk as ‘moderate’ although systematic reviews of stroke risk factors all consider history of prior cerebral ischaemia as the most powerful predictor of stroke recurrence (relative risk 2.5, 95% CI 1.8 to 3.5). More recently, the low/moderate/high risk strata using the CHAD2 score was defined in the following way: CHAD2<0 – low risk, CHAD2=1 – moderate risk, CHAD2≥2 – high risk.30 Recommendations on initiation of anticoagulation therapy in several guidelines were revised correspondingly with the CHAD2≥1 as indication for oral anticoagulants.31,32

Nonetheless, the low risk stratum according to the CHAD2 score still appears to have an adjusted stroke rate of 1.9 (95% CI 1.2-3.0) per 100 patient-years. In the Danish nationwide cohort study (total number of participants 47576), there were 19444 patients at low stroke risk using the CHAD2 score (score=0). They developed 275 strokes during 1-year follow-up, with a stroke rate was 1.59 (1.41-1.79).33 If these patients were stratified by the CHA2-Ds2-VASc score (see later), the stroke rate ranged from 0.84 (95% CI 0.65-1.08) if CHA2-Ds2-VASc=0 versus 3.2 (95% CI 1.60-6.40) if CHA2-Ds2-VASc=3.33. In the United Kingdom General Practice Research Database, which included 79844 patients with AF during approximately 4 years follow-up, the average annual incidence rate in the CHADS2=0 was lower (1.0 per 100 person-years), but still more than 2-times higher when compared with the CHA2-Ds2-VASc=0.34

The CHA2-Ds2-VASc Score

The CHA2-Ds2-VASc score was developed to refine stroke risk stratification of patients with particular emphasis on identifying those in the low risk category.30-33,38,41 CHA2-Ds2-VASc score consists of ‘major’ risk factors (prior stroke or TIA, or thromboembolism, and older age ≥75 years) and ‘clinically relevant non-major’ risk factors (heart failure [moderate to severe left ventricular systolic dysfunction, defined as left ventricular ejection fraction ≤40% or recent decompensated heart failure requiring hospitalization], hypertension, diabetes, female sex, age 65–74 years, and vascular disease (specifically, myocardial infarction, complex aortic plaque and peripheral artery disease).

Improvement of stratification has been achieved in part by adding ‘non-CHADS2’ factors to the CHA2-Ds2-VASc score. CHADS2 score has been frequently criticized because of not including these important stroke risk factors.36,37

Support for the ‘new’ risk factors was derived from the Swedish Atrial Fibrillation cohort study, which included 182 678 patients with AF and followed-up for about 1.4 years.38 The risk of stroke in this study was found to be increased from age ≥65 years, with even greater risk at age 75 years or older: hazard ratio (HR) 2.97 (95% CI 2.54-3.48) and HR 5.28 (95% CI 4.57-6.09), respectively, when compared with the ‘reference’ age <65 years.38 Consistent results were reported from the Taiwanese nationwide cohort study: odds ratios (OR) of 1.34 (95% CI 1.06-1.69) and 1.65 (95% CI 1.31-2.08) were seen for age 65-74 and ≥75 years categories, respectively.39 The stroke/thromboembolic event rate per 100 person-years in the Loire Valley Atrial Fibrillation Project was 0.23 (95% CI, 0.08-0.72) in patients <65 years old, 2.05 (95% CI 1.07-3.93) in those aged 65-74 years, and 3.99 (95% CI, 2.63-6.06) if ≥75 years.40

Female gender is a moderate risk factor for stroke in AF overall, but there is an age dependency. For example, HRs were 1.17 (95% CI 1.11-1.22) in the Swedish Atrial Fibrillation cohort study38;1.14 (95% CI 1.07-1.22) in the population-based cohort study of older patients with recently diagnosed AF in the Quebec, Canada;41 and 1.20 (95% CI 1.12-1.28) in the Danish nationwide cohort study.42 The age-dependency of the female gender as a stroke risk factor was underscored throughout all studies, i.e., females with AF younger than 65 years were at low stroke risk and no antithrombotic prophylaxis was required.40-41

Finally, vascular disease was found to be an independent risk factor for stroke in AF (HR 1.14, 95% CI 1.06-1.23) in the Swedish Atrial Fibrillation cohort study, significantly improving the predictive ability of CHADS2. Vascular disease remained significant even while peripheral artery disease (HR 1.22, 95% CI 1.12-1.32), myocardial infarction (HR 1.09, 95% CI 1.03-1.15), prior coronary artery bypass graft (HR 1.19, 95% CI 1.06-1.33) were considered separately.38 Predictive value of vascular disease was confirmed in other cohorts.39,40,44

Some confusion in the description of some risk factors, specifically heart failure and arterial hypertension, has been raised. As heart failure is often defined as ‘history of heart failure’ irrespectively of functional class, left ventricular function, need for hospitalization was found to be an independent risk factor for stroke both based on systematic literature reviews and analysis of contemporary data.26,38 In the CHA2-Ds2-VASc score, heart failure is used as ‘left ventricular moderate to severe systolic dysfunction or recent heart failure exacerbation that requires hospitalization’ (whether it is a heart failure with reduced or preserved ejection fraction).4 Questions still remain about impact of the heart failure with the preserved ejection fraction on stroke development in AF. Indeed, this type of heart failure includes about half of heart failure patients and AF is particularly prevalent amongst them.45 In the Loire Valley Atrial Fibrillation Project, there were no differences in rates of stroke and/or thromboembolism between patients with heart failure with preserved and those with heart failure and reduced ejection fraction.46 Another study showed 3.3-fold higher rates (20.6% vs. 6.7%) of ischemic stroke and 5.5-fold of deaths (27.2% vs. 2.0%) in patients with AF and heart failure with preserved ejection fraction compared to those with AF without heart failure at 3 years of follow-up.47

Hypertension in the CHA2-Ds2-VASc score is defined as a history of hypertension, assuming that prolonged history of hypertension, 10 years or longer may increase the risk of stroke.48 Clearly, uncontrolled blood pressure also increases stroke risk in AF.

The CHA2-Ds2-VASc score was found to be superior to other stratification schemes in selection of the ‘truly low-risk’ in several cohorts. Apart from Danish nationwide cohort and United Kingdom General Practice Research Databases, the CHA2-Ds2-VASc score did the best in the Belgrade Atrial Fibrillation study which targeted ‘lone’ AF patients as it was the only stratification scheme, in accordance to which low risk (i.e. CHA2-Ds2-VASc score=0) was associated with the absence of stroke (OR 5.1, 95% CI 1.5-16.8).48

This was consistent with a small study by Abu-Assi et al.49

Bleeding Risk Assessment In Atrial Fibrillation

Whilst prescribing oral anticoagulants for stroke prevention in AF patients, clinicians have to balance stroke prevention against the risk of bleeding, particularly major bleedings. Major bleeding is different from nonmajor by the following criteria: fatal bleeding, and/or symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intracranial, retroperitoneal, intra-articular or pericardial,
or intramuscular with compartment syndrome, and/or bleeding causing a fall in hemoglobin level of 20 g/L or more, or leading to transfusion of two or more units of whole blood or red cells.58

The reported rate of intracranial haemorrhage, which is the most devastating example of bleeding event, has increased markedly with spreading use of anticoagulants in older adults often with AF as the only indication.51 A recent meta-analysis of data on major bleeding in oral anticoagulation found an overall incidence of 2.1 (ranged 0.9–3.4) for the randomized clinical trials and 2.0 (ranged 0.2–7.6) per 100 patient-years for observational studies.52

In line with stroke risk in AF bleeding risk in anticoagulation also is not homogeneous. Different bleeding risk stratification schemes to evaluate it were developed, however only three of them were derived and validated in AF populations.53

The HEMORR2HAGES score (hepatic or renal disease, ethanol abuse, malignancy, older [aged ≥75 years], reduced platelet count or function, rebleeding risk, hypertension [uncontrolled], anaemia, genetic factors [CYP2C9 single nucleotide polymorphism], excessive fall risk, and stroke) was derived based on known bleeding risk factors from the National Registry of Atrial Fibrillation.44 Prediction of bleeding events was improved with the use of HEMORR2HAGES score, but its application to everyday clinical practice was limited because of necessity of genetic testing. In addition, genetic polymorphisms other than CYP2C9 gene, are also involved in warfarin metabolism have been shown, e.g., for example, VKORC1.55

The HAS-BLED score (hypertension, abnormal renal/liver function, previous stroke/TIA, bleeding history or predisposition, labile international normalized ratio, elderly [e.g. age ≥65, frailty, etc.], drugs/alcohol concomitantly)56 gained success as a very simple stratification scheme in comparison to the HEMORR2HAGES score performance, based on validations in various independent ‘real world’ cohorts.57,58 It was associated with improvement of bleeding risk classification when compared with variety of bleeding risk stratification schemes, including the new ATRIA score (see below) in the Loire Valley Atrial Fibrillation Project.58 Amongst major advantages of the HAS-BLED score its ability to predict intracranial haemorrhage, the high performance in both AF and non-AF populations, in patients taking warfarin or other anticoagulants, as well as for bridging therapy were highlighted.59,62

The ATRIA (anemia, severe renal disease [GFR<30 ml/min or dialysis-dependent], age≥75 years, previous bleed, hypertension) is the newest bleeding risk score proposed.63 The ATRIA bleeding score defines elderly patients as aged ≥75 years (versus ≥65 in the HAS-BLED score) and hypertension is defined ‘history of hypertension’ versus ‘uncontrolled hypertension’ in the HAS-BLED score.63 Thus, the predictive and discriminative ability ATRIA score was poorer when compared to HAS-BLED, including failure to predict intracranial haemorrhage.59,64

Current guidelines recommend to perform evaluation of bleeding risk in all patients with AF routinely but to focus on those with high bleeding risk (i.e. HAS-BLED score ≥3). This should be realized through regular follow-up and reduction of impact of potentially modifiable risk factors, e.g. achievement of blood pressure control, stable INR values, patients’ education to avoid alcohol intake and minimize use of aspirin or non-steroidal anti-inflammatory drugs. The benefits of anticoagulation clearly outweigh hazard of bleeding, furthermore, with higher bleeding risk even greater net clinical benefit might be expected.6,7 Indeed, anticoagulation therapy should not to be discontinued on the grounds of a high HAS-BLED score.4 It should be noted that the labile INR criterion in HAS-BLED is only considered only in case of vitamin K antagonist (e.g. warfarin) use. Stability of INR is very important, and only if patient spends more than 70% of time within therapeutic range (TTR), the best effectiveness and safety profiles can be expected; in contrast, low average TTR is associated with poor outcomes (stroke, bleeding mortality).65–68

Thus, efforts towards development of prediction tool for quality of INR control (as reflected by TTR) have been made. The SAme-TT2R2 score (female sex, age less than 50 years, medical history [2 of the following: hypertension, diabetes, coronary artery disease/myocardial infarction, peripheral artery disease, heart failure, previous stroke, pulmonary, hepatic or renal disease], treatment with interacting drugs [e.g. amiodarone], tobacco use (within 2 years), non-Caucasian race) was described from an analysis of the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) trial in order to aid decision-making between vitamin K antagonists and novel oral anticoagulants by identifying those AF patients who would do well on VKA (SAme-TT2R2 score 0–1), and those who less likely reach target TTR (SAme-TT2R2 score ≥2).69,70

### Integrated Stroke And Bleeding Risk Assessment

As many of the risk factors for stroke and bleeding in AF are overlapped is it possible to use one stratification scheme to get simultaneously individuals’ stroke and bleeding risk? This was tested in two ways. First, the predictive ability for major bleedings was assessed using the stroke risk stratification scores, that is, CHADS2, and CHA2DS2-VASc. For example, in the AMADEUS (evaluating the use of sr34006 compared to warfarin or acenocoumarol in patients with atrial fibrillation) trial incidence of bleeding was found to rise with increasing of either HAS-BLED, CHADS2 or CHA2DS2-VASc scores, but statistical significance was achieved only for the HAS-BLED score. Also, only HAS-BLED demonstrated significant discriminatory performance and net reclassification improvement when compared with the CHADS2, and CHA2DS2-VASc as well.71 Thus, stroke risk stratification schemes should not be applied for bleeding risk assessment instead of the HAS-BLED score.

Second, several composite scores for stroke and bleeding prediction have been developed.72–74 For example, evaluation of composite end point ‘stroke/thromboembolism or major bleeding’ was predicted by age, previous stroke/TIA, aspirin use, and time in therapeutic range. Predictors for another composite end point ‘stroke, systemic or venous embolism, myocardial infarction, cardiovascular death, or major bleeding’ were the same but included left ventricular dysfunction as well.72 Generally, regression models are likely to give more faithful conclusions on patient’s stroke or bleeding risk as they include appropriate regression coefficients which characterize the real impact of risk factors on the studied outcome instead of assumption of equal weight (1 or 2 points) for the range of stroke predictors. However, both models actually allowed comparative discriminative ability in comparison to the CHADS2-VASc and HAS-BLED scores, but did not outperform them.72 Thus, taking into account relative complexity of calculations with composite scores, the ‘traditional’ stroke and bleeding risk scores which are currently in use are more attractive in the aspect of usability, detailed assessment, individualized balancing of risks, and right decision making.
Further Directions To Improve Risk Scores: Are More 'Non-Traditional' Clinical Factors And Biomarkers The Answer?

Clearly, there are a lot of clinical risk factors for thromboembolism and bleeding, which were not included into the current risk stratification schemes but had potential to improve their performance.

For example, a history of both arterial (HR 1.39, 95% CI 1.08-1.79) and venous (HR 1.26, 95% CI 1.02-1.54) retinal occlusions was found to be associated with an increased risk of stroke/thromboembolism/TIA in patients with non-valvular AF. As cerebral and retinal circulation are adjacent, it was suggested that retinal vascular occlusion could be considered as a previous thromboembolic event when evaluating stroke risk.\(^3\) Despite that, AF in eye ischaemic events is much less prevalent than in cerebral ischaemia; indeed, the probability to diagnose AF in patient with stroke is about 3.6-fold higher than in patient with retinal artery occlusion. Hence, counterpoint view is that stroke and retinal thrombosis may represent pathophysiologically distinct patterns of vascular disease.\(^75\)

Obesity apart from being a risk factor for development of new-onset AF\(^76,77\) and stroke risk factor in the general population,\(^78\) does have an independent predictive role for stroke development in patients with AF.\(^79\) In the prospective Danish Diet, Cancer and Health study there was a 31% and 36% increase in risk of the composite end point of ‘ischaemic stroke, thromboembolism, or death’ in overweight and obese patients, respectively, even after adjustment for CHA\(_2\)DS\(_2\)-VASc score.\(^79\)

Data derived from the same cohort was indicative for relation of alcohol intake. Men with an intake of >27 drinks/week were more prone to develop thromboembolism or death (HR 1.33, 95% CI 1.08-1.63) compared to men with an intake of <14 drinks/week. Women with an intake of >20 drinks/week also had a higher risk (HR 1.23, 95% CI 0.78-1.96) than women in the low intake category (adjusted for oral anticoagulation and CHA\(_2\)DS\(_2\)-VASc scores).\(^80\) Heavy smoking, was found to be independently associated with a higher risk of thromboembolism or death as well (HR 3.64 [95% CI 1.88-7.07] for females, and HR 2.17 [95% CI 1.59-2.95] for males).\(^81\)

Ethnic differences are important for stroke prediction. Specifically, Asians represents large population with overall higher burden of AF than in Western countries.\(^82,83\) Despite stroke risk factors being common for both populations, oral anticoagulation is underused and decision-making does not correspond to individual risk, assessed via modern stratification schemes. Based on data from the China National Stroke Registry, only about 15% of moderate and high risk patients according to the CHADS\(_2\) score were taking warfarin.\(^84\) Moreover, stroke scores were derived and validated in predominantly Caucasians and, hence, may have lower prediction strength when applied to population in the Far Eastern countries. For example, in the nationwide database of patients with nonvalvular AF from Taiwan, CHADS\(_2\) and CHA\(_2\)DS\(_2\)-VASc scores had only modest predictive ability.\(^85\)

The role of ethnicity as well as some aforementioned risk factors (e.g., smoking, obesity) was advocated in a new QStroke score, that was proposed based on England and Wales general practice data. The QStroke score was validated for AF patients without a prior stroke only. Besides 9 categories that included self-assigned ethnicity and a wide range of other risk factors that included age, sex, smoking status, systolic blood pressure, ratio of total serum cholesterol to high density lipoprotein cholesterol concentrations, body mass index, family history of coronary heart disease in first degree relative under 60 years, Townsend deprivation score, treated hypertension, type 1 and type 2 diabetes, renal disease, rheumatoid arthritis, coronary heart disease, congestive heart failure, valvular heart disease, and AF. Incorporation of AF as a separate risk factor means that the QStroke score also can be used in non-AF patients. Unfortunately, the QStroke score did not outperform both the CHADS\(_2\) and the CHA\(_2\)DS\(_2\)-VASc score in patients without a prior stroke.\(^83\)

Also, future improvement of stroke risk stratification can be achieved by inclusion of biomarkers to complement clinical risk factors. Echocardiographic parameters (presence of spontaneous echocontrast, low left atrial appendage velocities, left atrial appendage thrombus, and complex aortic plaque on the descending aorta);\(^86,87\) blood biomarkers of prothrombotic or hypercoagulable state (von Willebrand factor, D-dimer);\(^88-91\) left-ventricular overload (brain natriuretic peptide, galectin-3);\(^92,93\) renal function (creatinine clearance, estimated glomerular filtration rate, proteinuria);\(^94-96\) detailed cerebral imaging with computer tomography or magnetic resonance imaging (presence of small-vessel disease);\(^3\) were shown to have prognostic implications in AF patients.

Of these, the impact of chronic kidney disease (CKD) in stroke stratification schemes is of particular importance as CKD is associated strongly with increased cardiovascular morbidity and mortality. The range of cardiovascular disorders associated with CKD is wide, with arterial stiffening causing heart failure, stroke, and arrhythmic sudden death and premature atherosclerosis causing vascular occlusive events.\(^97\) The prevalence of AF was recognized to be higher in CKD and prognosis is known to be negative regarding both thromboembolic and bleeding risk in comparison to general population.\(^97\) At the same time, there is relatively poor evidence for anticoagulation in the given cohort of patients as CKD was used as exclusion criterion in majority of studies (particularly if eGFR<30 ml/min/1.73 m\(^3\)).

The R\(_{2}\)CHADS\(_2\) score was derived from the ROCKET AF (Rivaroxaban Once-Daily, Oral, Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation) cohort. The score incorporated the components of the CHADS\(_2\) score and also awarded 2 points for creatinine clearance <60 ml/min.\(^98\) When validated in the ATRIA study, improvement of net reclassification index by 17.4% (95% CI 12.1-22.5) was seen, relative to CHADS\(_2\).\(^98\) However, some methodological issues were underscored and discussed that might limit spread of the R\(_{2}\)CHADS\(_2\) score in clinical practice.\(^99\)

Conclusions:

Numerous risk stratification schemes for stroke and bleeding prediction highlight the fact, that none is perfect and further research is needed to improve the individuals’ risk assessment. Given the global burden associated with AF and its complication such as stroke, new treatment options could have a major impact on reducing this healthcare burden associated with AF-related stroke, as recently shown for Europe and China.\(^100-102\) For now, the CHA\(_2\)DS\(_2\)-VASc and the HAS-BLED scores are currently superior to other prognostic tools in guiding anticoagulation in AF patients without losing simplicity and practicality for everyday use. With stroke risk, the focus now is the initial indenification of ‘low risk’ patients
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Featured Review


Featured Review

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Monitoring Atrial Fibrillation After Catheter Ablation

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Abstract
Although catheter ablation is an effective treatment for recurrent atrial fibrillation (AF), there is no consensus on the definition of success or follow-up strategies. Symptoms are the major motivation for undergoing catheter ablation in patients with AF, however it is well known that reliance on perception of AF by patients after AF ablation results in an underestimation of recurrence of the arrhythmia. Because symptoms of AF occurrence may be misleading, a reliable assessment of rhythm outcome is essential for the definition of success in both clinical care and research trials.

Continuous rhythm monitoring over long periods of time is superior to intermittent recording using external monitors to detect the presence of AF episodes and to quantify the AF burden. Today, new devices implanted subcutaneously using a minimally invasive technique have been developed for continuous AF monitoring. Implantable devices keep detailed information about arrhythmia recurrences and might allow identification of very brief episodes of AF, the significance of which is still uncertain. In particular, it is not known whether there is any critical value of daily AF burden that has a prognostic significance. This issue remains an area of active discussion, debate and investigation. Further investigation is required to determine if continuous AF monitoring with implantable devices is effective in reducing stroke risk and facilitating maintenance of sinus rhythm after AF ablation.

Introduction
Atrial fibrillation (AF) is one of the major common and chronic disorders seen in clinical practice and it is associated with a reduced quality of life and an increased long-term risk of stroke, heart failure and all cause mortality. A number of controlled, and randomized clinical trials have consistently shown that catheter ablation is superior to antiarrhythmic pharmacological treatment in maintaining sinus rhythm among patients with symptomatic drug-refractory AF. Remarkably there is no consensus on the definition of success or follow-up strategies after AF ablation. Even brief asymptomatic episodes can substantially raise the risk of stroke, therefore a reliable evaluation of AF recurrences is crucial after AF ablation and may be useful in making clinical decisions.

Irrespective of symptoms, assessment of rhythm can be conducted with the use of intermittent (noninvasive) or continuous (implanted devices) monitoring systems. Increased duration of monitoring appears to be associated with increased rates of detection of AF and, on the basis of different monitoring techniques, sensitivity in detecting AF recurrences after catheter ablation is reported to range between 31% and 71% and negative predictive value between 21% and 65%.

Non-Continuous AF Monitoring Systems
In addition to baseline ECG and symptom evaluation, several methods have been described to improve rhythm monitoring in AF patients. Intermittent monitoring includes periodical ECGs, Holter and event recorders with or without loop memory. The diagnostic accuracy of these methods is limited and it is well known that there is a clear relationship between the duration of monitoring and the diagnostic yield.

Follow-up evaluation after AF ablation has been traditionally performed by routine ECG recordings and ambulatory 24-hour Holter monitoring. Recently, new extended monitoring methods have been introduced, including trans-telephonic ECG transmissions, event recorders and external loop recorders. Systems without a loop memory allow intermittent rhythm monitoring and are useful to confirm recurrences in patients with symptoms suggestive...
of AF. External loop recorder systems are ideal for capturing also asymptomatic AF recurrences; the ECG recording is triggered either automatically, according to the arrhythmia detection algorithm, or manually by the patient; besides device data can be stored on a memory card or sent through a telephone/internet connection.

The main drawback of these systems is that they are tolerated only by highly motivated patients over a short period of time (usually few months). Thus, non-implantable recording systems play a limited role for a reliable and continuous monitoring of post-ablation recurrences. Furthermore, patients with infrequent AF recurrences are the most difficult to identify with intermittent monitoring and face a significant thromboembolic (TE) risk in the absence of appropriate oral anticoagulation (OAC) therapy.

Continuous AF Monitoring Systems

Continuous AF monitoring can only be achieved through the diagnostics of implantable device, which can store significant information regarding heart rhythm. The first experience with continuous AF monitoring is derived from the analysis of data stored in dual-chamber pacemakers and implantable cardioverter-defibrillators (ICD) capable of arrhythmia monitoring. If the atrial rate exceeds a programmable value for a given period of time, an atrial arrhythmia will be detected allowing the assessment of AF episodes irrespective of associated symptoms.

The use of cardiac pacemaker as an implanted arrhythmia monitor has been first evaluated in the MOST trial. In a population of 312 pacemaker patients, this study evaluated the correlation between the presence of atrial high rate events (AHRE) and clinical outcomes. The presence of AHRE longer than 5 min was found to be an independent predictor of total mortality and non-fatal stroke. Similarly, other large prospective multi-centric studies have examined the relationship between AF episodes detected by implanted devices and patient outcomes (Table 1).

Dual-chamber pacemakers and implantable cardioverter-defibrillators allow direct recording of atrial electrograms, but those devices are clearly not the ideal arrhythmia surveillance method, mainly because of the presence of intracardiac leads. To provide continuous information on cardiac rhythm, implantable leadless cardiac monitoring systems (ICM) with specific AF detection algorithms have been developed. Automatic triggers with physician-programmable parameters allow AF episodes detection as well as AF burden quantification and batteries can last up to 5 to 6 years affording the possibility of prolonged continuous monitoring. The ICM memory can store both automatically detected AF episodes and a number of patient-activated episodes, which can be easily transmitted via telephone or internet to remotely and continuously evaluate a patient for AF recurrences after AF ablation.

The XPECT study evaluated for the first time the performance of an implantable leadless cardiac monitor (Reveal XT; Medtronic Inc.) with dedicated AF detection capabilities. The study showed that the overall accuracy of the ICM for detecting AF was 98.5% and the ICM-measured AF burden was very well correlated (Pearson coefficient r = 0.97) with the reference value derived from Holter. Very recently, the CRYSTAL-AF study demonstrated that this system is more effective than standard non-invasive monitoring methods to find an AF episode in patients with cryptogenic stroke. This study included 441 patients randomized to Reveal-XT or standard cardiac monitoring within 90 days of a cryptogenic stroke. At 12 months, AF was detected in 12.4% of patients in the Reveal arm versus 2.0% of those in the control arm [HR 7.3 (95% CI 2.6-20.8, p<0.0001)].

Implantable leadless device monitoring systems might override the problems related to the patient compliance and several data on continuous monitoring after AF ablation have recently been published. Verma et al. in a large multicentric prospective study evaluated the incidence of asymptomatic AF episodes before and after CA, as assessed by an implantable cardiac monitor with AF detection. In this study, ICM detected 12% of patients with purely asymptomatic AF and the ratio of asymptomatic to symptomatic AF episodes increase from 1.1 before to 3.7 after catheter ablation. Consistent with the results of this study, we have recently demonstrated in 145 patients with paroxysmal or persistent AF, that continuous ECG monitoring is a valuable tool for long-term follow-up after AF catheter ablation facilitating reliable assessment of symptomatic and asymptomatic AF episodes. Furthermore, Bogachev-Prokophiev et al. confirmed the reliability of subcutaneous continuous monitoring also in patients who had undergone surgical AF ablation.

Is Procedural Success Truly Achieved Without Continuous AF Monitoring?

The definition of “long-term ablation success” remains controversial. Guidelines state that the primary indication of AF ablation is to reduce AF-related symptoms and to improve quality of life. Secondary endpoints might include elimination of symptomatic AF and control of AF with previously ineffective antiarrhythmic drugs (AAD). The poor correlation between symptoms and AF should caution physicians against making clinical decisions depending on symptoms. Asymptomatic AF has been reported to be up to 12 times more frequent than symptomatic AF, even in patients with histories of symptomatic AF. Although ablation significantly reduces the burden of AF, the proportion of asymptomatic AF episodes increases, consequently the procedural success is overestimated by patient

<table>
<thead>
<tr>
<th>Study, year</th>
<th>patients</th>
<th>Detection Methods</th>
<th>Follow-up</th>
<th>Endpoint</th>
<th>AT/AF burden cutoff</th>
<th>Hazard ratio and</th>
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<tbody>
<tr>
<td>MOST 2003</td>
<td>312</td>
<td>PM</td>
<td>27 months</td>
<td>Total mortality</td>
<td>&gt; 5 minutes</td>
<td>HR 2.48 P=0.0092</td>
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<td></td>
<td></td>
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<td></td>
<td>Death/non fatal stroke</td>
<td>&gt; 5 minutes</td>
<td>HR 2.79 P= 0.0011</td>
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<td>Capucci et al. 2006</td>
<td>725</td>
<td>PM</td>
<td>22 months</td>
<td>Arterial embolism</td>
<td>&gt; 24 hours</td>
<td>HR 3.1 p= 0.044</td>
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<td></td>
<td></td>
<td>&gt; 5 min</td>
<td>HR 0.98 p= 0.97</td>
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<tr>
<td>TRENDS 2009</td>
<td>2486</td>
<td>PM/ICD</td>
<td>1.4 years</td>
<td>Annualized TE rates</td>
<td>&lt; 5.5 hours</td>
<td>HR 2.20 p= 0.06</td>
</tr>
<tr>
<td>ASSERT 2012</td>
<td>2580</td>
<td>PM/ICD or alcohol excess/ abuse</td>
<td>2.5 years</td>
<td>Ischemic stroke/systemic embolism</td>
<td>&gt; 6 minutes</td>
<td>HR 5.56 P&lt;0.001</td>
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<td></td>
<td>10016</td>
<td>PM/ICD</td>
<td>24 months</td>
<td>Clinical atrial fibrillation</td>
<td>&gt; 6 minutes</td>
<td>HR 5.56 P&lt;0.001</td>
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Abbreviations: AT/AF= atrial tachycardia/fibrillation; HR= Hazard Ratio; ICD= internal cardioverter defibrillator; PM= pacemaker; TE= thromboembolic..
Silent AF is likely to be associated with morbidity and mortality rates not inferior to symptomatic AF;\textsuperscript{11,19,20} therefore, a reliable rhythm outcome analysis after AF ablation has the potential to reduce that risk. Post-procedure arrhythmia monitoring is also useful because in a significant number of patients, palpitations may be misinterpreted as AF episodes; in one study, 40% of pacemaker patients reported symptoms suggestive of AF that were not confirmed neither by standard ECG recording nor device interrogation.\textsuperscript{21}

Emerging evidence suggests that sinus rhythm restoration following AF ablation can provide clinical and prognostic benefits.\textsuperscript{32-38} Winkle et al\textsuperscript{39} have recently demonstrated that patients with prior stroke, who under successful AF ablation, have a low incidence of subsequent thromboembolic events, and most of those patients may be able to discontinue OAC. The consistency of these findings suggests that restoration of sinus rhythm by catheter ablation might result in lower rates of stroke and death. Of note, the Heart Rhythm Society’s consensus document on AF ablation recommends that success can be defined as freedom from AF or atrial tachycardia, lasting 30 seconds 12 months after AF ablation.\textsuperscript{40} Intermittent and symptoms-based monitoring is highly inaccurate for identifying patients with AF recurrences\textsuperscript{41,42} leaving untreated a vulnerable population. Thus, implantable devices are the most reliable method to precisely identify AF recurrences after AF ablation both in clinical care and in the setting of a clinical research study.

### Estimating AF Burden: The Importance Of Cutoff Length

The unexpectedly high incidence of ICM-detected non-sustained atrial arrhythmias raises the question of whether there is any clinical significance to these, often asymptomatic, AF episodes. Quantitative AT/AF burden detected by implanted devices may be a thromboembolic (TE) risk element independent of standard stroke risk factors and absence of symptoms can even increase the thromboembolic risk if objective information on AF status is lacking.

Current guidelines do not specifically address any anticoagulation use in case of non-sustained device-detected AF episodes. Generally, it has been demonstrated that patients with AHREs, compared to those without AHREs, are more likely to have adverse clinical outcomes, including a higher incidence of stroke, death and subsequent AF. The adverse effects of paroxysmal AF have been correlated to the amount of AF burden that conveys a substantial risk of stroke. Therefore, greater attention should be paid to device-detected AF episodes and treatment should be delivered accordingly. A comprehensive evaluation should combine AF burden and TE risk.\textsuperscript{18,20} Botto et al\textsuperscript{20} demonstrated that risk stratification for thromboembolic events in device-detected AF patients can be improved by combining CHADS\textsubscript{2} score with AF presence and duration.

### Continuous AF Monitoring: Impacting Patient Outcomes

Atrial fibrillation ablation has the potential to restore sinus rhythm, eliminating the need for AADs and potentially for long-term anticoagulation.\textsuperscript{27,46} Because AF symptoms may be misleading, appropriate rhythm monitoring surveillance after AF ablation may help to guide clinical decision making in certain subsets of patients. The present evidence suggests that a highly accurate follow-up, as provided by implantable devices, may add significant information to current clinical risk stratification schemes.\textsuperscript{32,47} The device-stored data can also be evaluated with remote monitoring systems, which can allow a prompt clinical reaction and may reduce hospitalizations and costs.

Optimal post-procedural anticoagulation strategy is essential for minimizing bleeding and thromboembolic risk after AF ablation. Hemorrhagic risk can be lowered by reducing unnecessary and prolonged OAC administration while the patient is in sinus rhythm. In patients with CHADS score ≤2, OAC are frequently discontinued after AF ablation if no recurrences have been documented during follow-up. In a large reported experience on 831 patients after AF ablation, warfarin was stopped within 12 months in 76.5% of patients with no arrhythmia recurrence.\textsuperscript{14} This approach is commonly performed despite the fact that patients are frequently followed-up with the use of limited temporal ECG monitoring duration. However, caution should be considered before OAC withdrawal because unrecognized recurrences might lead to devastating consequences, including death and thromboembolic stroke. If OAC are discontinued after AF ablation, the risk of asymptomatic AF recurrences cannot be ruled out without a continuous AF monitoring.
system.

The routine use of cardiac monitoring to identify AF patients who will benefit from anticoagulation has been reported to be cost-effective. Continuous AF monitoring with implanted devices increases sensitivity of AF detection when compared to conventional diagnostic methods and data transmission allows a remote and continuous evaluation for AF recurrences. Recently, the ANGELS of AF project demonstrated the possibility to improve OAC use as thrombo-prophylaxis through the use of information from ICD AF-diagnostics as compared with standard care.49

Early diagnosis triggers earlier treatment and in this regard novel OAC (dabigatran, rivaroxaban and apixaban), which might be early self-administered without dose titration, allows for rapid onset anticoagulation with a single oral dose early after an AF episode. Current evidence suggests that a prothrombotic state is evident within minutes after the onset of an AF episode.50-51 Since left atrial thrombi can develop early during AF episodes, an early AF detection afforded by ICM might increase the safety of discontinuing OAC after AF ablation. The ongoing IMPACT trial has been designed to test the hypothesis that initiation or withdrawal of oral anticoagulant therapy guided by continuous ambulatory monitoring of the atrial intracardiac electrograms improves clinical outcomes. This study has the potential to provide some answers to this important question but it has been stopped early and remains unpublished.

Beyond implementation of appropriate anticoagulation, an early intervention following device-detected AF episodes has other potential benefits in improving the management of patients after AF ablation. It is likely that the benefits of sinus rhythm are in part counterbalanced by the potential adverse effects of long-term AAD use.52 The detailed rhythm information obtained through continuous monitoring might allow an earlier AAD discontinuation reducing the potential side effects of medications.

Brief and predominantly asymptomatic AF episodes may remain undetected until the next scheduled evaluation delaying the appropriate management of AF recurrences. Early diagnosis, through continuous AF monitoring, triggers earlier treatment and might also facilitate the self-administration of a single oral dose of Ic drug (pill-in-the-pocket) shortly after the onset of the AF recurrence. The prolonged duration of AF negatively effects electrical and structural atrial remodelling, therefore early restoration of sinus rhythm might have potential benefits over the long-term follow-up.

Optimal Time And Duration Of AF Monitoring

Limited data are available on the optimal time and duration of monitoring after AF ablation. Continuous AF monitoring might be useful both in the short-term and over the long-term follow-up after AF ablation. Early recurrences of AF are quite common in the so-called blanking period and are often asymptomatic. However, appropriate surveillance during the early post-ablation period may identify patients who are at a higher risk of long term treatment failure since early recurrences strongly predict a lack of long-term success.

Pokushalov et al. demonstrated in 286 patients continuously monitored through an implantable device after AF ablation, that this strategy might be useful for deciding whether to perform a second ablation or to implement drug therapy. In this study patients were treated according to the onset mechanism of AF recurrences, as detected and stored by the implantable cardiac monitor. They observed that patients with recurrences after the first AF ablation are likely to respond to a second early ablation when AF is triggered by supraventricular arrhythmias or premature contractions.

Several clinical studies assessing the long-term efficacy of catheter ablation procedures have reported late AF recurrences in patients who were initially considered responders to catheter ablation. Therefore, longer-term monitoring might identify AF episodes in patients in whom the OAC had been previously suspended. Because of the recognition of the late AF recurrences, the HRS/EHRA/ECAS consensus document on AF ablation concluded that a decision regarding OAC discontinuation should be based on the CHADS stroke risk score rather than the apparent efficacy of the AF ablation procedure.

False Positive Device-Detected Events

Long-term AF monitoring by implanted devices may be of substantial clinical value. However, its practical application may, in part, be limited by the prevalence of false-positive events. The risk of false-positives detections mainly generated by myopotential and motion artefacts still exists, highlighting the importance of human revaluation of automatically detected episode. False-positive events might lead to unscheduled evaluations in patients with remote follow-up that significantly increase the physician work burden. Unscheduled patient evaluation after AF ablation procedures have reported late AF recurrences in patients in whom the OAC had been previously suspended. Therefore, longer-term monitoring might identify AF episodes in patients in whom the OAC had been previously suspended.

For AHREs lasting >6 hours, the rate of false positives is 3.3%, making physician review less crucial.

New sensing and detection algorithms for ICM have been developed in order to substantially reduce the occurrence of inappropriately detected AT/AF episodes. A higher specificity of the algorithm is necessary and would avoid unnecessary clinical evaluations once the alert system is activated. Future research will focus on optimal device programming that will offer maximal benefit, increasing the clinical utility of ICM algorithms.

Conclusions:

Because AF symptoms may be misleading, appropriate rhythm monitoring surveillance after AF ablation may help to guide clinical decision making in certain subsets of patients. The present evidence suggests that a highly accurate follow-up, as provided by implantable devices, may add significant information to current clinical risk stratification schemes.

Implantable devices keep detailed information about arrhythmia recurrences and might allow identification of very brief episodes of AF, the significance of which is still uncertain. In particular, it is not known whether there is a critical value of daily AF burden that has any prognostic significance. This issue remains an area of active discussion, debate and investigation. Further investigation is required to determine if continuous AF monitoring with implantable devices is effective in reducing stroke risk and facilitating maintenance of sinus rhythm after AF ablation.

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Abstract
The inability to achieve durable pulmonary vein isolation (PVI) remains a major limitation to catheter ablation for the treatment of atrial fibrillation (AF), potentially resulting in AF recurrence. In this review, we discuss the research performed investigating methods to improve lesion permanence for the goal of durable PVI. Investigations evaluating procedural techniques, various catheters utilized, adjunctive pharmacologic therapy, and novel energy sources designed to improve ablation lesion permanence are discussed.

Introduction
Catheter ablation to treat atrial fibrillation (AF) has evolved dramatically over the past decade. It is currently considered first line therapy in patients with paroxysmal AF refractory to anti-arrhythmic medication. A common target during AF ablation is the wide area around the pulmonary veins (PV), the so-called “antrum”. Although clinically successful AF ablation has been reported without pulmonary vein isolation (PVI), the Task Force recommends in the 2012 HRS/EHRA/ECAS Expert Consensus Statement on Catheter and Surgical Ablation of AF that “ablation strategies that target the PVs and/or PV antrum are the cornerstone for most AF ablation procedures and that complete electrical isolation of all PVs should be the goal”. Despite advancement in PVI techniques, recurrence rate of AF remains significant with recurrence rates at 1 year after a single radiofrequency (RF) ablation procedure for paroxysmal AF approximately around 20%–30% and even higher rates of recurrence for persistent AF. Some of those recurrences may be due to pulmonary vein reconnection. PV reconnection generally result from anatomical gaps in the ablation lines or from failure to create permanent transmural lesions. While acute PV isolation is obtained in the vast majority of patients, there is a significant rate of subsequent PV reconnection, up to 80% presumably due to the resolution of swelling and inflammation after ablation. In addition to PV trigger elimination, PVI also suppresses AF by eliminating the substrate located in the PV antrum area, as demonstrated by the better efficacy of antral PVI compared to ostial PVI. The objective of this review is to discuss the tools available to minimize antral PV reconnection.

Catheter Contact
The majority of AF recurrences (54%) originate from reconnection of previously isolated PVs, suggesting the importance of delivering durable ablation lesions in decreasing recurrence rate. Optimal catheter contact is a critical factor in ensuring durable PV lesions. Good catheter-tissue contact allows optimal energy coupling to tissue and less energy dissipation into the circulating blood pool. Furthermore, the resolution of the edema after the procedure may result in recovery of conduction in myocardial cells that had temporarily disabled by the edema. This was demonstrated in a recent MRI study where the high burden of atrial tissue edema immediately after ablation increased the odds of arrhythmia recurrence compared to patients with true atrial necrosis (effective lesions). Therefore, delivering effective transmural lesions during the first ablation at a given location may be critical in ensuring long-term success.

Effective Ablation With First Lesion
Poor contact leads to ineffective lesions as well as local edema and inflammation. This inflammatory process may render tissue resistant to further ablation. After RF delivery, swelling and inflammation typically occurs immediately, resulting in thickening of the left atrial wall. Further ablation in this area may therefore become ineffective. Furthermore, the resolution of the edema after the procedure may result in recovery of conduction in myocardial cells that had temporarily disabled by the edema. This was demonstrated in a recent MRI study where the high burden of atrial tissue edema immediately after ablation increased the odds of arrhythmia recur–rence compared to patients with true atrial necrosis (effective lesions). Therefore, delivering effective transmural lesions during the first ablation at a given location may be critical in ensuring long-term success.

Use Of Sheaths
Efficient catheter contact can be facilitated through the use of non-steerable and steerable sheaths that allow easy maneuverability, access and contact to target sites. Piorkowski et al compared the use of steerable sheaths with the use of non-steerable sheaths during

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AF ablations in a prospective randomized trial. Although the rate of acute PV isolation and total RF application time did not differ between both groups, single procedure success was significantly higher in patients treated with a steerable sheath (76% vs. 53% at 6 months). The difference persisted at 12 months (75.7% success) after a single AF catheter ablation procedure using steerable sheath. Therefore the utilization of a steerable sheath may help to improve the maneuverability of the ablation catheter, catheter stability and, tissue contact. This could potentially reduce recurrence through the enhancement of lesion continuity and transmurality.

Use Of Intracardiac Echocardiogram (ICE)
ICE allows real-time visualization of the anatomic structures and their relationship to ablation catheter. ICE can thus be used to verify adequate catheter contact. In animal model comparing the use of ICE to fluoroscopy, ICE guidance resulted in higher percentage of successful applications (P=0.02) and mean achieved temperature (P=0.004). Another study demonstrated a significant correlation between utility of ICE to evaluate tissue contact and lesion size. It was shown that ICE can be used to improve the percentage of applications with good contact. Furthermore, ICE has demonstrated the presence of significant catheter ‘sliding’ despite apparent stability based on electrogram assessment. However, one of the limitations of ICE is the difficulty to maintain clear and stable images during the entire ablation lesion.

Use Of Electroanatomical Mapping Systems

There is no absolute need for an electroanatomical mapping (EAM) system to guide PVI. How-ever, the addition of EAM may help to reduce fluoroscopy exposure and help define certain complex areas in the LA, such as the ridge between left superior pulmonary vein and left atrial appendage, a common area of poor stability, and therefore potential site of reconnection. One study that compared fluoroscopy alone versus image integration in EAM guided PVI even found a higher procedural success rate after a mean follow-up of 14 months in the group of patients that received ablation guided by EAM.

Ablation Catheter Choice
Surface cooling technology with saline used in irrigated catheters during energy delivery reduces heating at the point of highest current density where excessive temperatures would usually produce a significant rise in impedance. These irrigated catheters can deliver higher energy to tissue when compared to standard 4mm tip ablation catheters resulting in larger and deeper lesions. RF ablation performed using irrigated tip catheter has been shown to result in lower symptomatic AF recurrence compared to 4mm tip ablation catheter. A novel porous tipped irriga-tion catheter (ThermoCool SF Biosense-Webster, Diamond Bar, CA, USA and Therapy Cool Flex, St.Jude Medical) is now available as an alternative to the conventional 6 pores irrigation catheter. The porous irrigation catheter was able to achieve PVI with a significant decrease in the procedure and total RF time; however, a clinical benefit has not been demonstrated at this stage.

Alternative Energies To RF For PVI
Several sources of energy alternative to RF have been developed. Cryoballoon (CB) ablation is a recently introduced technique to isolate the PVs in patients with AF. Recurrence rate of PVI in patients with paroxysmal and persistent AF has not been shown to be better than RF ablation. According to a worldwide survey, RF remained the dominant form of energy used.

Laser balloon technology seems an effective tool for endocardial ablation, resulting in electrical isolation and transmurality. Laser ablation PVI using a fiberoptic balloon catheter was tested in a porcine model showing its ability to achieve PVI in a reliable, reproducible and persistent man-ner. A study tested the utility of this technology in humans through a multicenter study. In 56 patients, 98% of PV’s were acutely isolated, and most importantly, 86% of PV’s remained isolated in 52 patients that returned for PV remapping. Interestingly, 62% of patient remapped had all 4 veins chronically isolated, suggesting the effectiveness of this therapy for chronic lesion formation. Another recent study compared 2 balloon catheter technologies: laser versus CB, showing that 99% of PV’s can be isolated with a single balloon catheter, however no difference in AF free survival was appreciated between the two technologies. Further studies are needed to investigate the efficacy of laser balloon in reducing AF recurrence.

Impedance Monitoring
Decrease in impedance during RF application occurs as a result of tissue heating. Data has specifically shown that increased tissue contact is associated with a higher initial impedance drop during an RF application. An initial drop in impedance using standard irrigation catheter is a good indicator of adequate tissue contact during PVI.

Contact Force Sensing
Contact force sensing is a novel technology used to assess the degree of catheter contact during ablation through the use of a sensor at the distal tip of the ablation catheter. In the multi-center TOCCATA trial average contact force during ablation was an important determinant of clinical recurrence of AF. A mean contact force >20 g predicted indeed the best outcomes (80% freedom from AF recurrence over 12 months), whereas 100% of patients with mean contact force <10 g had evidence of AF recurrence during the follow-up period. In a prospective case control study the efficiency of contact force sensing in reducing AF recurrence was demonstrated. PV reconnection occurred in 21% of patients when the operator was blinded to contact force sensing while it occurred in only 4% of patients in which the operator was not blinded (p=0.001). In addition, catheter contact was shown to be higher when contact force sensing was utilized (p=0.002). Therefore, contact force monitoring during PVI is a promising tool that may allow optimal lesions delivery with less PV reconnection and potentially less AF recurrence.

Pharmacological Methods
Ineffective ablation lesions may lead to reversible injury with a temporary loss of PV connection immediately post-ablation, with a potential to recover when the acute inflammation and swelling resolves. The identification of dormant tissue that has been rendered unexcitable by “stunning” or edema is a significant challenge that may potentially increase risk of AF recurrence. The de-tection of such “dormant conduction” during the initial ablation procedure may therefore help identify PVs that have a potential to reconnect after the index procedure, and targeted ablation at these sites may reduce the risk of recurrent AF. In animal model RF induced thermal injury resulted in reversible or irreversible (depending on the degree of injury) cardiomyocyte membrane depolarization, leading to sodium channel (INa) inactivation and loss of cellular excitability. Adenosine has been purported to uncover dormant conduction. The mechanism by which adeno-sine uncovers dormant conduction
was elucidated in an in vivo study in canine model.\textsuperscript{35} Fol-lowing ablation, adenosine selectively hyperpolarizes PV cells by increasing inward rectifier po-tassium current (IKAdo), thereby restoring excitability of inactivated voltage-dependent INa and reestablishing conduction in dormant PVs.\textsuperscript{35} Adenosine was shown to be clinically useful in identifying PV reconnection in multiple studies as well as cavotricuspid isthmus reconnection.\textsuperscript{36} An early study (2004) reported that adenosine induced reconnection in 25% of PVs imme-diately after successful isolation.\textsuperscript{37} Tritto et al further demonstrated that delivering additional RF lesions at electrical gap sites elicited by adenosine definitively eliminated recovery of PV re-connection in all cases.\textsuperscript{38} Subsequent studies have also shown that AF recurrence after PV isolation could be reduced by delivering additional ablation lesions to eliminate adenosine in-duced dormant PV conduction.\textsuperscript{39,40,41,42} Other studies\textsuperscript{43,44} did not confirm the usefulness of adenosine in AF recurrence after PVI, thereby fueling a need for a randomized trial. The Adenosine Following Pulmonary Vein Isolation to Target Dormant Conduction Elimination (ADVICE) study is an ongoing randomized clinical trial assessing the impact of adenosine-guided PVI in preventing AF recurrences compared to conventional PVI.\textsuperscript{45}

Another drug that has been used to reveal dormant PV triggers after PVI is the B-adrenergic stimulant, Isoproterenol.\textsuperscript{41,46,47} Although it has a similar mechanistic effect to adenosine in hyperpolarizing resting membrane potential of PV cells and, thus, restoring excitability and conduction,\textsuperscript{49} it is considered to be inferior to adenosine\textsuperscript{41} for the purpose of transient PV re-connection. Isoproterenol on the other hand has been shown to be useful particularly for PV ca-rina triggers and non PV triggers.\textsuperscript{47,48} A recent study demonstrated that the use of adenosine and isoproterenol guided ablation may be useful in decreasing AF recurrence.\textsuperscript{48}

Therefore, the utilization of pharmacological provocative testing serves as a valuable tool during AF ablation, by identifying PVs that may reconnect, by potentially accelerating PV reconnection and revealing various non-PV triggers.

**Conclusions:**

Durable antral PVI isolation can potentially be enhanced by optimizing catheter tissue contact and the utilization of drugs to guide additional ablation lesions. There is no convincing evidence at this stage that other sources of energy are superior to radiofrequency ablation.

**References:**


Atrial Fibrillation In Heart Failure: New Directions In Diagnosis, Risk Assessment And Risk Reduction

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Abstract
Heart failure and atrial fibrillation are common conditions which frequently co-exist. In patients with established systolic and diastolic dysfunction, atrial fibrillation increases the risk of stroke, mortality and reduces quality of life. Recent advances in implantable device technology have improved the detection of atrial fibrillation and reduced the time to intervention. Rate control remains the mainstay of treatment to improve symptoms in patients with heart failure. Currently evidence does not suggest that the routine use of a rhythm control strategy is beneficial, other than improving symptoms in patients resistant to or intolerant of rate control medications. Atrial fibrillation ablation in heart failure is safe and may be effective in maintaining sinus rhythm. Patients with AF and heart failure have more severe strokes and require longer hospital admissions. Warfarin has traditionally been the drug of choice to reduce the risk of stroke in patients with AF and heart failure, although it use is no longer recommended in patients with heart failure and sinus rhythm. Newer oral anticoagulants offer improved stroke prevention in patients with heart failure albeit at a higher drug cost. Alternative methods of stroke reduction such as left atrial appendage occlusion are emerging, although evidence for their benefit in patients with heart failure has not yet been published.

Introduction
Atrial Fibrillation And Heart Failure: A Perspective
Atrial fibrillation remains the most common cardiac arrhythmia and continues to add significantly to worldwide mortality and morbidity. In addition to the reduction in quality of life that occurs due to the symptoms of palpitation, dyspnoea and fatigue, AF significantly increases the risk of stroke. It also reduces life expectancy, is more common with advanced age, and the prevalence continues to increase. In England, data from death certification has shown that atrial fibrillation as a primary cause of death increased by 6.6% per year between 1995 and 2010.1 The management of the growing burden of atrial fibrillation occurring in ageing populations is a pressing issue for health systems throughout the world.

The prevalence of heart failure in Western populations has been estimated at 1-2%.2 Heart failure is also more common in older patients. Data from an English population has reported an incidence rate rising from 0.02/1000 population per year in those aged 25-34 to 11.6/1000 population per year in those aged over 85.3 Heart failure is a complex syndrome involving multiple organ systems. Both conditions share many risk factors, and frequently co-exist. The addition of atrial fibrillation can destabilise patients and balancing the risks and benefits of treatment with antiarrhythmic and antithrombotic therapies in patients with multiple co-morbidities can be challenging for physicians.

The symptoms of heart failure have been observed both in the presence and absence of normal left ventricular function. Heart failure physicians differentiate between ‘Heart Failure with Reduced Ejection Fraction’ (HFrEF) and ‘Heart Failure with preserved Ejection Fraction’ (HFpEF) depending on the measurement of ejection fraction on echocardiography. The commonest causes of systolic dysfunction in Western populations are ischaemic coronary heart disease and dilated cardiomyopathies. In other regions, conditions such as Chagas' disease and nutritional deficiencies, such as Beri Beri, also feature as causes. Diastolic dysfunction may occur due to hypertrophic and restrictive cardiomyopathies, and is also seen in the context of hypertension, advanced age and diabetes.

Pathophysiology Of Atrial Fibrillation In Heart Failure
The pathophysiology of atrial fibrillation remains an area of intense scientific interest. The factors affecting the initiation and propagation of AF appear to be multiple and complex. AF and heart failure share many common risk factors, and both may share a common aetiology, for example ventricular and atrial ischaemia.4 Through rapid ventricular rates, ventricular remodelling and increased left atrial size, atrial fibrillation may itself worsen, or even cause, left ventricular dysfunction.5

AF is initiated by ‘triggers’, usually in the form of ectopic electrical activity. In the otherwise structurally normal heart the pulmonary...
Economic Costs

Inpatient mortality rate. Present, AF is associated with a longer hospital stay and a higher rate by 1/3rd.

Characteristics Of Atrial Fibrillation In Heart Failure

Atrial fibrillation is common in patients with heart failure. Multiple studies have demonstrated an association between the two conditions and the prevalence of persistent atrial fibrillation appears to increase with heart failure severity. Data from randomised trials of drugs therapies in heart failure have reported a prevalence of ≤5% rising to 50% in patients with NYHA IV symptoms. The incidence of paroxysmal AF, which may be unnoticed by patients and therefore not reported, is more poorly understood.

The association between AF and mortality has been investigated for the past 2 decades. The consensus appears to be that AF is an indicator of poor prognosis in heart failure. Despite earlier evidence that did not establish a link between AF in heart failure and premature death, subsequent studies have suggested that AF acts as an independent risk factor for mortality, possibly increasing death rates by 1/3rd. Whether AF or heart failure presents first appears not to matter.

AF in heart failure is associated with clinical decompensation. Around 30% of patients admitted to hospital with acutely decompensated heart failure will be in atrial fibrillation, and where present, AF is associated with a longer hospital stay and a higher inpatient mortality rate.

Economic Costs

The costs of treating the AF and its complications are large and rising. Whist estimates of the costs of AF vary between health systems, the direct costs of managing AF in Europe have been estimated to range from €450-€3000 per patient year. Costs for treating atrial fibrillation in patients with heart failure are higher. An economic analysis of the AF-CHF trial reported that the costs of treating patients with heart failure with either a rate or rhythm control strategy were similar (€18,494 vs. €24,211).

Acute strokes due to AF add additional costs. For example in the German health system, the cost of treating strokes in atrial fibrillation vs non-AF related strokes is estimated at €11,799 per stroke admission vs €8,817. This is presumed to be due to the fact that strokes that occur in AF are more severe than those which occur in sinus rhythm.

Because of the large costs involved in treating the vascular complications of atrial fibrillation and the potential to reduce these by means of anticoagulant therapy, many health systems are attempting to improve case-finding and treatment.

Diagnosing AF

Classification Of Atrial Fibrillation

Current guidelines classify AF according to the duration of episodes. Atrial fibrillation may be persistent if episodes last for at least 7 days, or paroxysmal if when less than 7 days. Patients may alternate between the two states; for example, when a patient experiences a new episode of AF that has lasted for a few hours which has been preceded by episodes lasting several weeks. When AF is present for more than 7 days and cardioversion has either failed or will not be attempted, AF is considered permanent.

While persistent or permanent AF is easier to capture on electrocardiography and therefore well represented in clinical trials that assess the benefit of anticoagulation, paroxysmal AF, which by its nature is more difficult to capture, has been less well studied. Many of the earlier trials of warfarin in AF excluded patients with paroxysmal AF altogether. Therefore how much AF is required to warrant the risk of anticoagulant therapy is not yet known. The amount of time that a patients spends in AF is frequently referred to as the "AF burden". There are no accepted definitions of a clinically significant burden. Whether or not the total proportion of time in AF, length of individual episodes or frequency or pattern of episodes confer similar risk is still under investigation. In heart failure, as the risk of bleeding is higher than that found in the lone-AF population, a better understanding of the risk posed by an increasing burden of AF is needed to guide oral anticoagulant therapy (OAT).

Case Finding

Many of the initial observational and cohort studies which reported the prevalence of atrial fibrillation relied on ECG assessment at interval follow-up, either scheduled or on presentation to a physician, for the diagnosis of atrial fibrillation. Whether atrial fibrillation had occurred in the intervening period was not assessed. By this method, the Framingham study reported a 2% incidence of AF over a 22-year follow-up in a population without a history of AF.

The development of atrial fibrillation may not always be associated with symptoms, and therefore the first presentation is often with an acute stroke. In view of the significant potential for reducing morbidity, mortality and health service costs through the use of anticoagulation in atrial fibrillation, much effort has been invested in case finding.

Screening Programmes

The results of a randomised, controlled trial of opportunistic vs. systematic screening for AF were reported in 2005. In this study, 15,000 patients ≥ 65 years were randomised to either a control group, or to systematic or opportunistic screening protocols (Figure 1).
After 1 year, the results showed that both screening strategies were significantly better than conventional care and were comparable in terms of the number of new cases detected. However, the incremental cost per case detected for systematic screening was approximately 4.5 times higher than for opportunistic screening.

**Population Education And Self-Diagnosis**

With evidence in support of opportunistic pulse screening by physicians, attention in recent years has turned to population-wide education and the promotion of self-detection. Public education is promoted through programmes such as ‘Know Your Pulse’ in the United Kingdom, and ‘Beat Your Odds’ in the USA. Smart phone applications are also available and promoted by heart disease charities for the self-assessment of cardiac rhythm. The introduction of “wearable health technologies” such as smart watches will offer further opportunities for self-diagnosis and may become an increasingly important source of heart rhythm data.

**Atrial Fibrillation Detection In Heart Failure**

Careful assessment for the development of atrial fibrillation should be part of the routine care for all patients with heart failure. For patients with implantable electrical cardiac devices such as CRT and ICD generators, continuous intra-cardiac rhythm monitoring offers another opportunity for AF diagnosis. Most modern pacemakers and implantable cardioverter-defibrillators are capable of arrhythmia detection and in many instances are also capable of storing and transmitting intracardiac electrograms to the supervising physician. The wireless telemetry of heart rhythm data has been shown to be useful in the diagnosis of atrial fibrillation in a population at higher risk of thromboembolic complications.

There is emerging evidence that the incorporation of such technologies into models of device follow-up may improve outcomes by enabling the initiation of OAT at an earlier time than would otherwise occur. In a 2008 study of 166 patients undergoing home monitoring of implanted devices, Ricci et al reported that interventions for newly-detected atrial fibrillation occurred around 5 months earlier than the next scheduled hospital follow-up. Earlier treatment has significant potential to reduce the incidence of stroke in heart failure.

**Treatment Of AF In Heart Failure**

**Treatment Goals: Rate or Rhythm?**

The relative merits of cardioversion to sinus rhythm as opposed to the control of the ventricular rate in patients with atrial fibrillation have been discussed extensively elsewhere. Several large studies have failed to demonstrate the superiority of rhythm control over rate control in the reduction of stroke rates or mortality in patients with AF and structurally normal hearts.

Similar results have been observed in studies enrolling patients with heart failure. Several studies have been published over the last decade which looked at the benefits of rate vs. rhythm control in patients with AF and structurally normal hearts. Moreover, maintaining sinus rhythm was difficult, with all studies reporting a high recurrence rate of AF. Rhythm control strategies remains a recommended treatment where symptoms remain despite adequate rate control.

**Pharmacological Treatments Of AF**

Slowing the ventricular rate in atrial fibrillation improves survival and reduces the risk of systemic embolism. Various anti-arrhythmic drugs are used to control the ventricular rate in atrial fibrillation, but their efficacy is limited by the risk of proarrhythmia. Rate control is typically achieved with beta-blockers, calcium channel blockers, or digoxin. However, the long-term efficacy of rate control is limited due to the high recurrence rate of atrial fibrillation.

**Table 1:** Studies of AF treatment strategy (rate vs. rhythm) in patients with heart failure

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Heart failure</th>
<th>Heart failure criteria</th>
<th>End point(s)</th>
<th>Result for enrolled patients with HF</th>
</tr>
</thead>
<tbody>
<tr>
<td>STAF</td>
<td>200</td>
<td>55.5%</td>
<td>≥ NYHA II</td>
<td>Combined: death, cardiopulmonary resuscitation, cerebrovascular event, systemic embolism</td>
<td>No difference between rate or rhythm</td>
</tr>
<tr>
<td>AF-CHF</td>
<td>1376</td>
<td>100%</td>
<td>≥ NYHA II; EF ≤ 35%</td>
<td>Time to cardiovascular death</td>
<td>No difference between rate or rhythm</td>
</tr>
<tr>
<td>CAFÉ-II</td>
<td>61</td>
<td>100%</td>
<td>≥ NYHA II; systolic dysfunction on echo</td>
<td>NYHA class, 6MWT, LV function, NT-proBNP, QOL</td>
<td>6MWT and QOL: no difference</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>LV function, NT-proBNP, QOL: slight improvement with rhythm control</td>
</tr>
</tbody>
</table>
symptoms, but aggressive rate reduction strategies have not been shown to be superior to lenient, easier to achieve targets. The RACE II trial,\(^4\) which randomised 614 patients with permanent AF to either lenient (<110 bpm) or strict (<80 bpm) heart rate targets, reported no difference in the reduction of a composite outcome of death from cardiovascular causes, hospitalisation for heart failure, stroke, systemic embolism, bleeding and life-threatening arrhythmic events. For patients with heart failure (47% of patients enrolled) a separate post-hoc analysis of this group has also shown no benefit when a more strict rate-control target was adopted.\(^42\)

**Rhythm**

Where rate control is ineffective in reducing the symptoms of atrial fibrillation, rhythm control may be considered. Whilst ineffective at reducing mortality in heart failure,\(^43\) amiodarone is effective in maintaining sinus rhythm.\(^44\) However, the side effects of amiodarone use have meant that there is reluctance to use it for long periods of time.

Dronedarone, a newer antiarrhythmic developed as an alternative to amiodarone, is associated with a significantly higher mortality in patients with heart failure, and is therefore contraindicated in patients with NYHA IV heart failure or recent decompensation.\(^45\)

**Non-Pharmacological Treatments Of AF**

**Ablation In Heart Failure**

In the past decade, catheter ablation has emerged as a treatment option for patients with symptoms of recurrent atrial fibrillation not amenable to drug therapy. Multiple studies have demonstrated the effectiveness at improving symptoms and the relative safety of this procedure in the structurally normal heart.\(^46\) Patients who undergo catheter ablation often require multiple procedures to obtain satisfactory pulmonary vein isolation, and the procedural complication rate is around 3% and is higher in elderly patients.\(^47,48\) Whilst effective in reducing the symptoms of atrial fibrillation, whether or not catheter ablation reduces stroke risk remains unanswered.\(^49\)

Evidence from randomised trials for the role of catheter ablation in the management of AF in heart failure is emerging. In 2013, Jones et al\(^50\) reported a trial of 52 patients randomised to either catheter ablation or rate control. In this study, there was a significant increase in peak oxygen consumption in the ablation group (+3.07 ml/kg/min; \(p = 0.018\)), although the trends towards improvement in 6MWT and EF were not significant. A higher proportion of patients maintained sinus rhythm (92% at 12 months; 72% after single procedure) during follow-up (12 months) compared to other studies comparing rhythm and rate control. The recently reported CAMTAF trial\(^51\) randomised 50 patients with heart failure and persistent atrial fibrillation to receive either catheter ablation or conventional medical therapy. After a 6 month follow-up period, 81% of the patient in the catheter ablation arm were free of AF (vs. 0% in the conventional treatment arm), demonstrating the potential effectiveness of ablation in restoring sinus rhythm with a similar risk to procedures performed in patients without heart failure.

Ablation for atrial fibrillation in heart failure appears to be effective in maintaining sinus rhythm, albeit with high rates of repeat procedures (around 60–70% in most studies\(^56\)). The case for the role of ablation in reducing stroke risk, hospitalisation and mortality has, however, not been made.

For patients in whom atrial fibrillation ablation is not considered, another option is AV node ablation. The use of radiofrequency energy to disrupt the normal atrio-ventricular conduction at the AV node predates catheter ablation for AF in the left atrium. Although AV node ablation has no effect on fibrillation in the atria, the prevention of conduction of fast atrial rates across the AV node prevents a fast ventricular response. Because of the induction of iatrogenic complete heart block, AV node ablation requires the insertion of an artificial pacemaker prior to the procedure and is therefore often referred to as ‘ablate and pace’. Ablate and pace treatment strategies reduce symptoms and improve quality of life.\(^52\) Concerns regarding the introduction of interventricular dyssynchrony in patients with heart failure due to pacing from the right ventricle following AV node ablation has led many physicians to prefer a biventricular device when performing ‘ablate and pace’.\(^51\)

**Thromboembolic Risk Stratification And Reduction**

**Thromboembolic Risk In Heart Failure**

The earliest epidemiological studies on AF and stroke noted the association between the incidence of stroke in AF and heart failure.\(^54\) In the Framingham cohort, the risk of stroke in patients with heart failure was observed to be doubled when atrial fibrillation was present,\(^55\) and the increased risk of stroke in AF when heart failure is present has been observed in multiple studies since.\(^56,57\) AF also predicts mortality in patients with heart failure – new onset AF increases mortality risk in heart failure by 30%\(^12\). Current guidelines for the assessment of stroke risk in atrial fibrillation incorporate the risk of heart failure as part of the CHADS\(_2\)/CHADS\(_2\)\_Vasc classification schemes.\(^58\)

How much AF confers a higher stroke risk? The earliest studies of warfarin in AF were designed to enrol patients with persistent AF – patients with paroxysmal AF were either excluded or only included if AF was present at interval follow-up.\(^59,60\) With the advent of continuous cardiac monitoring through implanted electrical heart failure devices, a greater understanding of the risk of differing burdens of AF is starting to emerge. High atrial rates detected by CRT and ICD devices have been shown to be associated with strokes\(^30\), although further work is needed to answer the question of how much AF warrants OAT and whether or not certain patterns of

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**Table 2:** Comparison of NOAC trials with respect to participants with heart failure

<table>
<thead>
<tr>
<th>Drug</th>
<th>n</th>
<th>Proportion of enrolled patients with heart failure</th>
<th>Heart failure definition</th>
<th>Result for heart failure group</th>
</tr>
</thead>
<tbody>
<tr>
<td>RELY(^65)</td>
<td>Dabigatran</td>
<td>18,113</td>
<td>LVEF &lt; 40% or NYHA ≥ II</td>
<td>110mg: Non-inferior</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>150mg: Dabigatran superior</td>
</tr>
<tr>
<td>ROCKET HF(^57)</td>
<td>Rivaroxaban</td>
<td>14,264</td>
<td>LVEF ≤ 35%</td>
<td>Non-inferior</td>
</tr>
<tr>
<td>ARISTOTLE(^58)</td>
<td>Apixaban</td>
<td>18,201</td>
<td>LVEF ≤ 40% or symptomatic HF in prior 3 months</td>
<td>Apixaban superior</td>
</tr>
<tr>
<td>ENGAGE(^72)</td>
<td>Edoxaban</td>
<td>21,105</td>
<td>Not stated</td>
<td>Not reported</td>
</tr>
</tbody>
</table>
Novel Oral Anticoagulants In HF

Since the introduction of Dabigatran in 2008, several novel oral anticoagulants (‘NOACs’) have emerged as potential treatments to reduce the risk of stroke in atrial fibrillation. Based on evidence from RCTs such as RE-LY\textsuperscript{66,67}, ROCKET AF\textsuperscript{68} and ARISTOTLE\textsuperscript{69}, NOACs are as either as effective as or superior to warfarin in reducing the risk of stroke and mortality. Whilst the results vary between individual compounds and dosing regimens, most studies report a lower rate of major bleeding on NOACs compared to warfarin. There are no randomised trials comparing NOACs with one another, although indirect comparisons have been attempted.\textsuperscript{39} NOACs offer considerable advantages to the patient over older vitamin K antagonists, such as simpler dosing regimens without monitoring, shorter duration of action and fewer drug interactions, albeit at a higher drug cost. NOACs are now recommended as first-line treatment for patients with AF requiring OAT.\textsuperscript{70}

For patients with heart failure, the benefits of NOACs appear more mixed. Patients with heart failure were enrolled into all of the trials for NOACs to differing degrees, although in each trial the definition of heart failure was slightly different. Overall, for patients with impaired systolic function and ≥ NYHA II symptoms NOACs are likely to be non-inferior to warfarin in preventing strokes. A summary of the involvement and results of patients with heart failure in NOAC trials is given in table 2.

Non-Pharmacological Techniques

Occlusion of the left atrial appendage has recently emerged as an alternative to oral anticoagulation for the prevention of stroke in atrial fibrillation. Several devices have been developed to occlude the LAA, such as the PLAATO device (withdrawn due to lack of funding for phase II or III trials), the Amplatzer cardiac plug (St Jude\textsuperscript{71}, on-going trial) and the LARIAT\textsuperscript{72} (SentreHeart) percutaneous LAA suture device. Currently, the most widely used technique is the WATCHMAN\textsuperscript{73} device (Boston Scientific). The WATCHMAN is a percutaneously implanted device consisting of a polyester fabric stretched across a self-expanding nitinol frame. Permanently placed in the orifice of the left atrial appendage, the device should prevent the escape of thrombus from within the lumen of the appendage. The efficacy, safety and non-inferiority of the WATCHMAN device to warfarin has been demonstrated in the PROTECT-AF trial.\textsuperscript{74}

The initial experience with LAA occlusion devices has been to implant the device in patients in whom warfarin is contra-indicated. In heart failure, where the risk of bleeding is higher, this would be beneficial. However, evidence supporting the use of such devices in heart failure patients is, at best, limited - although patients with milder-moderate heart failure were included in the PROTECT-AF study, the trial excluded patients with more severe heart failure (NYHA IV symptoms or an ejection fraction < 30%) and results for patients with heart failure have not yet been separately reported.\textsuperscript{75} Comparison of efficacy with novel OATs is also limited.\textsuperscript{74}

Conclusions:

Atrial fibrillation in heart failure is common, and early detection and treatment can reduce the incidence of stroke, improve quality of life and reduce mortality. Modern technologies offer a new opportunity to increase case-finding and reduce the time to first diagnosis, and provide further insight into the risk of paroxysmal atrial fibrillation. Multiple strategies now exist for reducing the risk of stroke and improving the symptoms of atrial fibrillation and heart failure, but the assessment of the risk-benefit balance for individual patients remains complex.

References:


35. Falk RH. Is rate control or rhythm control preferable in patients with atrial fibrillation? Rate control is preferable to rhythm control in the majority of patients with atrial fibrillation. Circulation 2005;111:3141–50–discussion3157.


Sex Differences In Outcomes Of Ablation Of Atrial Fibrillation

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Abstract

Sex-related differences in the presentation, treatment, and outcomes of cardiovascular disease have been reported in many areas of cardiovascular medicine, including the clinical course and treatment of atrial fibrillation (AF). Women appear to be more symptomatic, have a lower quality of life, and are less tolerant of antiarrhythmic drugs than men. However, the rate of referral of women for catheter ablation of AF is significantly lower than men, and women are referred much later after failing more antiarrhythmic drugs. There is a trend toward a lower success rate and a higher failure rate for catheter-based AF ablation in women. This finding may be related to the later referral of women for the procedure, resulting in high risk features such as more severe hypertension, greater left atrial size, and more persistent AF at the time of the procedure, all of which are associated with future recurrences. The complication rate from AF ablation is significantly higher in women, particularly with respect to bleeding and vascular complications such as hematomas and pseudoaneurysms. Individualized care including earlier referrals, pre-procedural case planning, and close monitoring intra- and post procedure may improve the outcomes for women with catheter ablation of AF.

Introduction

Sex-related differences in the presentation, treatment, and outcomes of cardiovascular disease have received increasing attention in recent years. There is widespread underuse of cardiovascular procedures in women, including coronary angiography, revascularization, and implantable cardioverter-defibrillators. Such sex-related differences have also been reported in the presentation and management of atrial fibrillation (AF), including catheter ablation. Women appear to be more symptomatic from the arrhythmia, have higher heart rates at the time of presentation, and present with a lower quality of life. Although these characteristics would seem to encourage a rhythm control approach, the use of antiarrhythmic drugs is not always possible, as both bradyarrhythmias and torsade de pointes have been observed more frequently in women. In this setting, catheter ablation of AF is certainly an attractive option to both patients and physicians.

The use of catheter ablation is rapidly growing. In Cappato's worldwide survey between 1995 and 2002, the median number of procedures per center was 37.5 (range, 1-600), whereas in his updated survey between 2003-2006, it rose to 245 (range, 2-2715). The 2012 Heart Rhythm Society/European Heart Rhythm Association/European Cardiac Arrhythmia Society Expert Consensus Document on Catheter Ablation of AF determined that catheter ablation of AF should have a Class I Level of Evidence A recommendation in patients with paroxysmal AF who have failed treatment with at least one antiarrhythmic medication, and a Class IIa Level of Evidence B recommendation for patients with paroxysmal AF who have not failed antiarrhythmic drug therapy. Although commonly used in younger patients with paroxysmal AF, catheter ablation is increasingly employed as well in patients with persistent or long-standing persistent AF. With increasingly widespread use of the procedure, it is prudent to understand the various factors that affect outcomes in AF ablation. The purpose of this article is to review the presentation and treatment outcomes of AF in women, with particular attention to the success rates and complication rates of AF ablation, in order to highlight differences compared to men and opportunities for improved outcomes.

Search engines including PubMed were used for all publication types in the English language, using the search terms describing the concepts of AF and sex. These terms included atrial fibrillation ablation, sex, gender, women, outcome, success, efficacy, recurrence, complications, prevalence, incidence, epidemiology, presentation, and treatment. Full-length manuscripts were reviewed. The reference sections from the identified publications were also used for further search. Several studies specifically addressed sex differences in outcomes and complication rates, as discussed below. Most of the

Key Words:
Atrial Fibrillation, Stroke, Bleeding, Risk Assessment.

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other available major reports on outcomes of AF ablation did not specifically report on outcomes in men versus women, although sex was often included in multivariable analyses of predictors of success rates. In addition, several of them reported on sex differences in complication rates, which we have included in our review.  

**Presentation And Treatment Of AF In Women**

AF is the most common arrhythmia in clinical practice, with an estimated prevalence in the United States of 2.7 to 6.1 million that is expected to increase to 5.6 to 12.2 million by 2050.0,9,19-21 The prevalence of AF is higher at all ages in men than in women.22 However, since there are almost twice as many women as men older than 75 years in the general population, the absolute number of women with AF is equal to or greater than men.22,23

Multiple studies have found that women are more symptomatic from AF and have a lower quality of life.9,11 One of the explanations for this finding may be due to their higher presenting heart rates. A prospective study by Hnatkova et al. showed the mean heart rate of women at the onset of AF was 123±35 beats/minute vs. 115±50 beats/minute in men.25 Similar heart rate differences in AF between sexes were observed in an analysis of the Canadian Registry of AF, which found higher mean heart rates during AF in women (126±2±1.9 vs. 119±1.4 beats/minute in men). It has also been reported that women are more likely to experience longer (>24 hours) symptomatic episodes and frequent recurrences of AF.9 Women have a lower quality of life related to AF, which may be attributed to depression as well as a more heightened sense of symptoms. Ong et al. performed a cross-sectional study of 93 patients with AF to evaluate the role of depression on quality of life. It revealed that women reported higher depression scores relative to men, and depression was related to lower physical and mental quality of life.26

Women have more episodes of bradyarrhythmias when treated with antiarrhythmic drugs. In a sub-analysis from the Rate Control Versus Electrical Cardioversion (RACE) Study, severe adverse effects of antiarrhythmic drugs and pacemaker implantations occurred more often in women. Such adverse events included manifestations of sick sinus syndrome on flecainide, sotalol, or amiodarone, and torsades de pointes on sotalol.13,14 More frequent episodes of torsades de pointes in women have previously been reported on multiple antiarrhythmic drugs, including ibutilide and sotalol.27-29 Sex differences in susceptibility to torsades de pointes may be related to fluctuating QT intervals on antiarrhythmic drugs due to hormonal changes30,31 and longer baseline QT intervals in women.32

As women are more symptomatic from AF and less tolerant of antiarrhythmic drugs, catheter ablation appears to be a suitable option. However, multiple studies indicate that women are referred less often for catheter ablation.15,16,32,42 The percentage of women among patients referred for ablation in these studies ranged from 15.8 to 33.2%. Later referral of women is suggested by the significantly older age of women compared to men at the time of ablation, although this later referral may reflect at least in part the higher prevalence of AF in men in younger age groups.32,33,35 Roten et al. also reported a trend of fewer and later referrals of women to electrophysiology consultation in an outpatient-based study.43

**Overall Success and Complication Rates of AF Ablation**

Multiple studies have described overall outcomes and complication rates of AF ablation. A majority of these publications, including randomized clinical trials and meta-analyses, have high percentages of male patients with paroxysmal AF and few co-morbidities. With this caveat in mind, the efficacy of AF ablation in randomized trials has been reported to be in the range of 66 to 89% with up to 12 months of follow-up.17,18,36-42 Despite the heterogeneity of these studies due to variables such as definition of recurrence, ablation methods, choices of antiarrhythmic drugs, the number of repeat procedures and the above-mentioned patient characteristics, several meta-analyses report consistent overall success rates of 75.6-77.8% in the ablation arms as compared with 18.8-29% in the control groups of clinical studies.44-47 A more recent meta-analysis evaluated long-term outcomes of AF ablation and reported the overall long-term success rate after ≥3 years of follow-up to be 79.8%, with an average of 1.51 procedures per patient.48 In addition to these randomized clinical trials and meta-analyses, two worldwide surveys have been published, representing the outcomes from over 180 centers. An initial worldwide survey (1995-2002) reported the success rate, defined as freedom from symptomatic AF in the absence of antiarrhythmic therapy, to be 52%. In the updated worldwide survey (2003-2006), a 70% efficacy rate free of antiarrhythmic drugs and an additional 10% efficacy rate in the presence of previously ineffective antiarrhythmic drugs were reported.15,16

Complication rates from some of the meta-analyses, which included evaluations of 10 randomized controlled trials and 18 non-randomized controlled trials, are in the range of 2.9 to 7.96%.45,46,47 Two worldwide surveys reported major complication rates of 6% (1995-2002) and 4.5% (2003-2006).15,16 Recently, in-hospital complications associated with catheter ablation of AF in the U.S. were analyzed for 93,801 procedures performed between 2000-2010, utilizing data from the Nationwide Impatient Sample, a nationally representative survey of hospitalizations conducted by the Healthcare Cost and Utilization Project, including a 20% sample of U.S. community hospitals. This study reported the overall complication rate to be 6.29%, comparable to other findings.49

**Success Rates Of AF Ablation In Women**

There has not been any consistent evidence to support female sex as a predictor for recurrence after AF ablation based on multiple univariate and multivariate analyses.45,50,51 Balk et al. performed a systemic review of predictors of AF recurrence after catheter ablation and reported that none of 23 studies with Cox hazard predictor analyses found female sex to be a predictor of recurrence. A recent meta-analysis by Ganesan et al. reported conflicting data among various studies, including two that showed male sex as a predictor of recurrence and two other studies that found female sex to be a predictor of recurrence of AF. Heist et al. reported male sex as a multivariate predictor of overall clinical success in their analysis of 143 patients with persistent and longstanding persistent AF patients who failed antiarrhythmic therapy.51

In an attempt to evaluate sex-related differences in depth, at least four major studies have examined outcomes in women as primary end points in the past decade (Tables 1,2). A study by Forleo et al. evaluated 221 consecutive patients from two centers who underwent catheter ablation for drug-refractory AF.52 This study provided early objective evidence of sex-related differences in AF ablation. Women had a longer history of AF (median 60 vs. 47 months; P = 0.042), yet they represented only 32.1% of the patients referred for catheter ablation. Left atrial dimensions were significantly larger in women (Table 1). The success rate was evaluated in terms of freedom from arrhythmia recurrence on or off antiarrhythmic drugs after the last ablation following a one month blanking period. Despite these
null
the success rate. Anatomical differences in left atrial size have also been suggested as a possible culprit in the sex-related difference in success/failure rate; however, a recent study did not find a significant sex difference in left atrial antrum size despite significant differences in outcome.34

Complication Rates Of AF Ablation In Women

Female sex has been reported as a predictor of complications after AF ablation, and higher complication rates from AF ablation in women have been found repeatedly.15,33,34,48-73 The multicenter U.S. retrospective study by Patel et al. reported total complications of 3265 (518 in women vs. 2747 in men), with a 5% complication rate in women vs. 2.4% in men (P < 0.001). This study also found more hematomas and pseudoaneurysms in women (Table 2).33 In Zhang's study, the complication rate was higher in women, with a marked increase in hematomas.34 A prospective analysis of 641 procedures (22.3% women) who underwent catheter ablation of AF from a single center reported more major adverse clinical events, defined as those that required intervention, resulted in long-term disability, or prolonged hospitalization, in women (P = 0.014; odds ratio 3.0, 95% confidence interval 1.3-7.2).58 The same group reported female sex as a predictor of complications in both univariate and multivariate analyses.72

Another prospective single-center analysis of procedural complications in the Vanderbilt AF Registry evaluated 445 patients who underwent AF ablation. This study reported a significant increase in complications in obese women. Morbidly obese patients experienced a higher rate of complications (14.3% vs. 6.2% in non-morbidly obese patients; P = 0.046). Using a discrete BMI cutoff, the odds of complications increased 3.1-fold in those with morbid obesity and 2.1-fold in women. With BMI as a continuous variable, the odds ratio for complications increased by 5% per 1 unit increase in BMI, and the risk in women was increased 2.2-fold.69 A recent in-hospital analysis also revealed overall higher complication rates in women (7.51% vs. 5.49%; P < 0.001).49 A large multicenter registry data from Italy enrolling 2323 patients also reported a significantly higher complication rate in women (7% vs. 4.4%), and female sex was reported to be an independent predictor of a higher risk of complications by univariate analysis (odds ratio 2.643, 95% confidence interval 1.686-4.143, P < 0.0001).70 Shah et al. also reported female sex to be a predictor of a higher risk of complications from AF ablation in their retrospective data analysis of 4156 patients.73

Why do women, particularly those who are morbidly obese, pose a higher risk for complications? As hematomas and pseudoaneurysms are reported to occur more often in women, vascular access appears to play a significant role in the higher rate of complications. Variations in the anatomy of the femoral vasculature have been well reported.74,75 Schnyder et al. performed a prospective analysis of 200 consecutive common femoral artery angiograms. Their multivariate analysis revealed female sex as a predictor of small vessel size (P = 0.0005).76 Although no specific studies have been performed, femoral venous anatomy, size, and proximity to the femoral artery could well be affected by sex, potentially increasing the risk of access-related complications in women, particularly in morbidly obese individuals. As systemic heparinization is routinely used during AF ablation, a differential effect of heparin in men and women may also play a role in sex differences in complication rates. Campbell et al. prospectively studied 199 consecutive patients presenting with proximal deep vein thrombosis not related to catheter ablation procedures. They assessed activated partial thromboplastin time (aPTT) values and heparin levels every 4 to 6 hours after a standard heparin bolus and infusion. The results revealed significantly higher heparin levels and higher aPTT values in women (P = 0.0002). After achieving therapeutic aPTT levels, women received lower heparin doses than the men, yet had higher heparin levels.78 A sex difference in the pharmacokinetics of heparin was also suggested by Winkle et al., who found significantly higher activated clotting times (ACT) in women in an analysis of 1122 AF ablations. Women received less heparin but were over-represented in the higher ACT ranges (P < 0.0001).77 This variation in the pharmacokinetics of heparin in women may contribute to a higher bleeding risk, predisposing women to a greater risk for hematomas. With these anatomical and pharmacological variations in women, extra modalities, such as vascular ultrasound or closer monitoring of activated clotting time, may be necessary to help reduce the number of complications in women.

Conclusions:

Success rates for AF ablation are clearly higher in earlier stages of

Table 2: Outcomes of AF Ablation in Women

<table>
<thead>
<tr>
<th>Study</th>
<th>Design (enrollment, N)</th>
<th>% Women</th>
<th>Age, years</th>
<th>% Paroxysmal AF</th>
<th>Success Rate, % (includes redo)</th>
<th>Complication Rate, %</th>
<th>Major Complication Type, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Forleo, 2007</td>
<td>Prospective, two center, cohort (221)</td>
<td>32.1</td>
<td>61.6 ± 8.3</td>
<td>56.9 ± 10.8*</td>
<td>56.3</td>
<td>61.3</td>
<td>83.1</td>
</tr>
<tr>
<td>Patel, 2009</td>
<td>Retro-spective, multi-center (3265)</td>
<td>15.8</td>
<td>59 ± 13</td>
<td>56 ± 19*</td>
<td>46</td>
<td>55*</td>
<td>68.5</td>
</tr>
<tr>
<td>Zhang, 2013</td>
<td>Prospective, single center (220)</td>
<td>33.2</td>
<td>62.7 ± 10.6</td>
<td>61.1 ± 10.4</td>
<td>All persistent AF</td>
<td>35.6 (54.8)</td>
<td>57.1* (66.0)</td>
</tr>
<tr>
<td>Takigawa, 2013</td>
<td>Prospective, single center (1124)</td>
<td>24</td>
<td>63.2 ± 9.1</td>
<td>60.0 ± 10.5*</td>
<td>All paroxysmal AF</td>
<td>56.4 (76.5)</td>
<td>59.3 (81.3*)</td>
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</table>
the disease process, when the arrhythmia is paroxysmal, left atrial size is relatively normal, and left ventricular function is preserved. It is thus, becomes clear that in order to have a comparable success rate of AF ablation in women, symptomatic women need appropriately early referrals for ablation before they develop a high risk profile.

When ablation is chosen as the treatment option for AF, it should be performed with extra attention to complications in women, particularly with respect to vascular access, as women appear to be at increased risk for these complications.

Individualized care involving early referrals, pre-procedural case planning, and close monitoring intra- and post procedure may improve the odds for women to have better outcomes with catheter ablation of AF.

References:


Management of Atrial Fibrillation in Patients with Kidney Disease

Yee C Lau, Gregory Y H Lip

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Abstract

The increasing burden of Chronic Kidney Disease (CKD) is highly relevant to cardiologists, as cardiovascular mortality is 10-30 times higher amongst people with End-stage Renal Disease (ESRD), comparing with general population. One of the commonest associations is the increased frequency of atrial fibrillation (AF) amongst those experiencing CKD.

Overall, we know that AF is the most common cardiac arrhythmia. AF leads to a substantial risk of mortality and morbidity, from stroke and thromboembolism, heart failure, reduced cognitive function and impaired quality of life. However, most clinical trials in AF (for example, for stroke prevention in AF with anticoagulation therapy) have largely excluded patients with significant renal impairment.

In this review article, we will focus on stroke prevention in AF, and the clinical impact of CKD and its implications for management.

Introduction

Chronic Kidney Disease (CKD) is defined as a reduction in renal function, with a reduction in glomerular filtration rate (GFR) <60ml/min per 1.73m² for 3 months or longer, the presence of albuminuria, or both. The classification scheme of CKD stage 1-5 is traditionally based on glomerular filtration rate, with CKD stage 1 being one with preserved renal function (GFR >90ml/min) to CKD stage 5 being one with the worst renal function (GFR <15ml/min). Those with CKD stage 5, with accompanying signs of fluid and electrolyte imbalance, necessitates renal replacement therapy (eg. dialysis) and is classified as End-stage Renal Disease (ESRD).

CKD is increasingly being recognised as an important cause of death and morbidity globally. The prevalence of CKD is estimated to be between 8-16% globally and its upward trajectory has led to the rise in mortality (CKD listed as 27th in list of causes of total number of global death in 1990, to 18th in 2010) as well as increasing loss of disease adjusted life years. An important reason is the improving longevity and expansion in number of elderly people in the world. This trend is further exacerbated by the increasing incidence of diabetes and hypertension (which are the leading causes of CKD) in both developed and maturing economies, the lack of access to effective healthcare resources and low awareness of renal disease amongst the at risk population. Without an effective prevention and management strategy, CKD is rapidly becoming a global public health issue.

Besides nephrologists, this increasing burden of CKD highly relevant to cardiologists, as cardiovascular mortality is 10-30 times higher amongst people with ESRD, comparing with general population. One of the commonest associations is the increased frequency of atrial fibrillation (AF) amongst those experiencing CKD.

Overall, we know that AF is the most common cardiac arrhythmia. AF leads to a substantial risk of mortality and morbidity, from stroke and thromboembolism, heart failure, reduced cognitive function and impaired quality of life.

Nevertheless, most clinical trials in AF, for example, for stroke prevention in AF with anticoagulation therapy have largely excluded patients with significant renal impairment. In this review article, we will focus on stroke prevention in AF, and the clinical impact of CKD and its implications for management.

The Size Of The Problem

The prevalence of AF rises from 0.7% in general population age <60, to 27% amongst those with ESRD. Despite the presence of significant variability, the relationship AF among patients with CKD have been substantiated and independently verified by several studies. In the larger Chronic Renal Insufficient Cohort (CRIC) study in America, involving almost 3300 patients with CKD, nearly 20% have evidence of AF. The Atherosclerosis Risk in Community (ARIC)
Study has also shown that patients with GFR of 60 - 89, 30 - 59, and 15 - 29 mL/min/1.73 m² have hazard ratios of developing AF (within the 10 year follow-up period) of 1.3, 1.6, and 3.2, respectively, as compared to those with normal GFR. This further reinforces the association between reduced renal function and incidence of AF.11

In addition to increase of the risk of ischaemic stroke and thromboembolic event, the diagnosis of AF in pre-existing CKD also heralds early deterioration of renal function and risk of progression to ESRD.12-13 Henceforth, a bidirectional relationship between AF and CKD may exist. As one begets the other, the presence of both conditions has shown to result in even higher stroke and mortality risk.14 The 1-year mortality rate for patients with CKD Stage 3-5 with incident AF is as high as 35.6%.15

**Thromboembolism In AF And CKD: Pathophysiological Insights**

The presence of AF confers the presence of a prothrombotic hypercoagulable state through numerous pathophysiological pathways.16 The propensity of thrombus formation (thrombogenesis) can be described in relation to a triad of abnormalities first described by Virchow 150 years ago, hence this being referred to as ‘Virchow’s triad for thrombogenesis’.16

First, abnormalities of flow, caused by blood stasis within the left atrium and adjoining left atrium appendage. Second, abnormalities within the vessel wall, with structural heart disease macroscopically and – at a more microscopic level - endothelial or endocardial damage/dysfunction including increase expression of von Willebrand factor or tissue factor. The third component of Virchow’s triad refers to abnormalities of blood constituents, with abnormal coagulation, platelets and fibrinolysis (Table 1).

In CKD, many other potential contributing factors appear to contribute to this increased thromboembolic risk, for example, the up-regulation of rennin-angiotensin-aldosterone-system (RAAS) and chronic inflammation.17 The RAAS is demonstrated to be up-regulated in hypertensive state,18 and together with chronic elevation of inflammatory markers through various stages of CKD,19-20 would lead to the propagation of a prothrombotic state and consequently bring about an increase in the propensity to thrombogenesis. Additionally, the increase in thromboembolic risk may also be caused by chronic vascular calcification and/or dysfunction of calcium-phosphate metabolism in CKD.21-22

Given the above-mentioned pathophysiological pathways, the elevated thromboembolic risk will undeniably result in an increased risk of ischaemic stroke and thromboembolism.

**Thromboembolism In AF And CKD: Clinical Insights**

The close relationship between thromboembolism and CKD amongst AF patients has been reported by several large observational studies.

In the AntiCoagulation and Risk factors In Atrial fibrillation (ATRIA) study, Go et al.31 found that proteinuria increased risk of thromboembolism by 54% and progressive worsening of GFR is also associated with increased risk of stroke, so much so that those with GFR <45 mL/min/1.73 m² confers a increased risk of 39% as compared to those with normal GFR.

### Table 1: Pathophysiologic Mechanisms of Thromboembolism in Chronic Kidney Disease

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Type</th>
<th>N</th>
<th>Population</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>eGFR an independent predictor of reduced left atrial appendage emptying velocity and presence of left atrium spontaneous echo contrast</td>
<td></td>
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</tr>
<tr>
<td>Providência et al (2013)</td>
<td>Observational</td>
<td>372</td>
<td>Patients with nonvalvular atrial fibrillation</td>
<td>eGFR is positively associated with dense spontaneous echocardiographic contrast, and low flow velocities in the left atrial</td>
</tr>
<tr>
<td>endothelial damage/dysfunction</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Maximal release of active tPA and capacity for active tPA release markedly impaired in CKD pts vs controls</td>
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</tr>
<tr>
<td>Heintz et al (1994)</td>
<td>Comparative</td>
<td>40</td>
<td>CKD and healthy controls</td>
<td>CKD pts have higher endogenous levels of ET-1, plasma cAMP, and enhanced ET-1 stimulated ADP-induced platelet aggregation than healthy control</td>
</tr>
<tr>
<td>Carrero et al (2012)</td>
<td>Observational</td>
<td>630</td>
<td>NDD CKD vs ESRD</td>
<td>Prolactin levels increased along with reduced kidney function, related to FMD, PWD and increased risk of cardiovascular events and mortality.</td>
</tr>
<tr>
<td>Recio-Mayoral et al (2011)</td>
<td>Comparative</td>
<td>141</td>
<td>CKD vs 65 age and gender matched control</td>
<td>Platelet activation and coagulation abnormalities</td>
</tr>
<tr>
<td>CKD patients had increased CRP levels, reduced FMD and increased IMT values compared to controls</td>
<td></td>
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<tr>
<td>Shlipak et al (2003)</td>
<td>Cross-sectional</td>
<td>5888</td>
<td>Population-based cohort of age &gt;65 y</td>
<td>CRP, fibrinogen, IL-6, Factor VII, Factor VIII, plasmin-antiplasmin complex, and D-Dimer levels significantly higher in CKD</td>
</tr>
<tr>
<td>Keller et al (2008)</td>
<td>Cross-sectional</td>
<td>6814</td>
<td>Population-based cohort 45-84</td>
<td>CRP, IL-6, TNF, TNFαR1, intercellular adhesion molecule-1, fibrinogen, and Factor VIII levels are significantly higher in CKD</td>
</tr>
<tr>
<td>Landray et al (2004)</td>
<td>Comparative</td>
<td>522</td>
<td>334 CKD pts, 92 CAD pts, 96 healthy control with no prior CV or renal disease</td>
<td>CKD is associated with higher fibrinogen, plasma vWF, soluble P-selectin, but not CRP</td>
</tr>
<tr>
<td>Tanaka et al (2009)</td>
<td>Observational</td>
<td>190</td>
<td>Pts not receiving oral anticoagulant stratified to CC</td>
<td>Decreased GFR predicts for elevation of TAT and D-Dimer in pts with AF</td>
</tr>
<tr>
<td>Mercier et al (2001)</td>
<td>Cross-sectional</td>
<td>150</td>
<td>50 ESRD pts, 50 NDD CKD and 50 healthy controls</td>
<td>Reduced renal function associated with enhance tissue factor coagulation to platelet, monocyte and endothelial injury.</td>
</tr>
<tr>
<td>Adams et al (2008)</td>
<td>Comparative</td>
<td>102</td>
<td>66 CKD stage 4&amp;5 vs 66 healthy controls</td>
<td>Up-regulation of the tissue factor pathway, increased prothrombin fragment 1+2 and reduction in antithrombin III in CKD compared to healthy controls</td>
</tr>
</tbody>
</table>

Abbreviations: ADP, adenosine diphosphate; AF, atrial fibrillation; CAD, coronary artery disease; cAMP, cyclic adenosine monophosphate; CCr, Creatinine clearance; CKD, chronic kidney disease; CV, cardiovascular; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; MDRD, Modification of Diet in Renal Disease; NDD, non-dialysis dependent; pt, patient; PWV, pulse wave velocity; TAT, thrombin-antithrombin complex; TNF-αR1, tumour necrosis factor a soluble receptor 1; tPA, tissue plasminogen activator; vWF, von Willebrand factor.
In the Danish nationwide cohort study, Olesen et al. found that AF patients with CKD had significantly higher rate of stroke, thromboembolism, bleeding and death, as compared with those without renal disease. The risks were substantially higher if renal replacement therapy was needed (Table 2).

Amongst those with CKD (GFR <60mL/min per 1.73m²), the sequential deterioration of renal function over time has been shown to be associated with an increased risk of clinical adverse events. Indeed, an absolute reduction in eGFR ≥25 mL/min/1.73 m² or a relative reduction of eGFR ≥25% effectively more than doubles the risk of ischaemic stroke when compared to those with relatively “stable” renal function over 6 months period.

Recent evidence also revealed that GFR is not only can be an independent, reliable predictor of stroke mortality, but CKD also results in a more adverse clinical outcome after stroke, such as increased neurological deterioration or worsen functional outcomes.

**Bleeding Risk In CKD**

Even though CKD does increase the risk of thromboembolism and ischaemic stroke, the presence of this condition is also associated with an increased risk of intracranial or gastrointestinal haemorrhage.

In both the Rotterdam Study, as well as the Japanese CIRCS Study, the presence of reduced renal function (GFR <60 mL/min/1.73 m²) resulted in an increased risk of haemorrhagic stroke in males, with reported hazard ratios of 4.10 and 4.18, respectively. The hazard ratio of haemorrhagic stroke in females is even higher, in excess of 7.00.

Current imaging modalities have also revealed that patients with CKD possess an increased in presence and numbers of MRI-defined cerebral microbleeds (CMB), which are actually harbinger of potential intra-cranial haemorrhage. Even for those who have experienced an acute ischaemic stroke, lower GFR levels (<30 mL/min/1.73cm³) are found to have an association with haemorrhagic transformation, with an odds ratio of 2.90 (95% CI 1.26-6.68).

### Table 2: Stroke Risk in patients with AF with CKD

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Type</th>
<th>N</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Go et al 33(2009)</td>
<td>Retrospective</td>
<td>10908 AF with CKD</td>
<td>Comparing with GFR ≥ 60 mL/min/1.73 m²: eGFR 45-59mL/min, RR 1.16 (95% CI, 0.99 to 1.40)</td>
</tr>
<tr>
<td>Friberg et al 38 (2012)</td>
<td>Retrospective</td>
<td>182678 AF pts</td>
<td>CKD Stage 1 and below: Multivariate HR 1.11 (95% CI 0.99-1.25)</td>
</tr>
<tr>
<td>Olesen et al 34 (2012)</td>
<td>Retrospective</td>
<td>132372 AF pts (out of which 3587 NDD CKD, 901 ESRD)</td>
<td>Comparing with GFR ≥ 90 mL/min/1.73 m²: NDD CKD, HR 1.49 (95% CI 1.38-1.59) ESRD, HR 1.83 (95% CI, 1.57 to 2.14)</td>
</tr>
<tr>
<td>Guo et al 13 (2013)</td>
<td>Prospective</td>
<td>617 AF pts</td>
<td>Risk of stroke or death: HR 2.90 (95% CI 1.18-4.48)</td>
</tr>
</tbody>
</table>

For gastrointestinal bleeding, the recurrence, frequency and severity of such bleeds is linked to the reduction of renal function. Indeed, CKD and ESRD also predict higher risk of mortality as a sequala of gastrointestinal bleed, with corresponding odds ratios of 1.47 (95% CI 1.21-1.78) and 3.02 (95% CI 2.23-4.1), respectively.

The causes of increased risk of haemorrhage in CKD are multifold. It could be the concurrent use of anti-platelets or non-steroidal anti-inflammatory drugs, as a result of uremic toxins in ESRD, or increased vascular ectasia and angiodysplasia. Other pathophysiological causes of increased bleeding risk which have been proposed include platelet dysfunction, impaired platelet aggregation and adhesion, abnormal intraplatelet calcium mobilisation, impaired release of platelet alpha-granule protein, impaired platelet glycoprotein IIb IIIa receptor activation and its binding to glycoprotein and altered von Willebrand factor. In addition, patients at the terminal end of CKD (ESRD) will be subjected to an increased frequency of invasive diagnostic and treatment strategy, such as haemodialysis or central venous access, which consequently increases their propensity to bleed.

In summary, worsening renal function, from CKD to ESRD, has a graded relationship with an increased bleeding tendency. Thus CKD per se been shown to precipitate an increase in intra-cranial bleed, gastrointestinal haemorrhage and all cause mortality.

### Table 3: The CHADS2-VASc score

<table>
<thead>
<tr>
<th>Congestive Heart Failure</th>
<th>1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>1</td>
</tr>
<tr>
<td>Age ≥ 75 years</td>
<td>2</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>1</td>
</tr>
<tr>
<td>History of Stroke/TIA/thromboembolism</td>
<td>2</td>
</tr>
<tr>
<td>Vascular disease (previous myocardial infarction, peripheral vascular disease or aortic plaque)</td>
<td>1</td>
</tr>
<tr>
<td>Age (64-74 years)</td>
<td>1</td>
</tr>
<tr>
<td>Sex category (female)</td>
<td>1</td>
</tr>
</tbody>
</table>

Maximum score 9

### Table 4: The HAS-BLED Score

<table>
<thead>
<tr>
<th>Hypertension</th>
<th>1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abnormal renal and liver function (one point each)</td>
<td>1</td>
</tr>
<tr>
<td>Stroke</td>
<td>2</td>
</tr>
<tr>
<td>Bleeding history or propensity</td>
<td>1</td>
</tr>
<tr>
<td>Labile INR</td>
<td>2</td>
</tr>
<tr>
<td>Elderly (age &gt; 65 or frail condition)</td>
<td>1</td>
</tr>
<tr>
<td>Drugs or alcohol concomitant use (one point each)</td>
<td>1</td>
</tr>
</tbody>
</table>

Maximum score 9

Abbreviations: CI, confidence interval; CKD, chronic kidney disease; ESRD, end-stage renal disease; HR, hazard ratio; NDD, non-dialysis dependent; pts, patients; RR, relative risk

**Risk Stratification for Stroke in AF with CKD**

Despite the increased risk of ischaemic stroke and thromboembolism due to AF, this risk is not homogeneous and depends on the presence of several common stroke risk factors. Stroke risk can be evaluated by clustering of various risk, factors leading to several stroke risk stratification schemes being derived.

A commonly used stroke scoring system has been the CHADS₂ score, confers 1 point to each risk factor, and for each point corresponds to an approximate factor of 1.5 fold increase in stroke rate per 100 patient-years. However, the CHADS₂ score has various limitations since been superseded by CHA₂DS₂-VASc score, which is
more inclusive of common risk factors and given various limitations of the CHADS₂ score in particularly in defining those at ‘low risk’.

The CHA₂DSVASc score (Table 3) is recommended by the European Society of Cardiology AF guidelines,⁵⁰ and on the other hand, performs better than the CHADS₂ score in predicting stroke and thromboembolism especially in identifying those truly ‘low risk’ patients with AF who will not benefit from antithrombotic therapy.³⁸,⁵¹ The European guideline recommended that anticoagulation is not needed if the CHA₂DSVASc score is 0 in males or 1 in females, as such patients are low risk. Subsequent to the identification of low risk patients, effective stroke prevention can be offered to those with ≥1 stroke risk factors, and thus, oral anticoagulation should be considered with those with a CHA₂DSVASc score of 1 and above.

However, CKD or moderate-severe renal impairment is not currently included in the CHADS₂ or CHA₂DSVASc scores, despite been recognised as a contributor to thromboembolic risk. This is due to the limited data (at least when the scores were being derived and/or validated) and the exclusion of those with significant renal impairment from the major clinical trials. Nonetheless, much more attention has been directed to CKD as a contributor to stroke risk given its co-existence with AF in many patients.

There are ongoing attempts to incorporate renal impairment into stroke risk stratification schemes. For example, Piccini et al.³² proposed a new model to include creatinine clearance into stroke prediction, with the R-CHADS₂ score, where the addition of “R” signifies impaired renal function, and adds 2 points to the CHADS₂ score. Piccini et al showed that impaired renal function is a strong and independent predictor of stroke and systemic embolism, the R-CHADS₂ score improved the CHADS₂ and CHA₂DSVASc scores (a statistical measure of how good a score predicts events, with 1.0 offering perfect prediction whilst a c-index of 0.5 is 50:50 chance), but only very marginally. Nonetheless, the R-CHADS₂ score was derived from an anticoagulated clinical trial population, and the independent impact of a stroke risk factor should be evaluated in a non-anticoagulated cohort. Also, the ROCKET-AF trial⁶⁵ excluded those with severe CKD (creatinine clearance <30mls/min) and did not recruit a wide spectrum of AF stroke risk, given that the trial inclusion criteria mandated a CHADS₂ score of ≥2 and the proportion with a score=2 was capped at 10%.

Similar relationship between renal impaired and stroke risk was suggested in the ATRIA stroke risk score,⁵³ and as well as the R-CHA₂DSVASc score (albeit in patients with prior myocardial infarction).⁷³ The studies in selected cohorts confirm some additive value of adding CKD or renal impairment to the CHADS₂ and/or CHA₂DSVASc scores, but again, only improved the c-indexes very marginally.

Additional studies in ‘real world’ AF cohorts that included non-anticoagulated AF patients with a broad range of stroke and renal function do confirm an increased even rate with CKD or moderate–severe renal impairment in AF patients, but this did not independently improve the predictive value of CHADS₂ and CHA₂DSVASc scores.⁵⁴,⁵⁵ After all, CKD is commonly associated with age, heart failure, diabetes, vascular disease etc – which are all components of the CHA₂DSVASc score.

### Risk Stratification for Bleeding in AF: The HAS-BLED Score

Stroke and bleeding risk in AF are closely related to each other. In the presence of AF, the European guidelines recommend the use of the HAS-BLED score for assessing bleeding risk (Table 4). A high HAS-BLED score is used to ‘flag up’ the patients potentially at risk of bleeding for careful review and follow-up, and to make clinicians think about the potentially correctable risk factors such as uncontrolled hypertension (the H in HAS-BLED) or labile INRs in those patients on warfarin. A high HAS-BLED score per se should not be a reason to withhold oral anticoagulation therapy.

In HAS-BLED, renal failure was defined in validation cohorts as those requiring long-term dialysis, renal transplant and serum creatinine over 2.26mg/dL, given the risk of bleeding diathesis. Nonetheless, a more simple and practical approach is to consider ‘abnormal renal function’ in HAS-BLED as those with severe renal impairment or significant proteinuria.

### Table 5: VKA use and stroke rates in ESRD

<table>
<thead>
<tr>
<th>Study / Year</th>
<th>Study Type</th>
<th>Number (% with AF)</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wiesholzer et al 58 (2001)</td>
<td>Retrospective observational</td>
<td>430 (14.3%)</td>
<td>Stroke rate per 100 patient year: AF with VKA: 4.46, AF without VKA: 1.0</td>
</tr>
<tr>
<td>Abbott et al 59 (2003)</td>
<td>Retrospective observational</td>
<td>3374 (1.25%)</td>
<td>3-year survival rate: AF with VKA: 70% AF without VKA: 55%</td>
</tr>
<tr>
<td>Chan et al 60 (2009)</td>
<td>Retrospective observational</td>
<td>48825 (3.42%)</td>
<td>90-day HR – AF with VKA: 2.75 (95% CI 1.49 – 5.08)</td>
</tr>
<tr>
<td>Winnelmayr et al 6162 (2011)</td>
<td>Retrospective observational</td>
<td>[2313 ESRD patients with new AF]</td>
<td>HR for ischaemic stroke: VKA user 0.92 (95% CI 0.61 – 1.37)</td>
</tr>
<tr>
<td>Olesen et al 63 (2012)</td>
<td>Subgroup analysis</td>
<td>[901 patients with AF requiring dialysis]</td>
<td>HR comparing with no antithrombotic, dialysis dependent pts.</td>
</tr>
<tr>
<td>Sood et al 6263 (2013)</td>
<td>Observational</td>
<td>Drugs (e.g., concomitant antiplatelet or NSAIDs) or alcohol excess/abuse</td>
<td>1 or 2</td>
</tr>
</tbody>
</table>

Abbreviations: AF, atrial fibrillation; CI, confidence interval; DOPPS, Dialysis Outcomes and Practice Pattern Study; HR, hazard ratio; VKA, Vitamin K antagonist; a AF with VKA covariate adjusted model: adjusted for CHADS2 score, gender, race, Charlson comorbidity index, entry date, body mass index, facility standardised mortality ratio, cardiovascular drugs, dialysis adequacy, baseline laboratory values, heparin dosage and heparin regimes.

b VKA user includes patients with atrial fibrillation, thromboembolic disease or central vascular catheter.

### Table 6: VKA use and stroke/thromboembolic event rate in non-dialysis dependent CKD

<table>
<thead>
<tr>
<th>Study / Year</th>
<th>Study Type</th>
<th>Number</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hart et al 64 (2011)</td>
<td>Post-hoc analysis</td>
<td>516</td>
<td>Stroke/embolic event rate (% per year): Dose-adjusted warfarin: 1.45 Dose-adjusted warfarin plus aspirin: 7.05</td>
</tr>
<tr>
<td>Olesen et al 34 (2012)</td>
<td>Subgroup analysis</td>
<td>3587</td>
<td>HR of stroke comparing with no antithrombotic NDD CKD: Warfarin only: 0.84 (95% CI 0.69 – 1.01) Warfarin plus aspirin: 0.76 (0.56 – 1.03) Aspirin only: 1.25 (1.07 – 1.47)</td>
</tr>
</tbody>
</table>

Abbreviations: CKD, chronic kidney disease; INR, international normalised ratio; NDD, non-dialysis dependent; VKA, vitamin K antagonist
Table 7: Randomised Controlled Trials for Novel (or non-Warfarin) Oral Antiocoagulants in AF

<table>
<thead>
<tr>
<th></th>
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<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number</strong></td>
<td>18113</td>
<td>5999</td>
<td>18201</td>
<td>14264</td>
<td>21108</td>
</tr>
<tr>
<td><strong>Dosage</strong></td>
<td>Dabigatran 150 mg twice daily</td>
<td>Apixaban 5mg twice daily</td>
<td>Apixaban 5mg twice daily</td>
<td>Rivaroxaban 20mg once daily</td>
<td>Edoxaban 60mg once daily</td>
</tr>
<tr>
<td></td>
<td>Dabigatran 110mg twice daily</td>
<td>Aspirin 81-324mg daily</td>
<td>Apixaban 2.5mg twice daily (eGFR &lt;50mL/min)</td>
<td>Rivaroxaban 15mg once daily(eGFR 30-49mL/min)</td>
<td>Dose-adjusted Warfarin</td>
</tr>
<tr>
<td>Dose-adjusted Warfarin</td>
<td></td>
<td></td>
<td>Dose-adjusted Warfarin</td>
<td>Dose-adjusted Warfarin</td>
<td>Dose-adjusted Warfarin</td>
</tr>
<tr>
<td><strong>F/U (months)</strong></td>
<td>24</td>
<td>13.2</td>
<td>21.6</td>
<td>23.5</td>
<td>Median F/U 2.8 years</td>
</tr>
<tr>
<td><strong>CKD stages studied</strong></td>
<td>eGFR 30-50mL/min, eGFR 50-70mL/min</td>
<td>eGFR 30-60mL/min, eGFR 50-69mL/min</td>
<td>eGFR 25-30mL/min, eGFR 31-51mL/min, eGFR 51-80mL/min</td>
<td>eGFR 30-49mL/min, eGFR 50-69mL/min, eGFR 60-80mL/min</td>
<td>eGFR 30 - ≤50mL/min</td>
</tr>
<tr>
<td><strong>Pharmacokinetics</strong></td>
<td>80% renally excreted</td>
<td>25% renally excreted</td>
<td>25% renally excreted</td>
<td>33% renally excreted</td>
<td>35% renally excreted</td>
</tr>
<tr>
<td><strong>Key Results/Event rate %/year</strong></td>
<td>Superior to warfarin in reducing ischaemic stroke and thromboembolism (1.11 vs 1.53 vs 1.69)</td>
<td>Superior to warfarin in reducing ischaemic stroke and thromboembolism (1.6 vs 3.7)</td>
<td>Superior to warfarin in reducing ischaemic stroke and thromboembolism (1.27 vs 1.6)</td>
<td>Non-inferior to warfarin in reducing ischaemic stroke and thromboembolism (2.2 vs 2.4)</td>
<td>Non-inferior to warfarin in both doses in reducing ischaemic stroke and thromboembolism (1.49 vs 1.91 vs 1.69)</td>
</tr>
<tr>
<td><strong>Non-inferior in bleeding events</strong></td>
<td>(3.11 vs 2.71 vs 3.36)</td>
<td>(3.11 vs 2.71 vs 3.36)</td>
<td>(1.4 vs 1.2)</td>
<td>(1.4 vs 1.2)</td>
<td>(1.4 vs 1.2)</td>
</tr>
<tr>
<td><strong>Outcomes for CKD pts</strong></td>
<td>No difference in primary outcome</td>
<td>Lower stroke risk with no increase in bleeding risk</td>
<td>Non-inferior in stroke risk, but reduced bleeding risk for eGFR &gt;30mL/min</td>
<td>No difference in primary outcome</td>
<td>Lower bleeding risk at reduced dose</td>
</tr>
</tbody>
</table>

Given that the risk of ischaemic stroke and thromboembolism is closely intertwined with bleeding risk amongst CKD patients, those with CKD might potentially receive greater absolute risk reduction of ischaemic stroke or systemic thromboembolism from anticoagulation, which outweighs the smaller absolute increase in serious bleeding risk.

**Oral Anticoagulation in CKD: Using Vitamin K Antagonists (VKA)**

Oral anticoagulants are generally indicated in the general population with AF, for stroke prevention. However, is it feasible for the same to be recommended for those with CKD? The current recommendations and guidelines are drawn from cohort studies and extrapolations of results from clinical trials in the general AF population, as little evidence exists for those with severe renal impairment given that such patients were excluded from randomised trials.

Unsurprisingly, the prescription of anticoagulants (essentially Vitamin K antagonists eg. warfarin) amongst those with significant renal impairment varies from as low as 2% in Germany to as high as 37% in Canada. This heterogeneity in clinical practice reflects the uncertainty about the risks and benefits of anticoagulation use within this patient group.

Amongst CKD patients undergoing dialysis, there remain significant conflicting findings from various observational studies regarding the safety associated with use of VKA (Table 5). Besides Abbott et al showing a mortality benefit and Olesen et al demonstrating a reduction event rate for stroke or thromboembolism, other studies involving ESRD and VKA thromboprophylaxis have even suggested that VKA can potentially cause harm in CKD patients with ESRD. Patients were exclude from randomised trials.

Large observational studies have demonstrated that dialysis patients who are on Warfarin experience more than two-fold increase in the risk of ischaemic stroke as compared to non-VKA users. As shown by Winkelmayer et al, this increase in stroke risk may be secondary to haemorrhagic stroke rather than thromboembolic cerebral events.

The other possible explanations for this increase in stroke risk amongst VKA users may be due to the lack of close monitoring of the International Normalised Ratio (INR) amongst at risk group during warfarin initiation, thus potentially resulting in reduced time in therapeutic range. Without further randomised control trials, the propensity for harm due to VKAs is yet to be fully understood.

Conversely, amongst non-dialysis dependent CKD patients, there appears to be more robust data favouring the use of dose-adjusted VKA in AF (Table 6). In all 3 observational studies, dose-adjusted warfarin provided better ischaemic stroke and systemic embolic protection, than non-users. However, the use of warfarin amongst the Danish study cohort appears to significantly increase the tendency of bleeding by 36%, the event rate was further increased with concurrent use of both aspirin and warfarin (63%).

**Novel Oral Anticoagulants**

Over the past few years, the landscape of stroke prevention in AF had dramatically changed with the introduction of novel (or non-warfarin) oral anticoagulant agents (NOACs), specifically the direct thrombin inhibitor (dabigatran) and Factor Xa inhibitors (rivaroxaban, apixaban and edoxaban).

All four agents have been shown non-inferiority or even superiority in stroke prevention, and non-inferiority (or in some cases, superiority) in bleeding profile as compared to warfarin. Similar data exists even for those with varying degree of reduced renal function (eGFR 30-50mL/min) (Table 7). For example, a subgroup analysis of the ARISTOTLE trial for the use of apixaban in patients with significant CKD (eGFR 30 - ≤50mL/min) had demonstrated a marked reduced bleeding risk, as compared to warfarin. Additional benefits include medication delivery in fixed doses, not requiring monitoring, and have a lower propensity for interaction with food or other medications.
The most important caveat in all these trials is such that patients with ESRD or significant CKD (with creatinine clearance ≤25-30mL/min) were all excluded, thus making the extrapolation of the results to those with severe renal dysfunction hazardous, particularly since all agents have a degree of renal excretion. The latter varies from approximately 25% renal excretion with apixaban, to 33% with rivaroxaban, to 50% with edoxaban and 80% with dabigatran.

Based on no clinical trial outcome data but pharmacological modelling in patients with a creatinine clearance of 15-29mL/min, dabigatran 75mg bid is approved for AF patients in USA for those with a creatinine clearance 15-30mL/min. Similarly rivaroxaban 15mg od and apixaban 2.5mg bid is approved for use in moderate renal impairment (15-29 mls/min), with caution advised with regard to watching for bleeding risk.

Another oral Factor Xa inhibitor, betrixaban is currently being studied in a Phase 3 randomised trial in acute medically ill patients (but not AF per se) but this drug is only minimally renal excreted.

Conclusions:

The management of patients with both CKD and AF is often difficult, as not only do these 2 conditions have a close relationship, with an increase in thrombotic and haemorrhagic risks with sequential reduction in renal function. The risk of both ischaemic and bleeding events are particularly high amongst dialysis dependent patients with ESRD. However, there is increasing evidence that anticoagulation use among non-dialysis dependent CKD patients with AF can reduce morbidity and mortality from stroke and systemic thromboembolism.

The key would be for careful patient selection through the utilisation of risk stratification scores (CHA₂DS₂-VASc and HAS-BLED scores). Even those with ESRD may potentially benefit from anticoagulation, provided that substantial steps are taken to reduce bleeding risk (such as rigorous INR checks, aiming for a high Time in Therapeutic Range, >70%)

With the rapidly aging global demographics, the burden of disease will only increase, but there still remains relatively limited evidence regarding thromboprophylaxis in those patients with the most severe renal dysfunction. Despite the great potential for NOACs, the latter varies from approximately 25% renal excretion with apixaban, to 33% with rivaroxaban, to 50% with edoxaban and 80% with dabigatran.

References:


Abstract

Atrial fibrillation (AF) is the most prevalent arrhythmia and its incidence is on the rise. AF causes significant morbidity and mortality leading to rising AF-related healthcare costs. There is experimental and clinical evidence from animal and human studies that suggests a role for the renin angiotensin system (RAS) in the etiopathogenesis of AF. This review appraises the current understanding of RAS antagonism, using angiotensin converting enzyme inhibitors (ACE-I), angiotensin receptor blockers (ARB) and aldosterone antagonists (AA), for prevention of AF. RAS antagonism has proven to be effective for primary and secondary prevention of AF in subjects with heart failure and left ventricular (LV) dysfunction. However, most of the evidence for the protective effect of RAS antagonism is from clinical trials that had AF as a secondary outcome or from unspecified post-hoc analyses. The evidence for prevention in subjects without heart failure and with normal LV function is not as clear. RAS antagonism, in the absence of concomitant antiarrhythmic therapy, was not shown to reduce post cardioversion AF recurrences. RAS antagonism in subjects undergoing catheter ablation has also been ineffective in preventing AF recurrences.

Introduction

Atrial Fibrillation (AF) is the most commonly encountered cardiac arrhythmia and affects 1% of the North American population. The prevalence of AF increases to 8–10% in people older than 80 years.1–4 AF independently increases the risk of heart failure, stroke, dementia and mortality. There is also a steep increase in AF related morbidity and hospital admissions with increasing age.5–11 The rising burden of AF and related health care costs are responsible for placing a heavy economic burden on health care systems around the world.12–16 Anti-arrhythmic medications and non-pharmacological interventions, such as catheter ablation, aimed at secondary prevention of AF have thus far been unsuccessful in curing AF.17,18 There is a pressing need for primary and secondary prevention strategies to reduce AF related morbidity, mortality and health care costs.19–21 This review appraises the role of the Renin-Angiotensin system (RAS) in the etiopathogenesis of AF and the evidence for therapeutic RAS blockade in primary and secondary prevention of AF.

The Renin Angiotensin System And Human Atrial Fibrillation

RAS is an important neuro-endocrine/paracrine system involved in the regulation of multiple cardiovascular, pulmonary and renal processes in humans.22 Systemic hypertension and heart failure are the most important risk factors associated with the development of AF.3,6,23,24 The activation of RAS plays an integral part in the neurohumoral processes leading to changes seen in systemic hypertension and heart failure. There is some evidence to suggest that RAS is associated with the development of AF in subjects with systemic hypertension and heart failure.22,25,26 In addition multiple RAS gene polymorphisms have been linked to the development of AF in subjects with known conditions that directly or indirectly result in increased left atrial pressure, such as systemic hypertension or heart failure.27–32 Analysis of human atrial myocytes in subjects undergoing cardiac surgery has demonstrated increased tissue levels of angiotensin converting enzyme (ACE) and angiotensin II (AT-II) receptors in subjects with AF compared to those in sinus rhythm.33 Reduced density of AT-II -type 1 receptors, responsible for atrial fibrosis subjects with AF, was also noted and this was thought to be secondary to down regulation in response to high tissue ACE levels.34 The activation of RAS with consequent electrical and ultrastructural changes, called “atrial remodeling”, is thought to play a role in the development of AF in humans.
Postulated Mechanisms Linking The Renin Angiotensin System And Atrial Fibrillation (See Table 1)

Activation of RAS in hypertension and heart failure results in Angiotensin II mediated elevation in left atrial (LA) pressure, secondary to rise in left ventricular end diastolic pressure (LVEDP).35-37 Atrial dilatation is associated with stretch related alteration in ion-channels that is believed to be responsible for electrophysiological changes such as shortened refractory periods (electrical remodeling).38-41 Prolonged activation of RAS results in high myocardial tissue levels of ACE and density of AT-II receptors triggering inflammation and fibrosis. These effects are mediated by fibroblast-derived cytokines such as transforming growth factor-β (TGF-B) and AT II receptor activated phosphorylation cascade causing release of mitogen-activated protein kinases (MAPK). Extensive atrial collagen deposition results from uncontrolled extracellular matrix metabolism and angiotensin II mediated modulation of matrix –metalloproteinases (structural remodeling). AF is considered to be one of the clinical manifestations of atrial remodeling.22,25,42,43 Animal models of rapid atrial pacing induced AF have shown high atrial tissue levels of ACE, chymase and angiotensinogen. Increased production of tissue level AT II mediated by paracrine activation of ACE, chymase and angiotensinogen is also thought to be responsible for atrial remodeling leading to AF. The cascade of events leading up to AF has been summarized in Figure 1.

Interruption of key steps in the RAS cascade (RAS antagonism) using angiotensin converting enzyme inhibitors (ACE-I), angiotensin-II receptor blockers (ARB) and aldosterone antagonists (AA) has been shown to reverse some of the electrical and ultrastructural changes in patients with AF.44-46 The important basic science data has been summarized in Table 1.

The Renin Angiotensin System Gene Polymorphisms And Atrial Fibrillation

The evidence linking RAS to atrial remodeling in AF and the inherent variation among individuals with respect to the extent and consequences of RAS activation had led investigators to suspect a role for genetic polymorphisms in the ACE gene. The human

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Author</th>
<th>Experimental Model</th>
<th>Main Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Electrical Remodeling</td>
<td>Wijffels MC, et al.44</td>
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AERP: Atrial effective refractory period; AF: Atrial fibrillation; iCaL: long acting L-type calcium ion channel; AT-II: Angiotensin II; MI: Myocardial infarction; TGF: Transforming growth factor


**Renin Angiotensin System (RAS) in the Etiopathogenesis of AF**

ACE gene is situated in chromosome 17q23.3 and demonstrates a polymorphism consisting of insertion (I) or deletion (D) in the intron. Consequently three genotypes are encountered in human populations—homzygous D/D and I/I and heterozygous I/D. ACE I/D polymorphism accounts for half of the variance noticed in ACE levels in humans, with the D/D alleles manifesting highest levels of the enzyme. The I/D heterozygous polymorphism has been associated with cardiovascular diseases including left ventricular hypertrophy, essential hypertension, dilated cardiomyopathy and myocardial infarction. ACE I/D polymorphism has been shown to increase the risk for development of AF in case-control studies. ACE I/D polymorphism has been shown to be associated with poor response to anti-arrhythmic medications in subjects with AF. ACE D/D polymorphisms have also been identified in certain cases of nonfamilial AF. A recent meta-analysis of case-control studies failed to demonstrate a significant association between the ACE I/D polymorphism and AF risk. However, there was a significant association noted between the I/D polymorphism and AF risk in subjects with hypertension. Another prospective study evaluating 238 consecutive subjects with paroxysmal or persistent AF undergoing catheter ablation found that the ACE D/D homozygous gene variant to be associated with an increased risk of post ablation AF recurrence.

The aldosterone synthase (CYP11B2) T-344C gene polymorphism and resultant raised aldosterone levels have been independently linked to an increased risk of AF in subjects with symptomatic heart failure (left ventricular ejection fraction <40%). A more recent case-control study in 620 Chinese subjects showed that the aldosterone synthase (CYP11B2) T-344C gene polymorphism (the CC homozygous allele) was associated with echocardiographic markers of atrial remodeling in hypertensive subjects. However, the distribution of the different alleles of this gene (TT/TC/CC) did not differ among hypertensive and normotensive subjects.

**Renin Angiotensin System Antagonism And Primary Prevention Of Atrial Fibrillation (Table 2)**

**Heart Failure Trials**

A Retrospective, sub-group analyses from multiple large trials evaluating the role of RAS antagonism in subjects with heart failure and LV systolic dysfunction have found a lower incidence of new-onset AF. Systematic reviews of these studies have demonstrated a 21-50% risk-reduction for new-onset AF in heart failure subjects receiving RAS antagonists. However, RAS antagonism in subjects with heart failure and preserved LV systolic function has not shown benefit in preventing new onset AF.

**Systemic Hypertension Trials**

Systematic review of hypertension trials found a 25% reduction in new-onset AF. This was principally due to a 33% reduction noted in one trial evaluating losartan for AF prevention.

**Post Myocardial Infarction Trials**

Two trials have evaluated the incidence of new-onset AF in subjects treated with RAS antagonists following myocardial infarction (MI). Subjects with impaired LV function following MI had lower incidence of AF after treatment with trandolapril. The GISSI-3 trial reported a lower incidence of new-onset AF in post MI subjects treated with lisinopril. However, about a third of subjects showed AF on their admission EKG bringing into question whether this study truly evaluated RAS antagonism for primary prevention of AF.

**Subjects With Multiple Cardiovascular Risk Factors**

RAS antagonism (ramipril and telmisartan) for prevention of major adverse cardiac events in patients with multiple cardiovascular risk factors has not shown a reduction in the incidence of AF.

**Post-Cardiac Surgery Trials**

A prospective, multicenter analysis of subjects who had undergone coronary artery bypass graft (CABG) surgery found that postoperative use of ACE-I was associated with reduction in new-onset AF. A randomized trial in subjects undergoing cardiac surgery demonstrated that the use of ACE-I or the combination of ACE-I and candesartan reduced postoperative AF. However, this trial enrolled a relatively small number of subjects (N ≠ 60) and was not adequately powered to answer the primary hypothesis that RAS antagonism was capable of reducing the incidence of AF post cardiac surgery. Subgroup analyses from two large retrospective observational studies in patients undergoing cardiac surgery failed to demonstrate a protective effect for RAS antagonism.

**Renin Angiotensin System Antagonism And Secondary Prevention Of Atrial Fibrillation (Table 3)**

**Prevention Of Paroxysmal And Recurrent Persistent AF**

The GISSI-AF trial did not demonstrate an additional benefit for adding ARB (Valsartan) to ACE-I therapy for prevention of AF recurrence. Three recent trials evaluating the role of RAS antagonism (J-RHYTHMII, Fogari et al. and ANtipAF) showed conflicting results, with two of the trials (J-RHYTHM II and ANtipAF) failing to show any benefit of RAS antagonism for...
secondary prevention of AF.\(^2\)\(^3\)\(^4\)\(^5\) RAS antagonism does not seem to be effective for secondary prevention of AF in subjects without structural heart disease or LV dysfunction.

**Prevention Of Recurrent AF After Catheter Or Surgical AF Ablation**

RAS antagonism following catheter ablation has not proven to be effective in reducing AF recurrence.\(^8\)\(^3\)\(^4\) In contrast a recent study in subjects undergoing minimally invasive surgical ablation for AF showed that Irbesartan reduced the incidence of AF recurrence.\(^6\)

**Prevention Of Paroxysmal And Recurrent Persistent AF**

Multiple small prospective, randomized trials have demonstrated the benefit of RAS antagonism for preventing post cardioversion recurrence, in subjects with persistent AF. The benefit of RAS antagonism in this setting is complementary to concomitant antiarrhythmic medications, usually with amiodarone.\(^8\)\(^7\)\(^8\) A well-designed prospective, randomized-controlled trial (CAPRAF) failed to demonstrate the efficacy of candesartan for preventing post cardioversion AF recurrence. In contrast to the previously mentioned trials patients in the CAPRAF trial did not receive concomitant antiarrhythmic medications before and after cardioversion.\(^4\)\(^5\)

**Conclusions:**

There is experimental and clinical evidence from animal and human studies that suggests a role for RAS in the etiopathogenesis of AF. Genetic polymorphisms of the ACE and aldosterone synthase genes have been linked to the development of AF in subjects with pre-existent risk factors for AF such as systemic hypertension and heart failure. RAS antagonism has shown to reduce the incidence of AF in subjects with heart failure and left ventricular (LV) dysfunction. However, most of the evidence for the protective effect of RAS antagonism is from clinical trials that had AF as a secondary outcome or from unspecified post-hoc analyses. The evidence for prevention in subjects without heart failure and normal LV function is not as clear. RAS antagonism, in the absence of concomitant antiarrhythmic therapy, was not shown to reduce post cardioversion AF recurrences. RAS antagonism in subjects undergoing catheter ablation has also been ineffective in preventing AF recurrences. There is need for ongoing research to identify novel targets for intervention and develop effective therapeutic agents to combat the rising burden of AF.

**References:**

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Table 3: Summary of clinical studies evaluating RAS antagonism for secondary prevention of AF

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Mi: Myocardial infarction; RCT: Randomized controlled trial; AF: Atrial fibrillation; AHT: Anti hypertensive treatment; BB: Beta blockers; CCB: Calcium channel blockers; ACE-I: Angiotensin converting enzyme; ARB: Angiotensin receptor blocker


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The Evolving Utility Of Intracardiac Echocardiography In Cardiac Procedures

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Abstract

Intracardiac echocardiography (ICE) has gained increasing use in electrophysiology due to the need to visualize key anatomic structures. Precise guidance for transseptal puncture and visualization of the pulmonary veins are common essential uses for ICE, but many operators adept at ICE imaging have developed additional and specific uses. With heavy use of ICE guidance, electrophysiologists demonstrated feasibility of left atrial ablation with minimal use of fluoroscopy. With the advent of 3D mapping-integrated ICE, rendering of contours for the left atrium, aortic cusps, and left ventricular structures such as the papillary muscles have become possible. Improved understanding of the anatomy of these areas can facilitate mapping and ablation of these structurally complex sites. Additional uses of scar-visualization and integration into voltage maps have been explored. Left atrial appendage imaging has been an area of interest in the ICE community, although technological improvements are likely needed to make this more reliably complete. A new real-time 3D ICE catheter has also been developed, and work is in progress to delineate potential uses for this new frontier. Increasingly routine use of ICE has led to improved real-time guidance of all percutaneous cardiac procedures.

Imaging in Electrophysiology

As the field of cardiac electrophysiology continues to mature, it has become increasingly recognized that arrhythmias have unique relationships with anatomic structures of the heart and great vessels. Haissaguerre and colleagues made the seminal observation that atrial fibrillation (AF) was often triggered from the pulmonary veins (PVs). Atrial arrhythmia foci are also frequently found at the crista terminalis, superior vena cava (SVC), coronary sinus (CS), and the tricuspid and mitral valve annuli. Idiopathic ventricular arrhythmias commonly arise from the right ventricular outflow tract (RVOT), the aortic cusps, and papillary muscles. Ventricular tachycardias in cardiomyopathy tend to involve areas of myocardial scar, which may be endocardial, epicardial, or intramural. Accordingly, it is essential for physicians who perform electrophysiology procedures to gain precise knowledge of cardiac anatomy, and real-time imaging of these structures and their variations among individuals is a fundamental skill to achieve safe and effective ablation procedures.

Since its initial development for facilitating device closure of atrial septal defects, intracardiac echocardiography (ICE) has seen a significant adoption by electrophysiologists as an important tool to reduce dependence on fluoroscopy. Importantly, ultrasound allows identification of soft tissue structures that are invisible with fluoroscopy. Thus, the fossa ovalis can be visualized and transseptal puncture can be more precisely directed toward the left pulmonary veins – thereby avoiding an anterior trajectory (to reduce risk of aortic perforation) and facilitating catheter stability in the pulmonary veins (to improve the efficacy of ablation). In the beating heart with respiratory motion, maintaining optimal catheter-tissue contact is essential to achieve successful ablation of any arrhythmia, and ICE provides live visualization of catheter positioning and tissue contact. Finally, routine use of ICE allows the immediate recognition and expedited management of complications such as pericardial tamponade and thrombus formation on catheters and sheaths.

Comparison of Intracardiac vs. Transesophageal Echocardiography

Prior to the advent of ICE catheters, live ultrasound guidance of percutaneous cardiac procedures was limited to transesophageal echocardiography (TEE). TEE remains the sole ultrasound imaging method in many electrophysiology laboratories due to the higher cost of ICE catheters, which has diminished with reprocessing of...
Besides the common uses listed above, other uses of ICE have evolved in electrophysiology and non-electrophysiology procedures.

**Integration of ICE into the 3D Mapping System**

A major technological advance in this field was the development of an ICE catheter integrated into a 3D mapping system. The SoundStar® catheter contains a location sensor embedded within the ICE catheter, which allows the ultrasound image to be displayed and integrated into the electroanatomic mapping system. This CartoSound® module then allows tagging of structures visualized on the projected ICE image to be displayed on the 3D map. This breakthrough has bridged the gap between the aforementioned critical understanding of anatomy and electrophysiologic targets. For AF ablation, drawing contours of the left atrium and pulmonary veins creates a shell of the left atrium without the additional need for preoperative imaging or even transseptal access. Tagging the esophagus provides additional appreciation for its proximity to certain aspects of the posterior wall. For VT ablation, with the ICE catheter placed in the right ventricle, anatomic contours can be obtained for the left ventricle and papillary muscles to facilitate catheter movement with reduced need for fluoroscopy. Given the tilted position of the aortic cusps, mapping and ablation of arrhythmias in this region has been greatly simplified by the use of 3D mapping-integrated ICE, which allows tagging of the individual cusps and essential appreciation for the precise location of the mapping/ablation catheter relative to the commissures (Figure 1). Just as importantly, visualization of these sterile catheters. With regard to imaging capability, TEE continues to have the advantage of multipane imaging – where an electrical mechanism rotates the imaging plane up to 180° to provide a continuum of imaging planes with a single probe position. More recently, the advent of 3D TEE probes has allowed real-time 3D imaging of complex structures such as the pulmonary veins, left atrial appendage, and valves. However, TEE entails a different risk profile due the requirement for moderate sedation, so that patients with sedation risk, compromised airways, or known oral or esophageal abnormality are at increased risk of complications including oropharyngeal trauma, esophageal perforation, and aspiration pneumonitis. Furthermore, intra-procedural TEE-guidance requires general anesthesia due to lengthy duration of imaging, and requires the presence of a TEE specialist which adds to the cost of the procedure even though there is no incremental cost for use of the TEE equipment.

ICE catheters contain imaging elements (piezoelectric crystals) arranged either in circumferential fashion (radial ICE) or in linear fashion (phased array ICE). Most electrophysiology laboratories have adopted the phased array ICE catheters, in which the imaging plane is parallel to the catheter orientation. Simple manual rotation of the catheter can rotate/sweep the imaging plane 360° to provide circumferential view of the catheter proximity. Since the heart is a relatively small structure, relatively small movements of the ICE catheter can provide basic imaging of nearly all cardiac structures, although experience is needed to place the ICE catheter in more difficult locations for more comprehensive imaging of some structures. Ultimately a significant advantage of ICE is the control provided to the electrophysiologists performing the procedure, besides obviating the need for an additional TEE physician. Furthermore, since ICE imaging is done with standard venous access, this can be performed safely with local anesthesia and minimal sedation, even during prolonged imaging, with minimal patient discomfort.

**Emerging Uses of ICE**

Physicians adept at ICE have demonstrated that transseptal puncture and left atrial ablation can be performed with little to no fluoroscopy. This has greatly simplified the procedure, besides obviating the need for an additional TEE physician. Furthermore, since ICE imaging is done with standard venous access, this can be performed safely with local anesthesia and minimal sedation, even during prolonged imaging, with minimal patient discomfort.
ICE in Specific Ablation Procedures

As cryoballoon PV isolation is increasingly adopted, additional tools have been sought to guide the fundamental technique of this procedure: balloon occlusion of the pulmonary veins. Color Doppler from ICE imaging provides a relatively simple and effective method of assessing for leaks without the need for radiocontrast or fluoroscopy (Figure 3). Cavotricuspid isthmus ablation can be difficult due to anatomic variants such as a large pouch or a prominent Eustachian valve; these can be visualized on ICE and appropriate catheter adjustments can be made (Figure 4). Although no comparative studies are available, expeditiously making these necessary adjustments likely reduces ineffective ablation lesions and thereby may reduce complications such as perforation and injury to the right coronary artery.

ICE Imaging of the Left Atrial Appendage

Given the routine need in electrophysiology to assess for thrombus in the left atrial appendage (LAA), there has long been interest in utilizing ICE for this purpose in lieu of the gold standard TEE. However, due to proximity of the esophagus to the left atrium and the aforementioned power of multiplane imaging provided by TEE, it has been difficult to achieve similarly clear and complete imaging of and tagging of the coronary artery ostia helps the operator avoid unintended catheter advancement and ablation without need for additional arterial access or repeated contrast angiography. Mapping and ablation on the papillary muscles are also greatly facilitated by 3D-mapping integrated ICE due to the complexity of these structures (Figure 2). Routine tagging of the pulmonic valve annulus has demonstrated that many presumed RVOT arrhythmias in fact originate from pulmonary artery myocardium beyond the valve.

In an attempt to localize scar and provide the critical link between substrate and ablation target, Bunch and colleagues demonstrated a novel use for 3D mapping-integrated ICE. Areas of wall motion abnormality on ICE were tagged in the 3D map, and were found to correlate with areas of low voltage by catheter mapping. This provides a potentially powerful tool to localize potential targets of VT ablation prior to even entering the left ventricle.
the LAA with ICE, since ICE imaging depends heavily on operator skill. The high stakes nature of stroke prevention also increases the threshold for replacing the standard approach in this regard.10

Detailed scanning of the LAA from the right atrium is usually not possible due to intervening structures including the interatrial septum, aortic root, and pulmonary artery – all of which progressively attenuate the ultrasound beam and thereby cause reduction of the image resolution. In the ICE-CHIP study, ICE imaging of the LA body was excellent, but imaging of the LAA was overall inferior to TEE.11 Therefore, clear visualization of the LAA – particularly the distal portions where thrombus usually resides – requires placement of the ICE catheter in a structure adjacent to it: the left atrium proper (and left superior pulmonary vein), the coronary sinus, the right ventricular outflow tract, or the pulmonary artery (Figure 5).12 When transseptal access is already obtained, ICE imaging from the left atrium is relatively simple.13 However, ICE placement in the mid coronary sinus can be difficult and requires experience in order to avoid perforation with the relatively stiff ICE catheter. On the other hand, ICE placement into the RVOT is relatively simple, and clockwise rotation of the imaging plane leftward and superiorly provides excellent views of the distal LAA (Figure 5 bottom), although parts of the LAA neck may be obstructed from view by the aortic root. Finally, comprehensive scanning of the LAA is most reliably obtained with the ICE in the proximal pulmonary artery, but this position is difficult to reach with the current generation of stiff ICE catheters due to concern for perforation of the anterior RVOT. Again, in order to compensate for the lack of mechanized multiplane imaging, multiple manual scans of the imaging plane through the complex anatomy of the LAA is required with ICE, and a combination of the aforementioned approaches may be necessary in order to image the entire length of the LAA to definitively rule out thrombus. Further improvement in the technology of ICE catheters – including miniaturization, improvement in steering mechanisms, and 3D imaging – should increase the feasibility of complete LAA imaging in the future.

ICE in Non-Electrophysiology Procedures

With the growth of percutaneous interventions for structural heart disease, ICE has also found a natural fit for procedures besides ASD closures which require prolonged real-time imaging guidance. Bartel and colleagues reported a randomized study comparing ICE with TEE for guidance of transcatheter aortic valve replacement (TAVR).14 ICE provided continuous visualization of the area of interest with less need for repositioning, since it does not obstruct fluoroscopic views. Both coronary ostia were more frequently visualized by ICE than by TEE. Measurements made with ICE correlated well with pre-procedural TEE measurements. They concluded that ICE guidance for TAVR is feasible and probably equivalent to TEE. Similar to electrophysiologists before them, there will likely be increasing motivation for interventional cardiologists to gain comfort with using ICE as percutaneous structural heart interventions become more routine.

Real-Time 3D ICE

Since the introduction of matrix array probes, 3D TEE has become standard practice in assessing valves and guiding structural heart procedures. A volumetric 3D ICE catheter has been developed for clinical use as well,15 but the 3D imaging sector (22° x 90°) is relatively narrow compared with 3D TEE, and with added cost, introduction into clinical use has been slow. Potentially, real-time 3D ICE would provide better perception of depth while visualizing pulmonary veins, aortic cusps, and papillary muscles, as well as better appreciation of catheter orientation (Figure 6). If the 3D imaging frame rate is high enough, it could even allow efficient real-time guidance of catheter manipulation.

Conclusions:

Intracardiac echocardiography (ICE) has unique advantages for real-time use during electrophysiology and other percutaneous cardiac procedures. ICE provides the operator independence and flexibility with regard to structural and functional characteristics, which are essential to guide the procedure as well as monitor the patient. Integration of ICE into the 3D mapping system has improved electrophysiologists’ appreciation for anatomical correlates to various arrhythmias. Increased dexterity with catheter manipulation to achieve desired views creates evolving roles for ICE, including assessing the left atrial appendage and guiding TAVR. Emerging technological progress such as volumetric 3D ICE imaging will improve real-time visualization and potentially reduce need for fluoroscopy even further.

References:


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Abstract
Atrial fibrillation (AF) is associated with substantial structural changes at cell and tissue level. Cellular hypertrophy, disintegration of sarcomeres, mitochondrial swelling and apoptosis have been described as typical histo-morphologic alterations in AF. Main initiators for cellular alterations in fibrillating atrial myocytes are cytosolic calcium overload and oxidative stress. Calpains are intracellular Ca2+- activated proteases and important mediators of calcium overload. Activation of calpains and down-regulation of the calpain inhibitor, calpastatin, contribute to myocardial damage in fibrillating atria. Thus, deregulations of the expression, activity, or subcellular localization of calpain within atrial myocytes have been established as important mediators of atrial myopathy during AF.

Molecular Structure And Regulation Of Calpains And Calpastatin
Calpains are intracellular Ca2+- activated proteases and important mediators of the actions of calcium. The regulated cleavage by calpain is critical in a variety of calcium-regulated cellular processes such as muscle contraction, neuronal excitibility, secretion, signal transduction, cell proliferation, differentiation, cell cycle progression, and apoptosis. Deregulation of calpain caused by a disruption of calcium homeostasis during cardiac pathologies such as atrial fibrillation, heart failure, hypertrophy, or ischemia reperfusion, critically contributes to myocardial damage.

The term “calpain” was originally used for classical µ- and m-calpains that are heterodimers composed of a large 80 kDa catalytic subunit encoded by either CAPN1 for µ-calpains (calpain 1), or by CAPN2 for m-calpains (calpain 2), and a common 30 kDa regulatory subunit encoded by CAPNS1 (calpain 4). Whereas the small subunit is identical for both enzymes, the large subunits share 55-65% sequence homology. The µ- and m-calpains differ in their requirements of intracellular Ca2+, which need to be micromolar and millimolar in concentration, respectively. Based on sequence homology, 14 human genes have been identified as members of the calpain large catalytic 80 kDa family, and 2 human genes for the small regulatory 30 kDa family.

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Key Words:
Atrial Fibrillation, Calpain, Calcium, Protease, Pathophysiology.
play a regulatory role in important processes including remodeling of cytoskeletal proteins, modulation of signal transduction pathways, degradation of cell cycle-regulating enzymes, regulation of gene expression, and initiation of apoptotic pathways. The proteolytic activity of calpains is not specific for certain amino acid residues or motifs, but recognizes the overall three-dimensional structure of its substrates. Many proteins have been identified as potential substrates of calpain. These include a large number of cytoskeletal and myofibrillar proteins (myosin, troponin, tropomyosin, titin), membrane-associated proteins (receptors, ion channels), metabolic enzymes, signaling-modulated kinases and phosphatases (PKC, calcineurin), transcription factors (NF-κB), and proteins involved in apoptotic signaling.

Under physiological conditions, the activity of calpain is tightly regulated. Regulatory mechanisms include the existence of a specific endogenous inhibitor, calpastatin. The binding of calpastatin to calpain is calcium-dependent and reversible. Calpastatin contains four equivalent inhibitory domains, each bearing three conserved regions (A, B, and C). The regions A and C bind to domain IV of the large subunit and to domain VI of the small subunit of calpain, respectively. The region B shows inhibitory activity itself. Both μ- and m-calpains exhibit similar sensitivity to calpastatin. The presence of the two calmodulin-like domains IV and VI are necessary for effective inhibition of calpastatin. Thus, calpastatin can inhibit only dimeric calpain like μ-, m-calpain, and calpain. The atypical calpains are resistant to the inhibitory actions of calpastatin. The cloning and molecular characterization of calpastatin revealed the existence of potential phosphorylation sites for protein kinase C, cAMP- and cGMP-dependent protein kinase, and casein kinase II. Thus, these motifs are supposed to play an important role in molecular regulation of the calpain/calpastatin system.

An additional mechanism for regulation of calpain activity is its phosphorylation by protein kinase A (PKA) or by extracellular-signal regulated kinase (ERK). Glading et al. provided evidence that m-calpain can be activated after direct phosphorylation at Ser-50 by ERK in the absence of cytosolic calcium influx. However, more recent studies indicated that the phosphorylation of calpain by ERK and PKA regulates the enzyme indirectly by controlling its cellular redistribution. The phosphorylation by ERK promotes the translocation of m-calpain to the membrane and the binding to phospholipids which in turn facilitates the activation of calpain. In contrast, PKA-dependent phosphorylation of calpain at Ser-369 prevents domain movement and the formation of the calpain active site.

Most recently, it was shown that intracellular acidosis attenuates the activation of calpain. The study by Inserra et al. demonstrated that the prolongation of intracellular acidosis during reperfusion by either post-conditioning or by acidic perfusion of isolated rat hearts has cardioprotective effects through inhibition of calpain activation. Further investigations are necessary to demonstrate a relation between delayed acidosis and the putative involvement of kinases in the cardioprotective mechanisms.

Finally, results of many in vitro and in vivo studies support the potential value of cardioprotective strategies based on interfering with calpain activation. The first generations of synthetic calpain inhibitors inactivate calpains by forming a covalent bond within the active site of the calpain catalytic domain (E-64, leupeptin, ALLN, ALLM), or by interacting with the Ca2+-binding domain of the calpain large subunit (PD150606). Persisting problems resulting from low membrane permeability and target selectivity led to the continuing development of calpain inhibitors. Several studies have used screening approaches to identify novel calpain inhibitor templates, and these have produced a wide range of peptidic, peptidomimetic, and non-peptide inhibitors. They target the active site of calpain and exhibit an improved pharmacokinetic profile.

Amongst the synthetic calpain inhibitors developed so far, calpastatin peptide analogues and their truncated versions stand out due to their unique selectivity and affinity profile. Calpastatin is the only known inhibitor with absolute specificity for both μ- and m-calpains, but its large molecular mass (110 kDa), making it membrane-impermeable, limits its therapeutic use.

**Regulation Of Calpains In Fibrillating Atria**

Pathophysiologically, atrial fibrillation (AF) goes along with profound changes of the electrophysiologic and structural appearance of atrial tissue. Previous studies have shown that AF is characterized by an initial intracellular calcium overload, which causes atrial electrical remodeling. In addition, abnormal calcium handling during AF contributes to mechanical atrial dysfunction after successful cardioversion. The histopathology of fibrillating atria is similar to that of chronically ischemic ventricular myocardium. Ischemia/reperfusion injury is mediated by increased levels of cytosolic calcium, which causes activation of the calcium-dependent proteases μ- and m-calpain.

**Contribution Of Calpains To The Contractile Dysfunction During AF**

Recent data imply that activation of μ-calpain leads to the destruction of contractile filaments in fibrillating atria. In samples from 32 patients (16 with chronic AF, 16 with sinus rhythm; SR) the atrial expression of μ- and m-calpain, calpastatin, troponins T (TnT), and C (TnC) were determined. Expression of μ-calpain was increased during AF (461±201% vs 100±34%; p<0.05). Amounts of m-calpain and calpastatin remained unchanged. Total calpain enzymatic activity was more than doubled during AF (35.2±17.7U vs 12.4±9.2U; p<0.05). In contrast to TnC, TnT levels were reduced in fibrillating atria by 26% (p<0.05) corresponding to a myofilament disintegration as observed by electron microscopy. In accordance with previous studies, μ-calpain had no effect on TnC levels. In contrast to previous ischemia/reperfusion models, small fragments of TnT were not detected.

Loss of a regular sarcomere structure would help to explain the prolonged mechanical dysfunction of the atria after successful cardioversion of AF. Mechanical atrial dysfunction can last for several weeks after cardioversion. Schotten et al. have demonstrated that there is a strong correlation between the maximum force of contraction and sarcomere content in atrial muscle preparations. Recent, down-regulation of L-type calcium–channels and altered intracellular calcium handling have been implicated in the pathogenesis of contractile dysfunction during AF. An ex vivo study on HL-1 atrial myocytes showed that 24h electrical field stimulation at 5 Hz reduced plasmalemmal levels of L-type Ca2+ channel1C subunit by ~72% compared to controls, whereas the amounts of the potassium channel subunits Kv4.3 and Kv1.5 were not changed. Although changes in number and/or function of L-type calcium–channels seem to contribute predominantly to the reduced contractility during AF, the time-course of resolution...
Crosstalk between apoptotic and necrotic pathways and activation of caspase-7 being just one recent example. Nevertheless, it still needs to be verified that the described molecular events of ALLM directly influence the occurrence/persistence of AF. In conclusion, activation of μ-calpain (calpain 1) may well contribute to structural remodeling and contractile dysfunction of fibrillating atria. However, in addition to these intracellular changes, interstitial collagen accumulation as well as atrial dilatation may further contribute to sustained alterations of the atrial contractile performance.

Calpains Trigger Pro-Apoptotic Processes During AF

Rapid pacing induced marked structural changes; myolysis and nuclear condensation, paralleled by a 14-fold increase in calpain activity. Interestingly, inhibition of calpain prevented myofibril degradation and nuclear condensation. Li et al. show that the inhibitor of μ-calpain, ALLM, diminishes the extent of apoptotic cell death in an in vivo canine model of AF. They showed that inhibition of μ-calpain is able to reduce the rate of apoptosis (apoptosis index) and caspase expression as otherwise significantly increased after 3 weeks of atrial pacing. Anti-apoptotic proteins like bcl2 recovered in response to ALLM therapy. This is indicative of calpain activity being upstream of mitochondrial apoptotic pathways. Thus, the present paper using an in vivo model provides first evidence that inhibition of μ-calpain prevents pacing induced apoptosis. This finding has important implication since increased rate of apoptosis might affect the electrical and mechanical properties of fibrillating atrial tissue. Nevertheless, it still needs to be verified that the described molecular effects of ALLM directly influence the occurrence/persistence of AF or the mechanical atrial function.

The μ-calpain cleaves a variety of proteins to promote apoptosis with caspase-7 being just one recent example. However, there is apparent crosstalk between apoptotic and necrotic pathways and activation of calpain promotes apoptosis even during caspase inhibition. In the heart, caspase–independent induction of apoptosis has been recently shown to occur via the release of apoptosis-inducing factor (AIF) from mitochondria. This process was shown in other tissues to be mediated by elevated intracellular Ca2+-levels or μ-calpain. Interestingly, results of the present study are confirmed by data from previous studies obtained ex vivo. The pacing-induced reduction of L-type Ca2+-channel protein was fully prevented by treatment with verapamil, the active stereoisomer of methoxyveramil D600, the calpain inhibitors PD150606 and E64d, and LaCl. Interestingly, PD150606, E64d, but not verapamil, prevented structural changes such myofibril degradation, or nuclear condensation. Swelling and disruption of mitochondria are typical morphologic findings in fibrillating atrial tissue. Mitochondrial dysfunction and concomitant opening of the permeability transition pore are strongly correlated with cell death, and interventions to prevent pore opening have been shown to protect the myocardium. AF causes severe damage of mitochondrial structure and provokes mitochondrial dysfunction, which is in part due to the frequency–dependent intracellular Ca2+-overload. Accordingly, verapamil has been shown to preserve mitochondrial structure and function. The critical requirement for mitochondrial participation in the death process is underscored by the protective effect of the mitochondrial ATP-sensitive potassium channel in preconditioning. This channel has been suggested to preserve calcium homeostasis and would, therefore, limit calpain activation. Recent studies revealed the presence of m-calpain, and μ-calpain, and calpain 10 within mitochondria. Calpain 10 has been linked to Ca2+-induced mitochondrial dysfunction and its capability to cleave complex I proteins may contribute to β-cell death in diabetes. Intracellular Ca2+-overload as observed in AF activates mitochondrial calpains and promotes apoptotic cell death via a multitude of actions excellently reviewed by Kar et al.
Interaction With Other Calcium-Dependent Signalpathways During AF

Altered intracellular calcium homeostasis and activation of atrial renin-angiotensin-system have been identified as important factors contributing to the oxidative stress in the endocardium of fibrillating atrial tissue. Elevated levels of intracellular Ca2+ and reactive oxygen species (ROS) are major activators of the immediate early response transcription factor NF-αB, which is a redox sensor in atrial tissue. Typical target genes of NF-αB are pro-inflammatory cytokines such as interleukin-8 and tumor necrosis factor α (TNF-α), but also the endothelial adhesion molecules 82,84. Interestingly, regulation of NF-kappaB signaling is linked to antioxidant levels, oxidative stress, and enhanced cell death. Concomitantly, calpain becomes activated, and treatment with calpain inhibitors, therefore, is able to restore NF-kappaB-p65 levels and to increase cell viability. Thus, calpastatin and an altered NF-kappaB-p65 signaling are crucial factors involved in oxidative stress and cell death.80

Calcium-dependent phosphatase, calcineurin (CnA), is also activated in atrial tissue during AF 73,91-92. Rapid pacing causes an upregulation of CnA activity that is associated with increased dephosphorylation of the transcription factor NFATc3, allowing dephosphorylated NFATc3 to enter the cell nucleus. Thereby, NFATc3 increased the transcription of genes responsible for the atrial hypertrophic cellular response, as demonstrated by an increased expression of ANP and β-myosin heavy chain.81 In accordance with this finding, a study by Wang et al. indicated that calpain 1 is responsible for the formation of constitutively active calcineurin in the ventricular myocardium from patients with heart failure.82

Finally, there is apparent crosstalk between activated calpain and calcium-dependent signalling pathways during atrial fibrillation (Figure 2). The calpain-dependent apoptosis of atrial cardiomyocytes and degradation of contractile proteins contribute to the occurrence of contractile dysfunction. Moreover, activation of calcium-dependent signalling pathways (NF-αB, Calcineurin) influence the extracellular matrix and support the progress of structural remodeling in atrial tissue. These all processes collectively change the architecture of atrial tissue and may further contribute to sustained alterations in the atrial contractile performance.

Conclusions:

Calpains are important modulators of the normal signal transduction, gene expression and muscle contraction. Deregulation of their activity is associated with cardiovascular pathologies such as heart failure, myocardial infarction, and atrial fibrillation. The increased expression and activity of calpains during atrial fibrillation may result from the deregulation in calcium homeostasis and contribute to the occurrence of contractile dysfunction due to degradation of contractile proteins. Moreover, activation of calpains initiates apoptosis processes and mediates damage of atrial cardiomyocytes. Results of in vitro and in vivo studies have shown the beneficial effects of calpain inhibitors in different models of atrial fibrillation. Therefore, this protease has attracted a special attention in the medical science as a potential drug target. Nevertheless, calpain inhibitors have not been tested in clinical trials, yet, to validate the role of calpain inhibition in the clinical setting. Persisting problems resulting from the lower target selectivity, membrane permeability, and pharmacokinetic properties hinder the introduction of calpain inhibitors into clinical trials. Therefore, efforts should be dedicated to development of compounds resolving these problems.

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References:


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