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Dear Readers

Welcome to the April issue of JAFIB. Hope you all had a relaxing and enjoyable spring break. Weather in Kansas City has been wonderful with a full bloom of spring on the way.

This issue of the journal brings you several important articles with tremendous scientific merit. In an original article Ganga et al attempted to assess the relation between chronic anemia and new onset AF in elderly population in a community setting. In this large study of more than 2300 patients, prevalence of chronic anemia seems to be quite prevalent. However, no significant difference in AF incidence was noticed. A case report by Bittinger et al describes non-interventional management of symptomatic pulmonary vein occlusion after radiofrequency ablation of AF ablation. An epidemiological paper by Peterelli et al described the demographic characteristics and medication patterns in AF patients from a large primary care database in southwest Ontario.

At a more mechanistic level three articles do a fine job of throwing more light on the intricacies of AF initiation, maintenance and termination. Grandi et al described the altered excitation-contraction coupling in human chronic AF. This paves way for the identification of potential new targets for AF therapy. The UCSD group presented a current review on how AF regularization indices can predict intraprocedural AF termination and outcomes. Akar et al discussed the recent evidence linking epicardial fat and AF.

Engelbertz et al reviewed the issues surrounding AF and oral anticoagulation in patients with chronic kidney disease. Adlan et al summarized current literature in stroke prophylaxis for AF patients. Alt-

Cardiac resynchronization therapy (CRT) is an important therapy for heart failure. Often times, AF complicates and compromises the effectiveness of CRT devices. Two fantastic articles this issue cover the entire spectrum of issues related to CHF, AF and CRT.

Well that is all for this issue. We will see you all in Boston at Heart Rhythm.

Best wishes

Dhanunjaya (Dj) Lakkireddy MD, FACC, FHRS
Associate-Editor, JAFIB
Non-interventional Management of Symptomatic Pulmonary Vein Occlusion after Radiofrequency Ablation for Atrial Fibrillation

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Abstract

Pulmonary vein occlusion (PVO) after atrial fibrillation ablation is often highly symptomatic. In cases with a clear target, balloon angioplasty and stenting can be successful. In the absence of such a target, surgical lobectomy has been reported as a treatment option, but the natural history of physiological adaptation may outweigh the risks of invasive therapies and a non-invasive strategy is valid in these situations. We present a case of highly symptomatic PVO managed non-invasively, with complete symptom resolution and return to high-intensity exercise. Catheter intervention may not always be possible in the absence of a target vessel, and lobectomy may not be necessary to manage PVO.

Introduction

Pulmonary vein occlusion (PVO) after radiofrequency (RF) ablation for atrial fibrillation (AF) is rare and decreasing in frequency, but may be highly symptomatic. Management can be challenging and can include angioplasty or surgical lobectomy, but invasive strategies may not be necessary. We present a case of successful conservative management and discuss issues for management of PV occlusion.

History

A 36-year-old man with drug refractory symptomatic paroxysmal atrial fibrillation (AF) presented for catheter ablation. His heart was structurally normal (CHADS2 score of 0). He underwent a pulmonary vein (PV) isolation procedure with wide antral lesions, using a 4mm irrigated tip radiofrequency catheter with power limited to 30W anteriorly and 25W posteriorly. All PV were isolated. A recurrence of AF occurred at 6 weeks, and the patient returned for redo-ablation 3 months later. Computed tomography (CT) revealed new stenosis in the left superior PV (LSPV) of 50% [Image 1] with normal left inferior PV (LIPV). All veins had electrically reconnected and were re-isolated with wide antral lesions. The patient took warfarin for 6 months then changed to aspirin. Two weeks later, he reported severe dyspnea, cough, pleuritic pain and hemoptysis. Chest X-ray (CXR) showed left upper lobe consolidation with pleural effusion. CT angiography revealed occlusion of the LSPV, [Image 2] with venous congestion and edema/hemorrhage in the lingula.

Ventilation/perfusion (V/Q) scan showed decreased perfusion in the left upper lobe, consistent with pulmonary infarction. Imaging of the left atrium with angiography via transeptal puncture could not demonstrate the ostium of the LSPV. Pulmonary wedge angiog-
raphy revealed venous drainage only via the left inferior PV. A diagnosis was made of an ostial occlusion of the LSPV. No attempt at angioplasty was made due to concerns of the lack of a venous stump to target. Management options were presented to the patient and he expressed a desire for an initial trial of conservative management. Treatment included oxygen, analgesia, antibiotics, and mobilization, with no anticoagulation due to hemoptysis. The majority of symptoms resolved within a week, at which time the patient was discharged. A CXR, four months later revealed resolution of the pulmonary infarct with minimal scarring. Pulmonary function testing revealed normal lung function, including spirometry, lung volumes, diffusing capacity and flow-volume. Clinical review at 18 months found no residual symptoms, such as dyspnea, cough, or hemoptysis, with normal exercise tolerance, and the patient had returned to high-level aerobic exercise training. No further AF has been documented.

Discussion

Pulmonary vein stenosis is an infrequent complication of AF ablation, with an estimated prevalence of 0.4% . Stenosis rates have reduced with adoption of wide antral circumferential ablation. PV occlusion is rarer, with rates decreasing from 1.4% in 2000 to 0.1% in 2004 with a change from ostial segmental ablation to antral ablation. Risk of stenosis correlates with ablation within PVs, RF power levels, operator experience, venous diameter and pre-existing stenosis. Previously stenosed veins carry higher risk of occlusion, and this progression may be asymptomatic. Up to 34% of occlusions occur after two or more ablations, with left veins occluding most frequently (LSPV 54%, LIPV 29%) as ablation within the vein is often required to avoid ablating within the atrial appendage.

Thrombotic PV occlusion may correspond to warfarin cessation, the anticoagulation having maintained patency of a severely stenosed vein, but progression may occur despite anticoagulation. Some centers routinely screen for stenosis after RF ablation, though cost, availability of screening modalities, radiation exposure for CT and refusal by asymptomatic patients are limiting factors. CT frequently over-diagnoses PVO and occlusion should be confirmed by selective pulmonary artery wedge angiography, which may reveal a target for angioplasty.

Severity of symptoms has been shown to correlate with percentage stenosis of total venous drainage of a lung, although PVO can be asymptomatic. Factors corresponding to symptoms include size of vein occluded, area of lung drained, presence of an ipsilateral PV stenosis, and the degree of collateral drainage. Severe symptoms, particularly dyspnea and pulmonary congestion, are indications for intervention as earlier intervention may result in better long-term segmental perfusion. If an ip-
silateral vein is also stenosed, dilation of that stenosis relieves hemodynamic burden on the pulmonary vasculature and can improve symptoms.

In symptomatic cases of PVO (or subtotally occluded veins) with an identifiable target (eg venous stump), angioplasty ± stenting has been shown to reduce stenosis, improve pulmonary perfusion and resolve symptoms, particularly if performed early post occlusion. Intervention to adequately define anatomy should be offered to all patients with presumed occlusion on CT with subsequent dilation or stenting if possible. Angioplasty is frequently though not always successful and restenosis may occur despite stenting.

In cases without a target for angioplasty, management decisions are more challenging and include conservative therapy, surgical lobectomy or angioplasty of ipsilateral stenoses if present. Steliga et al. recently reported use of pulmonary lobectomy for symptoms secondary to lobar thrombosis after a PV occlusion. Nuclear perfusion scanning showed minimal blood flow to the affected lobe and a subsequent lobectomy resulted in resolution of symptoms of pain and cough. While lobectomy may potentially reduce symptoms and complications related to the infarcted lung, the risks of surgical morbidity are significant. In patients without the option of catheter intervention, conservative management may result in symptomatic improvement and obviate the need for lobectomy. A physiologically based argument can be made for conservative management: after occlusion, altered pulmonary hemodynamics result in redistribution of blood flow, opening of pulmonary vascular channels, maximization of collaterals, and neovascularisation. Di Biase et al. reported no or only mild residual symptoms in all of 18 patients after 14 months, regardless of PVO recannalisation, suggesting a natural history of symptom resolution with physiological adaptation, at least in mid-term follow-up. Longer follow-up out to ≥4 years suggests that patients with severe stenosis or total occlusion of a single vein without intervention may eventually develop symptoms, warranting continued follow-up in patients managed conservatively. Currently, data does not exist of follow-up of sufficient numbers of patients with conservatively managed PVO to draw definite conclusions of the natural history of these patients. The principles of conservative management are oxygeanation, analgesia, managing hemoptysis, and antibiotic treatment to prevent infection, to allow time for collateralisation and alterations in pulmonary vasculature. This strategy was highly successful for our patient.

Conclusions

Management of PV occlusion can be challenging and controversial and an observation that symptomatic resolution may occur could support a conservative strategy. Every effort needs be made to confirm PVO, including pulmonary wedge angiography, to determine if a target for angioplasty is possible as this therapy can improve symptoms and perfusion. If a PVO lacks a target for angioplasty and an ipsilateral vein is stenosed, that vein should receive angioplasty, leaving the occlusion untouched. If there are no ipsilateral stenoses, the patient should be managed non-invasively with supportive therapies. Patients with known stenoses undergoing redo-ablation should have more intensive and routine re-imaging of PVs with consideration of intervention on a stenosed PV before ceasing warfarin.

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Impact of Chronic Anemia on the New-Onset Atrial Fibrillation in the Elderly: It May Not Be What We Have Thought

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Abstract

Objective
To determine if a clinically significant relation exists between chronic anemia and the new-onset atrial fibrillation (AF) in the elderly population from a community setting.

Patients and Methods
This is a single center community-based retrospective cohort study. Data were collected on 3867 patients over the age of 65 years presenting to the Mercy Medical Center in the year 2006. Patients without AF were divided into anemic and non-anemic groups and were followed over the next two years for the new-onset AF. Chronic anemia was defined as hemoglobin level less than 13g/dl in males and less than 12g/dl in females from two laboratory values checked at least 4 months apart.

Results
Of the 2873 patients without AF, 2382 (83%) patients were non-anemic. 491 patients were anemic. New-onset AF was found in 7.5 % of the anemic patients and 5.5% of the non-anemic patients. After the adjustment for comorbid conditions, chronic anemia is not associated with new-onset AF (p=0.922).

Conclusion
In this study cohort of elderly community-based patients, chronic anemia is not associated with the new-onset AF.

Introduction

Atrial Fibrillation (AF) is the most common arrhythmia in the elderly population. Out of the 2.3 million estimated patients with AF, 1.85 million (80%) are 65 years of age or older.1 By the year 2050, the number of patients with AF over the age of 65 years is expected to be 4.97 million, which is approximately 88% of the total patients with AF.1 AF cannot be adequately explained on the basis of current proven risk factors such as age, body mass index, gender, hypertension (HTN) or heart failure (HF) alone. Given the rapidly increasing incidence of AF and the increase in the elderly population, identifying the risk factors for AF and the prevention of AF has become an important clinical and economic priority [National Institutes of Health].2

The prevalence of anemia in persons aged 65 years and older is 11% in men and 10.2% in women and with age over 85 years, 25% of men and 20% of women develop anemia. 3, 4 Clinical studies completed in the past decade suggest that there is a
complex relationship among AF, HF, chronic kidney disease (CKD), and anemia. HF is a risk factor for AF and patients with AF and HF, irrespective of which condition develops first, have a poor prognosis. One study reported that anemia is associated with the new-onset HF in the elderly population, and anemia is an independent predictor of death and hospitalizations in elderly patients with HF, coronary artery disease (CAD), or AF. Therefore, our primary hypothesis is that chronic anemia is a direct determinant of new-onset AF in the elderly community-based population. We propose to address this question by examining the association between chronic anemia and prevalent and incident AF.

Methods

A retrospective cohort study was undertaken using data collected from the medical records of Mercy Medical Center, Mason City, IA. Mercy Medical Center Institutional Review Board approved the study.

Patient Population

We used the following criteria for this study: subjects aged 65 years of age or older, alive throughout the year 2006, presenting to the Mercy Medical Center and its integrated clinics for their initial and follow up medical care. AF and atrial flutter patients were identified using ICD 9 codes 427.3, 427.31 and 427.32. Abstracted comorbid conditions included HF, CKD, CAD, stroke, diabetes, sleep apnea, obesity, HTN, hyperlipidemia, chronic obstructive pulmonary disease (COPD), malignancy, and cardiac valve disorders. We screened 3867 patients initially. We excluded patients who died in the year 2006 (n=121). We characterized patients as deceased if data on death was recorded in the Medicare database. We were unable to identify either a death date or the evidence for follow up for 16 patients and these individuals were excluded from the analysis. The final cohort included 3730 patients. The number of patients with AF in the year 2006 was 857. We divided patients without AF (n=2873) into anemic (n=491) and non-anemic groups (n=2382). These two groups were followed for 2 years starting from January 1st, 2007 to December 31st, 2008 for new-onset AF. We obtained medical records for all hospitalizations and clinic visits.

Definition of Anemia

Anemia was defined based on the World Health Organization (WHO) criteria, which includes hemoglobin levels in males under 13g/dl and females under 12g/dl. Chronic anemia has no precise definition as far as the duration is concerned. Studies have regarded chronic anemia as persisting between 3 to 6 months. We included only patients who had anemia on two different occasions from labs drawn at least 4 months apart. We excluded patients with transient anemia or acute blood loss anemia. The ICD9 codes 280.x (Iron Deficiency Anemia), 282.x (hereditary hemolytic anemia), 283.x (acquired hemolytic anemia), 284.x ( aplastic anemia) and 285.x (Other unspecified anemias), were included. We excluded ICD9 code 285.1 which includes acute post hemorrhagic anemia.

Identification of AF

Cases of incident AF were identified by two methods – 12-lead electrocardiograms (ECG) and hospital discharge diagnoses. We considered AF to be present at the time of admission if the discharge diagnosis ICD code indicated AF or atrial flutter. Previous studies have shown that the use of hospital records for diagnosing AF has an accuracy of 98.6% and 24-hour Holter monitor picked up only 0.1% cases of sustained or intermittent AF not identified by the hospital records. The total number of patients with incident AF was 169. Out of the 169 patients, 146 had evidence (of AF) from ECG and hospital records, 20 had only ECG evidence and 3 had only hospital records evidence.

Statistical Analysis

We compared demographic and clinical variables between prevalent AF and no AF patients and anemic and non-anemic groups in the year 2006. Comparisons between these groups were made using Chi Square test for the categorical variables.
and two sample t-test for the continuous variables. Associations were considered significant at P values below 0.05. Effect of anemia on the prevalent AF was analyzed after adjusting for clinical variables that were associated with AF. Similarly, analysis between patients with incident AF and no AF and anemic and non-anemic groups was done using Chi Square test for categorical variables and two sample t-test for continuous variables. Odds ratio (OR) for incident AF was obtained from multiple logistic regression model that included factors that showed association with new-onset AF. We have used SAS (Statistical Analysis Systems) version 9.2 for analysis of the data.

Results

Baseline Characteristics

The baseline characteristics of the population in the year 2006 (Table 1) show that the mean age of the AF patients (79.6 years) was higher than the patients without AF (77.7 years). The mean age of anemic patients (80.2 years) was higher than that of the non-anemic (77.6 years) patients. The prevalence of anemia in those with AF was 23.8% (204 out of 857) compared to 17.0% (491 out of 2873) in those without AF. The converse, prevalence of AF in those with anemia was 29.3% (204 out of 695) compared to 21.5% (653 out of 3035) in the non-anemic group. Compared to the non-anemic patients, anemic patients had greater burden of AF, CAD, diabetes, HF and CKD. The prevalent AF group (n=857) when compared to those without AF, were older, had greater burden of HF, sleep apnea, CKD, CAD, COPD and valve disorders. Among the variables assessed HF, CAD, sleep apnea, HTN and valve disorders are significantly associated with prevalent AF (Table 2 and 3). Multiple logistic regression analysis, (Table 3) after adjusting for potential confounders, reveals that chronic anemia is not associated with prevalent AF (adjusted OR of 1.13, 95% CI=0.92 to 1.39; P=0.224).

Effect of Anemia on Incident AF:

During the two year retrospective follow-up, the incidence of new-onset AF was 37 (7.5%, P=0.873)

### Table 1: Characteristics of the Patient Population in the Year 2006

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<th>Variables</th>
<th>AF (n=857)</th>
<th>No AF (n=2873)</th>
<th>P value</th>
<th>Anemia (n=695)</th>
<th>No Anemia (n=3035)</th>
<th>P value</th>
</tr>
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<td>AF</td>
<td>204 (23.80%)</td>
<td>491 (17.09%)</td>
<td>&lt; 0.0001</td>
<td>653 (21.52%)</td>
<td>1611 (53.08%)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Anemia</td>
<td>204 (23.80%)</td>
<td>491 (17.09%)</td>
<td>&lt; 0.0001</td>
<td>653 (21.52%)</td>
<td>1611 (53.08%)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Age (mean±SD)</td>
<td>79.62 ± 7.64</td>
<td>77.70 ± 7.83</td>
<td>&lt; 0.0001</td>
<td>80.26 ± 8.00</td>
<td>77.66 ± 7.70</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Gender (female)</td>
<td>420 (49.01%)</td>
<td>1619 (56.35%)</td>
<td>0.0002</td>
<td>428 (61.58%)</td>
<td>1611 (53.08%)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Race (white)</td>
<td>851 (99.30%)</td>
<td>2105 (99.30%)</td>
<td>0.7491</td>
<td>689 (99.14%)</td>
<td>1611 (53.08%)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>HF</td>
<td>360 (42.01%)</td>
<td>424 (14.76%)</td>
<td>&lt; 0.0001</td>
<td>248 (35.68%)</td>
<td>536 (17.66%)</td>
<td>&lt; 0.0001</td>
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<td>CAD</td>
<td>467 (54.49%)</td>
<td>1035 (36.03%)</td>
<td>&lt; 0.0001</td>
<td>314 (45.18%)</td>
<td>1188 (39.14%)</td>
<td>&lt; 0.0034</td>
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<td>CKD</td>
<td>134 (15.64%)</td>
<td>272 (9.47%)</td>
<td>&lt; 0.0001</td>
<td>164 (23.60%)</td>
<td>242 (7.97%)</td>
<td>&lt; 0.0001</td>
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<tr>
<td>Diabetes</td>
<td>256 (29.87%)</td>
<td>714 (24.85%)</td>
<td>0.0333</td>
<td>231 (33.24%)</td>
<td>739 (24.35%)</td>
<td>&lt; 0.0001</td>
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<td>Obesity</td>
<td>63 (7.35%)</td>
<td>155 (5.40)</td>
<td>0.0322</td>
<td>49 (7.05%)</td>
<td>169 (5.57%)</td>
<td>&lt; 0.0322</td>
</tr>
<tr>
<td>COPD</td>
<td>190 (22.17%)</td>
<td>444 (15.45%)</td>
<td>0.0001</td>
<td>168 (24.17%)</td>
<td>466 (15.35%)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Sleep Apnea</td>
<td>72 (8.40%)</td>
<td>88 (3.06%)</td>
<td>0.0001</td>
<td>34 (4.89%)</td>
<td>126 (4.15%)</td>
<td>0.3848</td>
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<td>HTN</td>
<td>565 (65.93%)</td>
<td>1755 (61.09%)</td>
<td>0.0103</td>
<td>416 (59.86%)</td>
<td>1904 (62.86%)</td>
<td>0.0103</td>
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<td>Hyperlipidemia</td>
<td>364 (42.47%)</td>
<td>1020 (35.50%)</td>
<td>0.0002</td>
<td>250 (35.97%)</td>
<td>1134 (37.36%)</td>
<td>0.0002</td>
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<td>CVA</td>
<td>62 (7.23%)</td>
<td>186 (6.47%)</td>
<td>0.4329</td>
<td>48 (6.91%)</td>
<td>200 (6.59%)</td>
<td>0.7624</td>
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<td>Cancer</td>
<td>140 (25.09%)</td>
<td>551 (19.18%)</td>
<td>0.0601</td>
<td>158 (22.73%)</td>
<td>533 (17.56%)</td>
<td>0.0015</td>
</tr>
<tr>
<td>Valve Disorders</td>
<td>215 (25.09%)</td>
<td>244 (8.49%)</td>
<td>&lt; 0.0001</td>
<td>117 (16.83%)</td>
<td>342 (11.27%)</td>
<td>0.0015</td>
</tr>
<tr>
<td>Thyroxine (%)</td>
<td>18.0</td>
<td>12.8</td>
<td>0.39</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

AF=Atrial Fibrillation, HF=heart failure, CAD=coronary heart disease, CKD=chronic kidney disease, COPD=chronic obstructive pulmonary disease, HTN=hypertension, CVA=stroke
Table 2: Demographic and Clinical Variables Associated with AF

<table>
<thead>
<tr>
<th>Variables</th>
<th>Odds Ratio</th>
<th>Confidence Intervals</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (per 5 years)</td>
<td>1.131</td>
<td>1.072-1.194</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Sex (M versus F)</td>
<td>1.31</td>
<td>1.106-1.551</td>
<td>0.0118</td>
</tr>
<tr>
<td>HF</td>
<td>2.999</td>
<td>2.493-3.608</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>CAD</td>
<td>1.362</td>
<td>1.144-1.620</td>
<td>0.0005</td>
</tr>
<tr>
<td>Sleep Apnea</td>
<td>2.192</td>
<td>1.546-3.107</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>HTN</td>
<td>1.250</td>
<td>1.051-1.486</td>
<td>0.0114</td>
</tr>
<tr>
<td>Cancer</td>
<td>0.831</td>
<td>0.668-1.033</td>
<td>0.0956</td>
</tr>
<tr>
<td>Valve Disorders</td>
<td>2.434</td>
<td>1.956-3.029</td>
<td>&lt; 0.0001</td>
</tr>
</tbody>
</table>

HF=heart failure, CAD=coronary heart disease, HTN=hypertension.

Table 3: Effect of Anemia on AF after Adjusting for Demographic and Clinical Variables

<table>
<thead>
<tr>
<th>Variables</th>
<th>Odds Ratio</th>
<th>95% Confidence Limits</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia</td>
<td>1.136</td>
<td>0.926-1.393</td>
<td>0.2214</td>
</tr>
<tr>
<td>Age (per 5 years)</td>
<td>1.128</td>
<td>1.069-1.191</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>1.319</td>
<td>1.113-1.563</td>
<td>0.0014</td>
</tr>
<tr>
<td>HF</td>
<td>2.947</td>
<td>2.445-3.553</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>CAD</td>
<td>1.357</td>
<td>1.141-1.615</td>
<td>0.0006</td>
</tr>
<tr>
<td>Sleep Apnea</td>
<td>2.188</td>
<td>1.543-3.103</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>HTN</td>
<td>1.254</td>
<td>1.055-1.490</td>
<td>0.0104</td>
</tr>
<tr>
<td>Cancer</td>
<td>0.823</td>
<td>0.662-1.024</td>
<td>0.0813</td>
</tr>
<tr>
<td>Valve Disorder</td>
<td>2.427</td>
<td>1.950-3.021</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

HF=heart failure, CAD=coronary heart disease, HTN=hypertension.

Table 4: Analysis of Incidence of new-onset AF in 2007-2008 from the 2006 patients that did not have AF Comparison of the demographic and clinical variables between those that had anemia and no anemia and between those that had AF in 2007-2008 vs. No AF. Two-sample t-test was used for age. Pearson’s Chi-Square was used for all other variables.

<table>
<thead>
<tr>
<th>Variables</th>
<th>AF (n=169)</th>
<th>No AF (n=2704)</th>
<th>P value</th>
<th>Anemia (n=491)</th>
<th>No Anemia (n=2382)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>New-onset AF</td>
<td>37 (7.54%)</td>
<td>132 (5.54%)</td>
<td>0.0873</td>
<td>108 (21.90%)</td>
<td>1056 (44.70%)</td>
<td>0.0011</td>
</tr>
<tr>
<td>Age (Mean ± SD)</td>
<td>80.33 ± 7.39</td>
<td>77.63 ± 7.84</td>
<td>&lt;.0001</td>
<td>80.09 ± 7.39</td>
<td>77.31 ± 7.70</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Gender (female)</td>
<td>70 (41.42%)</td>
<td>1549 (57.29%)</td>
<td>&lt;.0001</td>
<td>173 (35.23%)</td>
<td>1081 (45.38%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Race (white)</td>
<td>169 (100%)</td>
<td>2684 (99.26%)</td>
<td>0.9391</td>
<td>487 (99.19%)</td>
<td>2366 (99.33%)</td>
<td>0.0575</td>
</tr>
<tr>
<td>HF</td>
<td>54 (31.95%)</td>
<td>370 (13.68%)</td>
<td>&lt;.0001</td>
<td>122 (24.85%)</td>
<td>302 (12.68%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>CAD</td>
<td>85 (50.30%)</td>
<td>950 (35.13%)</td>
<td>&lt;0.0001</td>
<td>186 (37.88%)</td>
<td>849 (35.64%)</td>
<td>0.3466</td>
</tr>
<tr>
<td>CKD</td>
<td>35 (20.71%)</td>
<td>237 (8.76%)</td>
<td>&lt;0.0001</td>
<td>99 (20.16%)</td>
<td>173 (7.26%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Diabetes</td>
<td>50 (29.59%)</td>
<td>664 (24.56%)</td>
<td>0.1422</td>
<td>160 (32.59%)</td>
<td>554 (23.26%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Obesity</td>
<td>7 (4.14%)</td>
<td>148 (5.47%)</td>
<td>0.4573</td>
<td>29 (5.91%)</td>
<td>126 (5.29%)</td>
<td>0.5818</td>
</tr>
<tr>
<td>COPD</td>
<td>50 (29.59%)</td>
<td>394 (14.57%)</td>
<td>&lt;0.0001</td>
<td>103 (20.98%)</td>
<td>341 (14.32%)</td>
<td>0.0002</td>
</tr>
<tr>
<td>Sleep Apnea</td>
<td>10 (5.92%)</td>
<td>78 (2.88%)</td>
<td>0.0264</td>
<td>15 (3.05%)</td>
<td>73 (3.06%)</td>
<td>0.9910</td>
</tr>
<tr>
<td>HTN</td>
<td>119 (70.41%)</td>
<td>1636 (60.50%)</td>
<td>0.0104</td>
<td>296 (60.29%)</td>
<td>1459 (61.25%)</td>
<td>0.6894</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>70 (41.42%)</td>
<td>950 (35.13%)</td>
<td>0.0975</td>
<td>161 (32.79%)</td>
<td>859 (36.06%)</td>
<td>0.1677</td>
</tr>
<tr>
<td>CVA</td>
<td>11 (6.51%)</td>
<td>175 (6.47%)</td>
<td>0.9849</td>
<td>25 (5.09%)</td>
<td>161 (6.76%)</td>
<td>0.1716</td>
</tr>
<tr>
<td>Cancer</td>
<td>30 (17.75%)</td>
<td>521 (19.27%)</td>
<td>0.6272</td>
<td>120 (24.44%)</td>
<td>431 (18.09%)</td>
<td>0.0011</td>
</tr>
<tr>
<td>Valve Disorder</td>
<td>27 (15.98%)</td>
<td>217 (8.03%)</td>
<td>0.0003</td>
<td>59 (12.02%)</td>
<td>185 (7.77%)</td>
<td>0.0021</td>
</tr>
</tbody>
</table>

AF=Atrial Fibrillation, HF=heart failure, CAD=coronary heart disease, CKD=chronic kidney disease, COPD=chronic obstructive pulmonary disease, HTN=hypertension, CVA=stroke
Discussion

The primary analysis of this study demonstrates that chronic anemia alone is not a determinant for new-onset AF in an elderly community-based population. To our knowledge, there are no previous studies on anemia and incident AF in an elderly cohort. This comprehensive study in a large community-based elderly population shows that chronic anemia alone is not directly associated with incident and prevalent AF. Our study analysis shows that elderly patients with chronic anemia but without underlying comorbid disease are not prone to incident AF. Rather, chronic anemia seems to require other comorbid factor(s) like HF to precipitate AF as suggested in this study cohort. The study is unique as it is the first to show that chronic anemia is not directly associated with AF which has significant implications for this rapidly growing segment of the population. The study findings also question whether in elderly individuals, the mechanism of chronic

Table 5: Demographic and clinical variables associated with new-onset AF. Odds Ratio (OR) for AF was obtained from multi-factor logistic regression model that included factors that showed an association with AF by either stepwise or backward selection.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Odds Ratio</th>
<th>95% Confidence Limits</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (per 5 years)</td>
<td>1.243</td>
<td>1.119-1.382</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Sex (M vs F)</td>
<td>1.850</td>
<td>1.326-2.581</td>
<td>0.0003</td>
</tr>
<tr>
<td>HF</td>
<td>1.777</td>
<td>1.200-2.632</td>
<td>0.0041</td>
</tr>
<tr>
<td>CKD</td>
<td>2.005</td>
<td>1.260-3.190</td>
<td>0.0033</td>
</tr>
<tr>
<td>COPD</td>
<td>1.971</td>
<td>1.354-2.870</td>
<td>0.0004</td>
</tr>
<tr>
<td>HTN</td>
<td>1.953</td>
<td>1.353-2.818</td>
<td>0.0003</td>
</tr>
<tr>
<td>Valve Disorder</td>
<td>1.522</td>
<td>0.959-2.415</td>
<td>0.0747</td>
</tr>
<tr>
<td>Cancer</td>
<td>0.823</td>
<td>0.662-1.024</td>
<td>0.0813</td>
</tr>
<tr>
<td>Valve Disorder</td>
<td>2.427</td>
<td>1.950-3.021</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

Table 6: Effect of Anemia on incidence of AF after adjusting for demographic and clinical variables.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Odds Ratio</th>
<th>95% Confidence Limits</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia</td>
<td>1.020</td>
<td>0.683-1.524</td>
<td>0.9222</td>
</tr>
<tr>
<td>Age (per 5 years)</td>
<td>1.243</td>
<td>1.117-1.382</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>1.853</td>
<td>1.327-2.987</td>
<td>0.0003</td>
</tr>
<tr>
<td>HF</td>
<td>1.775</td>
<td>1.198-2.630</td>
<td>0.0042</td>
</tr>
<tr>
<td>CKD</td>
<td>1.999</td>
<td>1.252-3.192</td>
<td>0.0037</td>
</tr>
<tr>
<td>COPD</td>
<td>1.968</td>
<td>1.350-2.869</td>
<td>0.0004</td>
</tr>
<tr>
<td>HTN</td>
<td>1.952</td>
<td>1.353-2.817</td>
<td>0.0004</td>
</tr>
<tr>
<td>Valve Disorder</td>
<td>1.520</td>
<td>0.958-2.414</td>
<td>0.0757</td>
</tr>
</tbody>
</table>

HF=heart failure, CKD=chronic kidney disease, COPD=chronic obstructive pulmonary disease, HTN=hypertension.

patients in the anemic group (n=491) compared to 132 (5.5%) in the non-anemic group (n=2382). Patients with new-onset AF when compared to those without AF were older, more frequently males, had greater burden of CKD, CAD, COPD, diabetes, HTN, and valve disorders. Since AF could occur as a result of the preceding conditions like HF, we evaluated the anemia-AF relationship after adjusting for CHF, CKD, HTN, COPD and valve disorders. After multivariable analysis with adjustment for potential confounders, anemia was not associated with incident AF (adjusted OR of 1.02 95% CI =0.68 to 1.52; P=0.922, see Table 6). After adjustment of variables with multiple logistic regression analysis, CKD, COPD, HTN, and HF were significantly associated with the new-onset AF (Tables 5 and 6). Interestingly, CAD and sleep apnea though significantly associated with prevalent AF, did not predict the incident AF. Despite high prevalence of CAD in the new-onset AF patients (50.3%), CAD did not predict new-onset AF.
anemia in AF is different from that of acute anemia. Dynamics such as baseline cardiac status, severity of anemia and rapidity of onset of anemia can affect heart rate, hemodynamic status and symptoms. Acute severe anemia can cause hemodynamic stress on the heart due to the sudden drop in hemoglobin. Rapid onset of anemia can cause tachycardia as compensatory physiologic responses have less time to adapt. The observation that acute severe anemia can cause new-onset AF was first reported by Buxbaum et al.\textsuperscript{12} Heart rate has also been shown to increase linearly in response to acute isovolemic anemia in healthy adults.\textsuperscript{13}

In case of chronic anemia, gradual decrease in hemoglobin levels could allow the heart to adapt to a certain extent, before HF or AF occurs. One echocardiographic study reported that chronic severe anemia is well tolerated by the aging heart, in the absence of overt heart disease.\textsuperscript{14} The study included 41 elderly patients over the age of 65 years with recently established chronic anemia (3-5 months) and no history of heart disease, COPD or CKD.

Certain age-related factors in the elderly could assist in adapting to gradual decrease in hemoglobin levels before a certain threshold is reached. There is diminished intrinsic inotropic response of the myocardium to catecholamines and age related decrease in chronotropic response to sympathetic stimulation.\textsuperscript{15, 16} Decreased muscle mass with age and subsequent decreased need for blood supply and oxygen can help elderly adapt to the gradual decrease in hemoglobin levels.\textsuperscript{17, 18} The degree of physical activity is also less in the elderly. It is likely that majority of elderly patients in our study with chronic anemia had adequate levels of hemoglobin to lower their risk for HF and new-onset AF.

In contrast to a direct association of anemia with incident AF, our analysis suggests that HF, COPD, HTN, CKD and valve disorders are strongly associated with incident AF. Framingham study data showed HF to be the strongest risk factor for AF.\textsuperscript{5} While chronic anemia is associated with incident HF in the elderly,\textsuperscript{7} it is plausible for elderly patients with chronic anemia left untreated for a prolonged period to develop congestive HF and subsequent AF. The most common disease listed as primary diagnosis for patients hospitalized with AF was HF.\textsuperscript{19} Like AF, HF is an epidemic in the elderly and its incidence approaches 10 per 1000 population after 65 years of age.\textsuperscript{20} Data suggest that adjustment for comorbid disease largely neutralizes the effect of anemia on physical function; however, persistent anemia results in poor survival of HF patients.\textsuperscript{21} It is unclear how long anemia must be present and what hemoglobin threshold is required (if any) before elderly patients are at increased risk for HF and AF. There is a clear dose-response relationship between severity of anemia and risk of death.\textsuperscript{21} The subgroup of patients with HF and anemia are likely to be at higher risk for incident AF compared to those anemic patients without HF.

**Limitations**

Our study is retrospective in design and, therefore, subject to the inherent limitations of such a design. The large cohort, however, gives excellent power and even though we employed strict parameters for diagnosing new-onset AF, asymptomatic cases of paroxysmal AF could have been missed. Also, the incidence of AF could be underestimated due to the short follow-up period of 2 years. The contribution of hemodilutional anemia could not be estimated but we tried to achieve consistency by including only chronic anemia patients. Despite strict inclusion criteria, it is still possible that we could have underestimated the number of anemia patients as anemia is often under-diagnosed in the elderly.\textsuperscript{28} Our findings are confined by design to the community-based elderly population and, therefore, cannot be generalized to all age groups.

**Conclusions**

The results of our study support the conclusion that chronic anemia alone is not a determinant of new-onset AF in a large elderly non-clinical trial community-based population. In elderly patients without underlying comorbid factors, intervening to correct anemia might not be efficacious or necessary in preventing AF. However, our data show that HF, COPD, CKD, and HTN are risk factors for the new-onset AF in this population. Chronic anemia may, therefore, indirectly impact...
AF by multiple, interrelated mechanisms. One likely mechanism is through HF. Studies are needed to assess the hemoglobin threshold and the time period after which elderly chronic anemic patients are most likely to develop HF and subsequent AF. This information would enable clinicians to identify the elderly subgroups who might benefit from treatment for chronic anemia.

Acknowledgments

The authors thank Vickie Peters for technical support and Sherry Sturges for clinical data review (Mercy Medical Center, Mason City, Iowa).

References

29. Ikaz GJ, Westendorp RG, Knook DL. The definition of anemia in older persons. JAMA 1999;281:1714-1717
Demographic Characteristics and Patterns of Medication in Atrial Fibrillation Patients in South West Ontario: Insights from a Large Primary Care Database

Robert J Petrella, MD, PhD, Luc Sauriol, PhD

Abstract

Background
Information about current practice in primary care-based management of atrial fibrillation (AF) can help to improve care quality.

Purpose
To assess the epidemiology of AF and current patterns of treatment in order to identify therapeutic trends and aspects of current practice that may allow for care-gap identification.

Methods
We scrutinized the anonymized records of the South Western Ontario database (SWO) collected between July 2002 and October 2008 for information about the characteristics and management of AF patients.

Results
From a population of ~168,000 patients we identified 4922 patients with a diagnosis of AF (2.9%). The recorded prevalence of AF increased with age, from <2% at age <60 years to 6% in the age range 71–75 years and 10% at age ≥81 years. AF patients were characterized by an unfavourable cardiovascular risk profile including widespread hypertension (54% of all cases), coronary artery disease (37%) and heart failure (21%), many cases of which were advanced (New York Heart Association class III or IV). Diabetes (22%) and dyslipidaemia (31%) were also widely prevalent.

The most frequently prescribed anti-arrhythmic drugs (AADs) were sotalol (n=798), amiodarone (n=712) and propafenone (n=451). Recorded use of flecainide was relatively low (n=175). Rate control-agents were being prescribed for 1838 patients, beta-blockers for 1311 patients and calcium channel blockers (CCBs) for 784 patients.

Use of anticoagulants was higher among patients assigned to AADs than among those assigned to rate-control drugs (≥25% vs. ~10%). Overall prescription rates for other concomitant medications were >50% for ACE inhibitors/ARBs, 30–35% for statins and beta-blockers, and 27–29% for diuretics, digoxin and CCBs.

Conclusions
These Canadian patients with AF were relatively elderly and had multiple concomitant cardiovascular conditions and medications.
Management of patients with AF represents a substantial challenge by virtue of the complexities of the condition, the need for multiple therapies to address all aspects of AF-related risk and the number of patients who are candidates for treatment. Although rhythm control has traditionally been regarded as the definitive clinical response, several large controlled trials comparing these approaches have shown no significant differences in major endpoints including mortality and current expert guidelines recognize a role for both approaches. 3–5

Coincidentally, it is recognized that the prevention of hospitalization due to cardiovascular causes and the avoidance of treatment-related toxicities may be at least as relevant to AF management as the prevention of recurrence of AF.

These considerations form part of the background to the present study, which had the objective of assessing the epidemiology of AF and current patterns of treatment in order to identify therapeutic trends and aspects of current practice that may allow for care-gap identification. Accordingly, we examined the South Western Ontario (SWO) primary care database to gain insights into the demographics of AF patients in this cohort and patterns of drug therapy for AF.

Materials and Methods

The SWO database contains anonymized health-related information about >225,000 adult patients in rural and urban primary care practices in south-western Ontario, with a total population of about 1.5 million people. The SWO thus contains data on ~20% of the region’s inhabitants.

The SWO was established in 2000; there are currently 53 participating primary care practices and >225,000 patients records are maintained. Previous studies have described the generalizability of the cohort to Canadian health data. 6 Baseline records were established for all participating patients documenting demographic, complete morbidity profile, medications, and other clinical data. Thereafter, the cohort database has been updated quarterly in response to clinical activity/events, including hospitalizations, morbidity and mortality. The trigger for an update is a billed patient encounter. Data collated into the SWO are extracted from charts at point of care, and then entered into a proprietary Structured Query Language (SQL) program which includes data verification. Data collection is conducted by a designated data abstraction team who also conducts verification on a random sample of 10% of records quarterly. Error rates are less than 1.3% per annum. Phase 1 of this interrogation of the SWO database was conducted using data collected between 1 July 2002 and 18 October 2008. Objectives for this first 1 July 2002 and 18 October 2008. Objectives for this first phase included the development of demographic profiles for AF patients prescribed rhythm- or rate-control drugs. Specific items of epidemiology included age, gender, weight, type of AF, creatinine level, cardiovascular history, morbidity and concomitant medications. Presence of AF was identified by at least one of the following: using ICD-9/10 coding for AF; text entry for AF (atrial fibrillation, arrhythmia-atrial, rhythm disturbance-atrial or supraventricular) and cross-referenced with medication prescribed for AF.

In the second part of our investigation we extracted epidemiological and demographic data for all patients who had a diagnosis of AF and sought to relate patterns of AF drug therapy with major clinical events such as emergency presentation, hospitalization and toxicity incidents presumed due to use of anti-arrhythmic agents.

Results

During the period of our review the SWO accrued information on 168,023 patients. Our inspection identified 4922 patients with a diagnosis of AF (2.9% of the total population). The age distribution of those patients differed markedly from the non-AF contingent of the SWO (n=163,101). Thus, only six patients younger than 36 years of age had a diagnosis of AF and fewer than 3% of all AF cases (n=141) were identified in patients under the age of 46 years. Conversely, 69.4% of AF patients were ≥71 years old, compared with 23.8% of the non-AF cohort, and 40.6% of the AF patients were ≥81 years old (cf. 11.4% in the non-AF cohort). The recorded prevalence of AF increased with age, from less than 2% at age <60 years to 6% in the age range 71–75 years and 10% at age ≥81 years (Figure 1).
Figure 1.(a): Age distribution of patients in the SWO with a diagnosis of AF (n=4922); (b) Prevalence of AF by age

Table 1: Demographic and clinical details of the 4922 patients with a case record of AF

<table>
<thead>
<tr>
<th>Mean age (years)</th>
<th>74</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males (%)</td>
<td>50%</td>
</tr>
<tr>
<td>Mean weight (kg)</td>
<td>74kg</td>
</tr>
<tr>
<td>Average creatinine level (uM/L)</td>
<td>137</td>
</tr>
<tr>
<td>CV history</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>2637</td>
</tr>
<tr>
<td>CHF</td>
<td>1025</td>
</tr>
<tr>
<td>NYHA Class 1</td>
<td>121</td>
</tr>
<tr>
<td>NYHA Class 2</td>
<td>180</td>
</tr>
<tr>
<td>NYHA Class 3</td>
<td>337</td>
</tr>
<tr>
<td>NYHA Class 4</td>
<td>387</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>1821</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1079</td>
</tr>
<tr>
<td>Dyslipidaemia</td>
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<td>Concomitant medications</td>
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</tr>
<tr>
<td>Oral anticoagulant</td>
<td>2235</td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>1717</td>
</tr>
<tr>
<td>ACEI / ARBS</td>
<td>2751</td>
</tr>
<tr>
<td>Diuretics</td>
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<tr>
<td>Digoxin</td>
<td>1358</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>1337</td>
</tr>
<tr>
<td>Statins</td>
<td>1478</td>
</tr>
<tr>
<td>NSAID</td>
<td>603</td>
</tr>
</tbody>
</table>

CV – Cardiovascular; CHF – Coronary Heart Failure; NYHA – New York Heart association; ACEI – Angiotensin-converting enzyme inhibitor; ARBS – Angiotensin receptor blockers; NSAID – Non-steroidal anti-inflammatory drugs
Summary demographic particulars of the AF cohort, including the age distribution and classification of AF (persistent, permanent or paroxysmal) are presented in Table 1.

Table 2: Demographic and clinical data for patients with a case record of AF, stratified according to the recorded use of AADs. (Percentage may exceed 100 for NYHA classes 1–4 because status was often recorded as NYHA 2–3 or NYHA 3–4, with information then entered in both cells.)

<table>
<thead>
<tr>
<th></th>
<th>Any AAD (N=3443)</th>
<th>AMIODARONE (n=712)</th>
<th>SOTALOL (n=798)</th>
<th>PROPAFENONE (n=451)</th>
<th>FLECAINIDE (N=176)</th>
<th>OTHER (n=558)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (years)</td>
<td>78</td>
<td>80</td>
<td>79</td>
<td>89</td>
<td>76</td>
<td>75</td>
</tr>
<tr>
<td>Males (%)</td>
<td>53%</td>
<td>63%</td>
<td>50%</td>
<td>58%</td>
<td>67%</td>
<td>47%</td>
</tr>
<tr>
<td>Mean weight (kg)</td>
<td>79kg</td>
<td>91kg</td>
<td>77kg</td>
<td>75kg</td>
<td>80kg</td>
<td>77kg</td>
</tr>
<tr>
<td>Average creatinine level (uM/L)</td>
<td>134</td>
<td>127</td>
<td>136</td>
<td>127</td>
<td>130</td>
<td>141</td>
</tr>
<tr>
<td>Type of AF (persistent; paroxysmal; permanent) %</td>
<td>44%; 38%; 18%</td>
<td>41%; 21%; 38%</td>
<td>44%; 35%; 21%</td>
<td>39%; 31%; 30%</td>
<td>43%; 42%; 15%</td>
<td>35%; 49%; 16%</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Hypertension</td>
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<td>212</td>
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<td>357</td>
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<td>CHF</td>
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<td>NYHA Class 1</td>
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<tr>
<td>NYHA Class 2</td>
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<td>50</td>
<td>7</td>
<td>1</td>
<td>74</td>
</tr>
<tr>
<td>NYHA Class 3</td>
<td>319</td>
<td>94</td>
<td>81</td>
<td>20</td>
<td>2</td>
<td>122</td>
</tr>
<tr>
<td>NYHA Class 4</td>
<td>366</td>
<td>137</td>
<td>109</td>
<td>51</td>
<td>0</td>
<td>69</td>
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<tr>
<td>Coronary heart disease</td>
<td>1394</td>
<td>397</td>
<td>581</td>
<td>112</td>
<td>73</td>
<td>291</td>
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<tr>
<td>Diabetes</td>
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<td>188</td>
<td>315</td>
<td>12</td>
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<tr>
<td>Dyslipidaemia</td>
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<td>415</td>
<td>423</td>
<td>123</td>
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<td>100</td>
</tr>
<tr>
<td>Concomitant medications</td>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Oral anticoagulant</td>
<td>1233</td>
<td>330</td>
<td>521</td>
<td>113</td>
<td>82</td>
<td>267</td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>348</td>
<td>184</td>
<td>12</td>
<td>101</td>
<td>77</td>
<td>139</td>
</tr>
<tr>
<td>ACEI / ARBS</td>
<td>1488</td>
<td>339</td>
<td>224</td>
<td>124</td>
<td>131</td>
<td>799a</td>
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<td>Diureticsa</td>
<td>775</td>
<td>236</td>
<td>220</td>
<td>26</td>
<td>82</td>
<td>293b</td>
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<tr>
<td>Digoxin</td>
<td>937</td>
<td>121</td>
<td>486</td>
<td>22</td>
<td>14</td>
<td>308</td>
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<tr>
<td>Calcium channel blockers</td>
<td>847</td>
<td>301</td>
<td>167</td>
<td>36</td>
<td>27</td>
<td>263</td>
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<tr>
<td>Statinsb</td>
<td>1263</td>
<td>429</td>
<td>391</td>
<td>116</td>
<td>62</td>
<td>278c</td>
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<tr>
<td>NSAID</td>
<td>539</td>
<td>218</td>
<td>167</td>
<td>51</td>
<td>91</td>
<td>103</td>
</tr>
</tbody>
</table>

AAD – Anti-arrhythmic drugs; AF – Atrial Fibrillation; CV – Cardiovascular; CHF – Coronary Heart Failure; NYHA – New York Heart association; ACEI – Angiotensin-converting enzyme inhibitor; ARBS – Angiotensin receptor blockers; NSAID – Non-steroidal anti-inflammatory drugs; a = Large N due to intra-class use, and ACE/ARB concomitant use, and switching; b = All classes/combinations of diuretics included; c = Includes switching and combinations
Table 3: Demographic and clinical data for patients with a case record of AF, stratified according to the recorded use of rate-control drugs, beta blockers and calcium channel blockers

<table>
<thead>
<tr>
<th></th>
<th>Rate control agents (n=1838)</th>
<th>Beta blockers (n=1311)</th>
<th>CCBs (n=784)</th>
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</thead>
<tbody>
<tr>
<td>Mean age (years)</td>
<td>76</td>
<td>71</td>
<td>69</td>
</tr>
<tr>
<td>Males (%)</td>
<td>58%</td>
<td>48%</td>
<td>49%</td>
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<tr>
<td>Mean weight (kg)</td>
<td>83kg</td>
<td>77kg</td>
<td>67kg</td>
</tr>
<tr>
<td>Average creatinine level (μM/L)</td>
<td>134</td>
<td>136</td>
<td>130</td>
</tr>
<tr>
<td>Type of AF (persistent, paroxysmal, permanent) %</td>
<td>37%; 46%; 17%</td>
<td>43%; 45%; 12%</td>
<td>31%; 49%; 20%</td>
</tr>
<tr>
<td><strong>CV history</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>924</td>
<td>495</td>
<td>429</td>
</tr>
<tr>
<td>CHF</td>
<td>640</td>
<td>118</td>
<td>522</td>
</tr>
<tr>
<td>NYHA Class 1</td>
<td>132</td>
<td>6</td>
<td>86</td>
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<tr>
<td>NYHA Class 2</td>
<td>108</td>
<td>17</td>
<td>76</td>
</tr>
<tr>
<td>NYHA Class 3</td>
<td>176</td>
<td>24</td>
<td>151</td>
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<tr>
<td>NYHA Class 4</td>
<td>224</td>
<td>71</td>
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<tr>
<td>Coronary heart disease</td>
<td>1294</td>
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<tr>
<td>Diabetes</td>
<td>778</td>
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<td>Dyslipidaemia</td>
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<td>Oral anticoagulant</td>
<td>234</td>
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<td>98</td>
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<tr>
<td>Beta-blockers</td>
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<td>1311</td>
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<td>Digoxin</td>
<td>138</td>
<td>74</td>
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<tr>
<td>Calcium channel blockers</td>
<td>529</td>
<td>173</td>
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</tr>
<tr>
<td>Statins</td>
<td>1843</td>
<td>646</td>
<td>723</td>
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<tr>
<td>NSAIDs</td>
<td>523</td>
<td>359</td>
<td>296</td>
</tr>
</tbody>
</table>

CCBs – Calcium channel blockers; AF – Atrial Fibrillation; CV – Cardiovascular; CHF – Coronary Heart Failure; NYHA – New York Heart association; ACE – Angiotensin-converting enzyme; ARBS – Angiotensin receptor blockers; NSAIDs – Non-steroidal anti-inflammatory drugs

**Patients Receiving Anti-arrhythmic Drugs**

Eighty percent of patients in the AF cohort (n=3443) were recorded as receiving one or more anti-arrhythmic drugs (AADs).

Table 2 displays data for these 3443 patients, stratified according to the recorded use of AADs. Overall the cohort was elderly (mean age 78 years) with a small preponderance of men. Hypertension was widely prevalent and just over a quarter of the patients had congestive heart failure (CHF), predominantly (n=685; ~70%) in New York Heart Association (NYHA) class III or IV. Diabetes, dyslipidaemia and coronary artery disease were widely prevalent and there was extensive polypharmacy.
There were deviations from this overall pattern within sub-sets of patients receiving specified AADs. Hypertension and dyslipidaemia were markedly more prevalent than average in patients with prescription records for amiodarone or sotalol, as was a history of coronary artery disease. High-grade (NYHA III or IV) heart failure was conspicuous among the amiodarone sub-set. Conversely, both CHF and other major risk factors for cardiovascular disease were noted only infrequently in patients recorded as receiving either propafenone or flecainide. Patients receiving propafenone were noticeably older on average (80 years) than patients in other specified sub-groups. The proportion of men receiving flecainide was 67%, higher than the average.

Patients recorded as receiving ‘Other’ AADs had a marked prevalence of diabetes and coronary artery disease.

Anticoagulant use was higher than average in the amiodarone and sotalol sub-sets (Table 2). Concomitant use of beta-blockers was higher than average in patients receiving amiodarone or propafenone (~26% vs. ~10%, respectively). In all sub-sets except the flecainide group there was extensive use of ACE inhibitors/ARBs in relation to the proportions of patients recorded as having CHF. Use of diuretics appeared to be relatively low in the propafenone group. Extensive use of digoxin (60% of patients) was recorded in the sotalol subgroup.

Within the subsets defined by recorded therapy in Table 2, patients receiving amiodarone or propafenone were more likely than others to have a diagnosis of permanent AF.

Patients Receiving Anti-arrhythmic Drugs

Among the 1838 patients recorded as receiving rate-control drugs, half had hypertension and one-third had CHF, though the severity distribution was less skewed towards higher NYHA classes than for some other sub-sets defined by drug use (Table 3). The prevalence of diabetes was lower (28%) in patients treated with beta-blockers than in those treated with rate-control agents (42%) or CCBs (53%), as was hypertension (38% vs. 50–55%) (Table 3). Use of concomitant statin or ACE inhibitor/ARB therapy was also lower among the beta-blocker cohort than in the rate-control or CCB sub-sets (Table 3).

Hypertension and diabetes were documented in >50% of patients receiving CCBs and almost all the patients in this sub-set (753 of 784) had a record of coronary heart disease. Two-thirds had CHF, a percentage considerably higher than in the AF cohort overall, and a high proportion of those patients (40%) had advanced (NYHA class IV) heart failure. Anticoagulants were prescribed for 13% of these patients. Digoxin use (16%) was higher than in patients receiving rate-control agents (8%) or beta-blockers (6%). Recorded use of ACE inhibitors/ARBs and of diuretics exceeded 100%, a finding that may reflect prescription of multiple drugs within these classes, or drug switching.

In all three categories of patients described in Table 3 the proportion of patients receiving anticoagu-
lants was considerably lower than among patients prescribed at least one AAD (Table 2) (10–13% vs. 35%), whereas patients receiving flecainide were slightly less likely than the average to have a diagnosis of permanent AF. Paroxysmal AF was more apparent than average in the sub-sets of patients defined by use of rate control agents, beta-blockers or CCBs (Table 3). The recorded incidence of permanent AF was lower than average in patients treated with beta-blockers (12% vs. 18%).

Discussion

The AF data from the SWO reported here provide insights into the current characteristics and real-life management of patients with AF in the most populous province of Ontario. They also offer opportunities to examine changes over time within Canada7, 8 and to make some international comparisons. 9 – 13

We identified 4922 patients with a diagnosis of AF. As the SWO database is updated in response to billed patient encounters and as it was initiated 10 years ago some of our AF cases may be of long standing. Hence ours is not necessarily a profile of patients with new-onset AF. This may be one explanation for the finding that the average age of our patients was higher than reported by some other groups9 – 11, 14. A delay in the time between first symptoms of AF and clinical diag-
nosis, as described by Aliot et al, may also have contributed to this situation. Of note in this context is a recent analysis of the Régie de l’assurance maladie du Québec (RAMQ) database, which describes a demographic profile similar to our own in a random sample of >66,000 AF patients first diagnosed between January 1998 and April 2009.

Our AF cohort comprised 50% female patients. This is a higher proportion of women than is usually reported but is consistent with the findings of the RAMQ analysis and some other reports. The relative predominance of women at the upper end of the age distribution is a factor in this finding. This observation might also be an indication of greater attention to the management of AF in women, which we would see as a positive trend. The aggregate prevalence rate of AF in our population (2.6%) was in line with other reports based on Canadian research.

The prevalence of AF in our cohort increased very markedly with age, especially after age 70 years. This finding was fully in accordance with expectations and with other reports. Our AF population was characterized by high rates of cardiovascular morbidity and by the presence of other conditions associated with poor prognosis in AF. In particular, there was widespread hypertension (54%) and a substantial number of patients with heart failure, which in many cases was well advanced (Table 1). Hypertension was recorded in 54% of our patients. This is similar to the rate reported in the ATRIA study. The profile of concomitant diseases likely to impact overall cardiovascular risk was substantially worse in our patient population than in the Canadian Trial of Atrial Fibrillation (CTAF) .

This may reflect a general deterioration in risk profile of the Canadian AF population during the years since the CTAF study was completed or selection bias arising from CTAF exclusion criteria. The latter seems to us a more likely explanation and one that highlights the information value of an all-comers registry. There is strong correspondence between the cardiovascular disease profile of our population and that of the RAMQ.

The diagnoses of AF as paroxysmal, persistent or permanent in the SWO database are fluid and may change (forwards or backwards) over time. This is fully consistent with the ‘3P’ conception of AF that prevailed when the database was started and which continues, with some modification, today, however, this concept can complicate the interpretation of medication patterns and underlying prescriber motives. Rate control appears to have been the central aim of therapy, regardless of whether the means to that end was ‘pure’ rate-control drugs or drugs with both rate- and rhythm-control applications. The extensive use of amiodarone and sotalol suggests that physicians appreciate the value of drugs that combine rhythm- and rate-control effects, perhaps especially in medically complex cases. The extensive use of sotalol might, for example, be indicative of an emphasis on rhythm control in patients with concomitant conditions such as hypertension and coronary artery disease (Table 2). Most (79%) of SWO patients being prescribed amiodarone were recorded as having persistent or permanent AF and 33% had heart failure in NYHA class III or IV. Prescription rates increased with age. Given that our data were accrued over several years it is possible that some of the amiodarone-treated patients had lapsed into permanent AF and were receiving amiodarone for rate control; this would represent inappropriate use of the drug when better-tolerated alternatives are available. Alternatively, these patients may have had concomitant conditions that individual physicians regarded as warranting continuance of amiodarone therapy. The proportion of patient’s co-administered beta-blockers was relatively low.

Despite having an average age of 76 years, patients recorded as receiving flecainide had a conspicuously better cardiovascular risk profile than other sub-sets in our analysis. These patients also had a higher proportion of paroxysmal AF. This profile would seem to be compatible with use of flecainide as a ‘pill-in-the-pocket’ strategy in selected patients, but our findings provide no definitive proof that such an express rhythm-control policy was in action.

The demographic profiles of patients assigned to rate control with either beta-blockers or CCBs were broadly similar apart from a very much greater use of CCBs in patients with heart failure. We currently have no explanation for this striking disparity, which is all the more notable given cur-
rent recommendations on the use of beta-blockers in heart failure. Overall, beta-blocker use as a percentage of the whole SWO AF cohort was lower than might have been expected on the basis of the results of the CARAF I & II surveys. 7

Usage rates for anticoagulants seems quite low given the generally poor cardiovascular health profile of our patients; this may be further evidence for the underuse of anticoagulation therapy in AF. 21, 22 We have no data on anticoagulation adequacy. Thus, even if the recorded prescription rates are shown to be an accurate appraisal of need, we cannot be certain that all patients who were candidates for anticoagulation received optimal therapy. We have no data on antplatelet medications, and therefore cannot exclude the possibility that low rates of anticoagulant use may reflect the (possibly inappropriate) use of antiplatelet drugs. 21

The low rates of digoxin use recorded in most categories of the SWO database (Tables 2 & 3) likely represent a continuance of the trend of declining usage identified in the CARAF I & II surveys. 7 The only exception to this finding was in the cohort of sotalol-treated patients, in which digoxin use was recorded in 61% of cases. These 486 patients accounted for more than half of all digoxin prescriptions.

Our database has various limitations. First, the study population is very old and the vast majority have co-morbid conditions. Nevertheless, the results from this study are valuable because they provide insights into real world data on the demographic characteristics of patients with atrial fibrillation. Second, we have no specific information about symptom severity associated with AF, or the frequency of symptomatic episodes. Symptomatology has an important influence on clinicians’ decision to aim for rate or rhythm control and, if attempting rate control, whether to impose strict or lenient goals. Lack of this information limits our capacity to interpret physicians’ intentions from prescription data. Third, we have no data on race or stroke incidence in participating patients. Fourth, we have no data on the use of electrical cardioversion or ablation procedures. We are therefore unable to comment on the interplay between pharmacological and non-pharmacological approaches to AF management.

Conclusions

In conclusion, the SWO is a very large real-world database that provides information likely to be broadly representative of the demographics of AF patients in Ontario and of the treatment these patients receive. Insights from the SWO can be used to inform future developments in the management of AF. In our primary analysis we identified 4922 patients (2.9% of the database population) with a diagnosis of AF; prevalence increased with age, reaching 10% at age ≥81 years. Our AF patients were characterized by an unfavorable cardiovascular risk profile. The most frequently prescribed AADs were sotalol (n=798) and amiodarone (n=712). Rate control agents were being prescribed for 1838 patients.

References

Risk Factors for the Development of Atrial Fibrillation in HIV Infected Patients

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Department of Cardiology, Seton Hall University, St. Michael Medical Center, NJ.

Abstract

Background
Patients with Human Immunodeficiency Virus (HIV) have an array of multi-organ involvement, including cardiovascular disease. CD4 count is one of the best parameters to monitor the severity of HIV disease. The arrhythmic potential of HIV disease has not been well defined. The aim of the study is to establish whether an association between the severity of HIV and atrial fibrillation (AF) exists.

Methods
Out of a retrospective cohort of 780 HIV patients from January 2006 to December 2008, 40 patients were selected that developed AF during this period. The age and sex matched controls (n=40) were selected for comparison. The comparison between both groups was done using Fischer Exact Test. Bivariate and multivariate analysis was also performed to analyze the results.

Results
The data shows that 47%(19/40) of the patients with HIV who developed AF had CD4 count lower than 250 as compared to 20%(8/40) in the control group (P value = 0.017)

Conclusions
The data supports the presence of a relationship between HIV and AF. Patients with lower CD4 counts are more susceptible to develop AF.

Introduction

Despite a declining rate of HIV (Human Immunodeficiency Virus) related death, proportions of HIV infected patients dying of other causes have increased.1 As an example, a death certificate study in New York City showed that the proportion of deaths among HIV-infected patients due to non–HIV-related causes increased from 19.8% to 26.3% between 1999 and 2006, reflecting mortality resulting from cardiovascular disease (CVD), substance abuse, and non–AIDS-defining cancers.2 Among individuals aged 55 years or older, CVD was the leading cause of death.

Atrial fibrillation is associated with a wide range of organ damage, ranging from stroke to heart failure. Furthermore, management of patients with this arrhythmia is a challenge. Once patients develop AF, it is incumbent upon the physician to balance rate control, anti coagulation and if needed rhythm control. Although there are many risk factors for developing this arrhythmia, there has not been any data to show that HIV is a risk factor.

Patients with HIV have an array of multi-organ involvement, amongst which is cardiovascular disease. Cardiovascular manifestations...
include but are not limited to dilated cardiomyopathy, pericardial effusion, endocarditis, myocarditis, pulmonary hypertension and atherosclerotic heart disease. Literature review shows that there aren’t any published data on the arrhythmogenic potential of HIV. This retrospective observational study was conducted to determine if there is an association between HIV and AF. Furthermore, we wanted to elucidate why certain HIV patients are more prone to developing AF.

**Subjects and Methods**

**Setting**

This was a multi-center retrospective study at three urban teaching hospitals in the north eastern United States that are affiliates of the School of Health and Medical Sciences of Seton Hall University. The protocol was approved by the Institution Review Boards (IRB) of St Michael’s Medical Center (Newark, NJ), St Joseph’s Medical Center (Paterson, NJ) and Trinitas Regional Medical Center (Elizabeth NJ). Seton Hall University’s IRB delegates the approval process to the individual facilities at which the studies are performed.

**Protocol and Patients**

This study examined a retrospective cohort of 780 HIV patients that developed AF after developing HIV during a period of 3 years from 2006-2008, inclusive. Within this cohort, we nested a case-control study consisting of subjects with AF (n=40) and subjects who did not demonstrate AF (n=40) during the above mentioned time period. The inclusion criteria for the study group were: HIV patients above the age of 18 and AF that developed after the diagnosis of HIV. All of the cases were persistent atrial fibrillation. In addition, all of the patients were treated with a rate and anticoagulation strategy; none of the patients were placed on rhythm control agents, such as amiodarone. This approach was primarily due to many of the interactions with most anti-retroviral medications. Furthermore, our approach was further attributed to the absence of strong data to support rhythm control, once rate control and anticoagulation has been addressed. Each patient was anticoagulated according the CHADS2 stroke risk. During the three year follow up we did not have any thrombo-embolic events that were recorded at our institution. Whether these patients had a complication and were admitted to other institutions, we cannot confirm.

All medications were reviewed extensively in every patient included in the study; there were no patients that were taking any known arrhythmogenic agents. Patients that were on arrhythmogenic agents were excluded, even if they fit the other inclusion criteria. The CD4 count was measured at the time of diagnosis of atrial fibrillation. All of these patients follow up in our HIV clinics and access to their CD4 count at the time of diagnosis of AF was possible. Patients were excluded from the study if they had a history of AF prior to the development of HIV. Baseline characteristics included: age, sex, history of hypertension, diabetes mellitus, dyslipidemia, echocardiography findings of an EF<35% and left atrial enlargement (LAE) > 4cm.

**Statistical Analysis**

Interval data (age) were tested for normality with the D’Agostino-Pearson omnibus normality test and were found to approximate a normal distribution. Thus, age was compared by an unpaired t-test. Categorical risk factors were cross tabulated with the two outcomes (presence/absence of AF) and tested for significance with Fisher’s exact test. Because of the retrospective nature of the study, clinical relevance was described by the odds ratio and 96% confidence intervals (CI). Characteristics for which univariate p values were ≤0.05 and lower 95% CI was ≥ 1.0, were considered as primary risk factors (RF). The level of significance for potential confounders was p ≤ 0.25. These were examined for interaction with the RF by logistic regression analysis and, if a significant interaction was observed, it was included in a model to adjust the RF for the confounder. For univariate analyses, we used Prism® software (GraphPad Corp., San Diego). For bivariate logistic regression analysis we used a web-based routine.15

**Results**

The two groups were compared with regard to baseline characteristics in Table 1. Based on the criteria described in the Methods, the only RF detected was CD4+ count <250 cells/mm3, which yielded an OR = 3.62 (95% CI: 1.34 to 9.77). Several
potential confounders ($p \leq 0.25$) were identified: HTN, dyslipidemia and LAE. These were used to adjust the odds ratio and the resulting data are provided in Figure 1. It can be seen that adjustment for both LAE and HTN tend to demonstrate a dependence of CD4+ cell count on these parameters. However, when tested, the $p$-value for the interaction of both of these potential confounders with CD4+ cell count was not statistically significant ($p = 0.14$ for LAE and $p = 0.31$ for HTN).

### Discussion

HIV infection is multisystemic and even with in an individual organ, it can manifest in multiple ways. The purpose of this study was to evaluate if patients with AIDS are more likely to have the arrhythmogenic effects of HIV. The results support the hypothesis by the presence of a statistically significant difference in the prevalence of AF between the two groups. This association was still significant when we considered dyslipidemia as a confounding factor. However, the association between CD4 count and AF was not as significant when we factored in HTN and LAE as a confounding variable. This result can be explained by two factors: firstly, hypertension is on its own the most common risk factor for developing AF. Secondly, the number of patients in the study is small, thus limiting our power. Despite the fact that HTN and LAE favored CD4 not being an independent risk factor, a larger study might reverse that and is certainly warranted. Further, when the odds ratios were adjusted for both HTN and LAE, the $P$ value approached a significant number (Figure 1) and thus demonstrates a dependence of CD4+ cell count on these parameters. As such, HIV infected patients with low CD4 counts have a greater risk of developing AF than those with better immune status. One possible explanation for this relationship may be through myocarditis. The aforementioned relationship may be a function of the severity of HIV infection. The incidence of AF was 5% (40 out of 780) which is not significantly more than the general population (1.2-6%) and AF was seen more in the patients with low CD4 counts. The true incidence of AF is likely higher; however, we had stringent exclusion criteria to shun any confounders. In addition to the listed exclusion criteria, all patients on any arrhythmogenic agents were excluded at the time of admission with AF. Further, patients that did not have a CD4 count at the time of diagnosis of AF were excluded. As such, we suspect that the incidence is higher than 5%. As an example there were patients that were excluded because we did not know which occurred first, the AF or HIV. This study was aimed to show that a low CD4 count is a risk for developing AF and warrants further investigations; the design was not to measure the incidence.

Atrial fibrillation (AF) is the most frequently diagnosed arrhythmia and affects 2.3 million people in the United States. Its prevalence increases with age, and as many as 9% of people older than 80 years are affected. Atrial fibrillation is characterized by a lack of coordinated atrial activity, and this loss of organized atrial contraction can lead to a myriad of clinical scenarios that include decompensated congestive heart failure (CHF), embolic cerebrovascular accident (CVA), ischemia, dizziness/weakness, and even asymptomatic patients with tachycardia. The pathogenesis of AF is now thought to involve an interaction
between initiating triggers, often in the form of rapidly firing ectopic foci located inside one or more pulmonary veins, and an abnormal atrial tissue substrate capable of maintaining the arrhythmia. Although structural heart disease underlies many cases of AF, the pathogenesis of AF in apparently normal hearts is less well understood. Although there is considerable overlap, pulmonary vein triggers may play a dominant role in younger patients with relatively normal hearts and short paroxysms of AF, whereas an abnormal atrial tissue substrate may play a more important role in patients with structural heart disease and persistent or permanent AF.

The known cardiovascular manifestations of HIV are: pericardial disease, myocardial disease, infective endocarditis, cardiac tumors, vasculitis, coronary artery disease, hypertension, pulmonary hypertension and thrombosis and embolism. Amongst the aforementioned, hypertension is the most common cardiovascular manifestation. To date there has not been any data to suggest that HIV may invade the electric network of the heart.

HIV infects and gradually depletes CD4+ lymphocytes but may also affect other cell types, including monocytes/macrophages, endothelial cells, glial cells, intestinal epithelial cells, and possibly neurons. Studies have suggested that HIV may exhibit a cardiac tropism. HIV disease is an important cause of dilated cardiomyopathy, with a prevalence reported as 3.6% among cardiomyopathic patients. The prevalence is increasing as patients with HIV infection live longer. Patients with HIV-infection and dilated cardiomyopathy have a much worse prognosis than those with idiopathic dilated cardiomyopathy, hazard ratio of death 4.0. Recent studies on patients with idiopathic dilated cardiomyopathy found evidence of viral particles in endomyocardial biopsy specimens in up to two thirds of the patients. Among the viruses found that cause Myocarditis HIV has been a culprit. Myocarditis is the best studied cause of dilated cardiomyopathy in HIV disease. Review of the literature shows that myocarditis is arrhythmogenic leading to atrial fibrillation (7-10%) and ventricular arrhythmia (39%). Review of all the literature did not yield any direct correlation between HIV and AF. In this study, we intended to evaluate whether HIV is a risk factor for developing AF. One possible explanation for this relationship may be through myocarditis. Although myocarditis is a well known cause of dilated cardiomyopathy, it is also a well known cause of AF. Furthermore, HIV is a well known cause of myocarditis, which once developed may cause AF. Unfortunately, we do not have any documented cases of myocarditis from these patients. However, this might be a plausible mechanism that could have preceded the onset of the atrial fibrillation. Many of our patients go to multiple hospitals within the same city and as such it is difficult to be certain of any recent admissions to other institutions for myocarditis.

**Conclusion**

HIV is a multisystemic disease, with many complications that arise as the CD4 count decreases and the immune system fails. The intent of this study was to show that there is a relationship between HIV and atrial fibrillation. This study shows that

| Table 1. Baseline characteristics of the two groups. Gender is given as M/f and shown as mean +/- 1 SD; all other variables are those with the characteristics/those without. |
|---|---|---|
| **Gender** | HIV & AFIB | HIV+ no Afib | P values |
| Gender | 27/13 | 26/14 | 1.00 |
| Age | 56.78 +/- 9.4 | 54.59 +/- 8.59 | 0.273 |
| HTN | 27/13 | 19/21 | 0.113 |
| DM | 11/29 | 10/30 | 1.00 |
| dyslipidemia | 13/27 | 5/35 | 0.059 |
| EF<35% | 10/30 | 5/35 | 0.252 |
| LAE | 13/27 | 5/35 | 0.059 |
| CD4<250 | 19/21 | 8/32 | 0.017 |
as the CD4 count decreases patients are at increased risk of developing Atrial fibrillation. One postulated mechanism is via myocarditis, which is relatively common in patients with a low CD4 count. Further studies are warranted to evaluate this subject.

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Introduction

Ablation has become a cornerstone of therapy for atrial fibrillation (AF), the most common arrhythmia in the Western world and an important cause of morbidity and mortality. However, the optimal approach for ablation remains hotly debated, and this is particularly true for the selection of procedural endpoints. Since seminal studies by Haïssaguerre et al. showed that ectopy from the pulmonary veins (PVs) may trigger paroxysms of AF, PV isolation has become central to most ablation approaches. However, PV isolation often fails to terminate AF, particularly in patients with persistent AF, indicating AF sustaining mechanisms that lie outside the PVs. For this reason or to eliminate additional triggers, many approaches to ablate extra-PV tissue have been devised whose AF termination rates range from 58% to 87%. However, some constants remain. First, the event of AF termination is currently extremely difficult if not impossible to predict a priori. Second, AF termination by current ablative approaches is typically to atrial tachycardia, rather than to the sinus rhythm from which AF usually initiates. Finally, despite the intuitive advantages of AF termination, it remains disputed whether AF termination by current approaches is a desirable endpoint that improves long-term outcome. This brief review focuses on these facets of intra-procedural AF termination.

Temporal and Spatial Indices of AF Regularization Predict Intraprocedural AF Termination and Outcome

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AF Regularization vis-à-vis AF Sustaining Mechanisms

The fashion in which AF regularizes en route to termination is fundamentally dependent upon the underlying sustaining mechanisms for AF. Two predominant hypotheses have been proposed. In the multiwavelet hypothesis, AF is caused by spatially distributed multiple reentrant wavelets that collide, extinguish and meander within the atria. Accordingly, AF should terminate if structural barriers are created to limit the mass of remaining patches of atrium below that required to sustain reentry – the concept of the Maze procedure. In this scenario, AF should regularize and terminate only after a substantial and possibly consistent proportion of the atrium has been compartmentalized to limit the degrees of freedom of wavelet migration. As will be discussed, AF regularization and termination by ablation often does not follow this pattern. Conversely, the localized source hypothesis is based on data from animal models in which spiral waves (electrical rotors) or focal beats activate rapidly to cause disorganized AF in surrounding tissue. In this model, regularization or termination of AF by ablation may occur whenever lesions approach critical sustaining sources, and thus should occur unpredictably at any time during the procedure including its initial, early or intermediate stages. In fact, this describes the patterns of AF termina-
tion most often reported, such as during the elegant stepwise ablation approach of Bordeaux. 

**Metrics of AF Organization and AF Regularization**

The organization of AF can be measured temporally using its cycle length (CL), spectrally using measures of dominant frequency (DF), and spatially between regions of the atria.

**Cycle Length**

Quantifying the varying cycle lengths of AF for clinical purposes was first popularized by Haissaguerre et al., who showed that the CL of paroxysmal AF (averaged over multiple cycles) showed a stepwise prolongation during sequential isolation of the PVs to the point of AF termination, that typically occurred when AF CL rose to 200 ms or longer. Subsequent studies have extended these results to show that longer baseline AF CL, measured from within the heart or from the surface ECG, is a multivariate predictor (along with factors such as a shorter duration of continuous AF) of the termination of longstanding persistent AF by ablation.

Several methods exist to measure CL. The simplest involves manually counting 10 or more consecutive atrial electrograms and taking their mean. This is typically easiest using left or right atrial appendage electrograms, but can also be performed on electrograms from other locations. In general, CL from fractionated or multicomponent waveforms must be interpreted with care, and such measurements remain controversial. Some commercially available electrophysiological recorders now provide automated measurements of AF CL.

One important issue pertains to technical reproducibility and spatial variability in AF CL measurement. Temporally, while it may be intuitively expected that AF CL should vary over time, several studies show that AF rate in any given patient is reproducible for hours or even days. Spatially, AF exhibits regional gradients in rate, that may also be consistent over hours, emphasizing the need to examine AF CL over time at a constant location.

**Spectral Dominant Frequency**

Spectral dominant frequency has been applied to measure AF organization in many settings. Spectral analysis mathematically represents an electrogram by a large number of sine waves of differing frequency (=1/rate), amplitude and phase (i.e. relative timing) that, when summed algebraically, reconstruct the waveform shapes of this electrogram. Several techniques exist to perform this “frequency-domain decomposition”, including Fourier analysis and the wavelet transform. Although spectral analyses were initially performed using investigational software, several commercially available electrophysiological and electroanatomic mapping systems now provide online (near-instantaneous) spectral analyses of dominant frequency.

Seminal studies by Bollmann et al. showed that spectral analysis can predict pharmacological termination of AF: in 61 AF patients, lower spectral DF peak (loosely, a lower rate) of AF on the ECG or intracardiac electrodes predicted AF termination within <5 minutes after ibutilide. Subsequently, Everett et al. showed in dogs with pace induced AF that electrical cardioversion or burst pacing to sinus rhythm were more effective when spectra revealed regularity in AF in the form of a narrow spectral DF peak – reflecting one predominant ‘driver’ frequency. More recent work showed that spectral DF of the ECG can quantify the spectrum of intra-atrial organization in patients with AF and other complex arrhythmias and, for a given AF patient, is reproducible over periods of many hours in the absence of an intervention.
More recent studies of spectral analysis have shed light on AF mechanisms vis-à-vis contemporary ablation. A gradient in spectral DF frequency has been reported from the PVs to the left and then right atrium in paroxysmal AF but not persistent AF, that is eliminated by PV isolation. Interestingly, the fact that AF may continue after PV isolation in these patients argues against a predominant role of the PVs or their DF gradient in AF maintenance, although both may contribute to the initiation and stabilization of AF. Of note, spectral DF in these studies should be interpreted to indicate gradients in organization rather than rate, because DF may not accurately measure AF rate from bipolar electrograms, although it is more accurate when applied to monophasic action potentials or unipolar electrograms.

Most recently, spectral DF has been used to identify sites where ablation may acutely terminate AF. Sanders et al. studied 32 AF patients (19 paroxysmal), in whom spectral DF was analyzed sequentially during AF at 126±13 points per patient. Ablation was performed blinded to DF maps, and sites of AF termination by ablation were compared to sites of high spectral DF. Ablation at sites of high DF terminated AF in 17/19 patients with paroxysmal AF, in whom high DF sites often lay in the PVs, but in none of the patients with persistent AF, in whom high DF sites lay throughout the atria but rarely in the PVs. In a more recent study, Atienza et al. studied 50 AF patients (18 persistent) in whom DF was mapped during AF at 117±38 points per patient. Ablation at sites of maximum DF significantly reduced average atrial DF and eliminated frequency gradients, but did not acutely terminate AF. On follow-up, significant DF reduction with loss of the left-to-right gradient associated with a greater likelihood of AF elimination. By spatial analyzing spectral data, Krummen et al. showed ‘centrifugal’ islands of regularized high spectral DF surrounded by regions of irregular and/or low spectral DF that identified successful AF ablation sites.

Most recently, spectral analyses have been used to predict AF termination intra-procedurally during the Bordeaux stepwise approach. Forclaz et al. systematically evaluated a spectral index of regularity (temporal regularity index, TRI) in 75 patients with persistent AF after each ablation step. Of note, AF terminated during the first step (circumferential PV isolation) in 11 patients, and indeed prior to completion of PV isolation in some patients, more consistent with localized than spatially widespread AF sustaining mechanisms. In the remaining 64 patients in whom AF continued after PV isolation, TRI abruptly increased at the point of termination (in n=48 patients). Using receiver operating characteristic analyses, increased TRI after PVI predicted procedural AF termination with high specificity and positive predictive value (although a less impressive negative predictive value). On long-term follow-up, AF was more successfully eliminated in patients who exhibited post-PVI increases in TRI.

In summary, spectral DF provides a clinically relevant index of AF regularity. Although ablation at sites of high spectral DF has had mixed results, an increase in spectrally measured AF regularity by PV isolation predicts intra-procedural AF termination during the Bordeaux stepwise approach. Notably, AF terminated at any stage of the procedure including during the first step, and AF showed most regularization just before termination.

Spatial Indices of Organization

Several studies have quantified AF organization by the extent to which atrial regions activate synchronously (‘in-phase’) over time. Studies in this area have focused on the vector of surface ECG f-waves, and showed that the consistency of this vector over time (spatial phase) reflected AF organization. Initial reports suggest that indices of spatial regularization can be an-
alyzed very rapidly but, at the current time, have only been conducted using custom-designed software in research laboratories.

Early intracardiac analyses showed organizational differences in the right atrium between persistent and paroxysmal AF, but did not relate this to AF termination or ablation outcome. In a recent study, Forclaz et al. tracked a novel intracardiac spectral regularity index (SRI) of cycle-to-cycle variations in the 3-dimensional AF activation vector between the right atrial appendage, proximal and distal coronary sinus. SRI remained reproducible over periods of minutes in the absence of an intervention. However, SRI dramatically increased after circumferential PV isolation in patients in whom AF later terminated during stepwise ablation. The dynamics of SRI during stepwise ablation paralleled those in the temporal regularity index above – after an initial SRI increase by PV isolation, minimal increases were then seen during continued ablation until just before AF termination.

Predictors of Acute Procedural Termination of AF

In patients with paroxysmal AF, prolongation of AF CL predicts AF termination during circumferential PV isolation. Interestingly, since AF may terminate before completion of wide encircling lesions, it is possible that ablation of atrial tissue within encircling lesions and/or adnexal structures such as ganglionic plexi may contribute to termination. In patients with persistent AF, AF termination during stepwise ablation is predicted by longer baseline AF CL and, intraprocedurally, by AF regularization measured spatially or temporally (using spectral DF). Notably, the fact that AF may terminate at any procedural stage including the first step, and that AF regularization is sometimes subtle despite increasing cumulative ablation until just prior to termination, may support the localized source hypothesis for AF rather than spatially distributed mechanisms.

Until recently, there was little or no evidence to support localized sources for human AF. However, the recently presented CONventional Ablation for AF with or without Focal Impulse and Rotor Modulation (CONFIRM) Trial detected rotors or focal beat sources for AF in nearly all (97%) patients using novel computational techniques that have recently become commercially available. Patients had 2.1±1.0 concurrent rotors or focal beats, that were detected for at least hundreds of cycles. Targeted ablation at these sources (FIRM) was able to acutely terminate or substantially slow AF within minutes prior to any conventional ablation, and improved long-term outcomes over conventional ablation alone using implanted continuous ECG monitors in 84% of patients to rigorously prove maintenance of sinus rhythm.

There are several other unanswered questions with regards to AF termination by ablation. In particular, it is unclear why conventional ablation typically terminates AF to atrial tachycardia, despite the fact that AF usually initiates from sinus rhythm. Of interest, FIRM ablation at rotors and focal beat sources predominantly terminated AF to sinus rhythm in the CONFIRM trial. Further studies are required to define variations, if any, in the mechanisms of AF termination and their long-term implications between different approaches.

Do Intraprocedural Regularization or Termination of AF Predict Long-Term AF Elimination?

At present, the primary procedural endpoint for AF ablation is PV isolation. Secondary procedural endpoints are less clear, and include confirmation of conduction block across linear lesions (when drawn), and elimination of CFAE (when targeted). One major question is whether intraproce-
dural AF regularization or termination may be useful adjunctive endpoints for ablation. Although several small, predominantly single center studies show that AF regularization may identify patients who are less likely to experience recurrent AF, few if any studies have used these indices prospectively to guide ablation approach. Thus, additional prospective studies are required before any specific index of AF regularization can be recommended as an ablation endpoint.

More pressing is the question of whether acute AF termination should be used as a procedural endpoint. Several studies confirm that patients in whom AF terminates intra-procedurally have a higher long term freedom from AF than those in whom AF does not terminate. Interestingly, some experienced groups have used precisely these data to argue the opposite case. Since the recurrence of any atrial tachyarrhythmia is similar whether AF does or does not terminate by ablation, AF termination may simply identify patients in whom recurrences are of atrial tachycardia (AF termination group) as opposed to AF (AF non-termination group). The final outcome of that debate will be operator dependent, reflecting among other factors the preference to perform a repeat procedure for atrial tachycardia or AF. Although atrial tachycardia is often very symptomatic, it may be easier to eliminate definitively by ablation in many instances.

We feel that preliminary data from the CONFIRM trial are promising, in which rapid targeted ablation (FIRM) at rotors or focal beat sources was able to terminate AF to sinus rhythm within minutes, prior to PV isolation, with improved long-term outcome using continuous ECG monitors. However, validation in additional centers is required before FIRM-guided ablation becomes a routine component of ablation.

Conclusions
Several quantitative indices may predict the acute procedural termination of AF. However, most have suboptimal predictive value and do not identify the stage at which AF will regularize or terminate during ablation. There continues to be lively debate on the value of procedural AF termination in improving long-term ablation outcomes. This debate may continue until such time as the precise mechanisms that sustain AF are identified and targeted directly for ablation, as we have now established for most other arrhythmias.

Disclosures
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References


Introduction

Atrial fibrillation (AF) is the most prevalent cardiac arrhythmia found in the clinical practice, affecting >2 million people in the United States alone. AF is often associated with other cardiovascular disorders, such as coronary artery disease, valve dysfunction, congestive heart failure (CHF), and is characterized by significant morbidity. A key determinant of this morbidity is embolic stroke, with loss of atrial contractility being one of the major causes of thrombus formation. AF is characterized by a rapid and irregular heartbeat caused when the atria quiver (fibrillate) erratically, sometimes faster than 200 times per minute.

Several studies have investigated the molecular and ionic mechanisms involved in the remodeling occurring in the atria of patients with AF, and suggest that structural, electrophysiological, and contractile remodeling are critical factors in the disease progression, i.e., they contribute to the development of a substrate that facilitates the tendency for persistence of AF. Structural remodeling involves changes in atrial myocyte and tissue morphology (e.g., cell hypertrophy, fibrosis). Electrical remodeling includes changes in Ca²⁺ and K⁺ currents leading to shortening of the action potential (AP) duration and effective refractory period, depressed intracellular Ca²⁺ transient, and reduced myocyte contractility. A growing body of experimental evidence points to perturbations in intracellular Ca²⁺ handling as important players in AF-induced atrial remodeling, with intracellular Ca²⁺ transients (CaTs) being reduced. Myofilament protein changes in AF are also likely to contribute to atrial contractile dysfunction. However, the mechanisms leading to self-perpetuation of the arrhythmia and depressed cardiac contractility are yet poorly understood. Recently, Llach et al. have studied the basis of irregular beat-to-beat response of human atrial myocytes when subjected to elevations of the beating frequency (which often precedes cardiac arrhythmias) and suggested that stability or instability of the response was determined by the sarcoplasmic reticulum (SR) and L-type Ca²⁺ channel activities.

In this review, we present the current knowledge...
about the changes occurring in excitation-contraction (E-C) coupling that characterize the remodeled human atrial myocytes from patients with chronic AF (cAF), and the postulated underlying ionic mechanisms.

**Phenotypic Consequences of AF on AP, CaT, and Contractility**

Myocytes from cAF patients are characterized by shorter APs (Fig. 1A) and effective refractory period (ERP), and loss of rate adaptation of both atrial repolarization (Fig. 1A) and refactoriness. Typically, the human atrial AP duration at 90% repolarization (APD_{90}) shortens when paced at faster frequencies, but in myocytes isolated from cAF patients this shortening is severely attenuated (Fig. 1A). CaT amplitude is strongly depressed in myocytes from cAF patients compared to those from subjects in sinus rhythm (Fig. 1B), although the SR Ca^{2+} content is unaltered. CaTs decay more slowly in cAF compared to sinus rhythm. Elevated diastolic [Ca^{2+}] has been reported and attributed to enhanced leak of Ca^{2+} from the SR. Intracellular [Ca^{2+}] measurements with aequorin light signals in atrial tissue from patients in sinus rhythm display a positive dependency of CaT amplitude on the pacing rate. Our recently published mathematical model of the human atrial AP and CaT recapitulated this positive rate-dependence, and importantly showed that this is impaired when simulating cAF conditions.

Baseline force of contraction of atrial trabeculae is also reduced in human cAF by approximately 70% compared to patients in sinus rhythm (Fig. 1C).

**Ionic Bases of Altered E-C Coupling in AF**

The molecular bases of AF-induced alterations in E-C coupling are summarized in Table 1 and discussed in detail in the following paragraphs. E-C coupling remodeling can occur at the level of ion channels/transporters expression, or by modification of ion channel/transporter properties (for example, trafficking or phosphorylation).
Table 1: Molecular bases of altered E-C Coupling in human AF (changes vs. sinus rhythm) [Modified from 16]

<table>
<thead>
<tr>
<th>Cell Size/Structure</th>
<th>Increase length and width (17)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Membrane capacitance</td>
<td>Increased (24)</td>
</tr>
</tbody>
</table>

### Sarcolemmal Ion Channels

<table>
<thead>
<tr>
<th>Channel</th>
<th>Changes</th>
</tr>
</thead>
<tbody>
<tr>
<td>$I_{Na}$</td>
<td>No changes (15, 35) Steady-state inactivation shifted right (15) Slightly reduced current density (36) Late current increased (36)</td>
</tr>
<tr>
<td>$I_{CaL}$</td>
<td>Reduced current density by ~50% (5, 11, 12, 18, 40) No changes in voltage dependence of activation and inactivation (11)</td>
</tr>
<tr>
<td>$I_i$</td>
<td>Increased mRNA levels (44)</td>
</tr>
<tr>
<td>$I_{k1}$</td>
<td>Reduced density -80% in the RA -45% in the LA (5, 12, 15, 24, 45-47)</td>
</tr>
<tr>
<td>$I_{Kur}$</td>
<td>Reduced density -55% in the RA -45% in the LA (5, 24, 45, 47, 49) Unchanged (12, 15, 46)</td>
</tr>
<tr>
<td>$I_{Ks}$</td>
<td>Increased 2-fold (24)</td>
</tr>
<tr>
<td>$I_{KATP}$</td>
<td>Upregulated +100% (5, 12, 13, 15, 45)</td>
</tr>
<tr>
<td>$I_{K,ACH}$</td>
<td>Increased basal current by receptor-independent, constitutively active component; increased (15) or reduced carbachol-activated current (13, 56, 57)</td>
</tr>
<tr>
<td>$I_{K,ATP}$</td>
<td>Decreased (60) Increased (61)</td>
</tr>
</tbody>
</table>

### Ca$^+$ and Na$^+$ handling

<table>
<thead>
<tr>
<th>Channel</th>
<th>Changes</th>
</tr>
</thead>
<tbody>
<tr>
<td>$I_{NCX}$</td>
<td>Upregulated (17, 18, 21, 34) Reduced maximal pump rate (18) and protein expression (34)</td>
</tr>
<tr>
<td>SERCA</td>
<td>Enhanced PKA and CaMKII phosphorylation (34) Unaltered CaMKII-dependent phosphorylation (17)</td>
</tr>
<tr>
<td>PLN</td>
<td>Increased phosphorylation at PKA and CaMKII sites (17, 18, 67) resulting in increased channel open probability (68) and SR Ca$^{2+}$ leak (17, 111)</td>
</tr>
<tr>
<td>RyR</td>
<td>Unchanged function (65)</td>
</tr>
<tr>
<td>Ankyrin-B</td>
<td>Downregulated (70)</td>
</tr>
</tbody>
</table>

### Protein kinases and phosphatases

<table>
<thead>
<tr>
<th>Kinase</th>
<th>Changes</th>
</tr>
</thead>
<tbody>
<tr>
<td>CaMKII</td>
<td>Increased expression (32) and phosphorylation (17)</td>
</tr>
<tr>
<td>PKA</td>
<td>Similar activity in cAF vs. sinus rhythm (34)</td>
</tr>
<tr>
<td>PP1, PP2A</td>
<td>Higher activity (34)</td>
</tr>
</tbody>
</table>

### Myofilaments

<table>
<thead>
<tr>
<th>Changes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduced maximum rate of tension generation and maximum active tension, reduced passive tension, and increase in myofilament Ca$^+$ sensitivity (9) No changes in maximum force and passive force, reduced rate of tension redevelopment (71) Increased phosphorylation of cMyBP-C (9) Decreased phosphorylation of cMyBP-C (34) No changes in cTnI phosphorylation (9, 34)</td>
</tr>
</tbody>
</table>
thermore, alterations of myofilament proteins may be involved in AF-induced hypocontractility.

Figure 2 depicts simulated APs and CaT for sinus rhythm and cAF myocytes (from (16)) and the major ionic currents that are active during the cardiac cycle, and provides a graphical representation of the main changes occurring in the electrophysiological and Ca²⁺ handling processes in human AF.

Atrial Cell Morphology

Cell capacitance of myocytes from cAF patients is greater than that of myocytes from SR patients, suggesting that AF cells are hypertrophied. In fact, cells from AF patients are both longer and wider than those from patients in sinus rhythm. Cell hypertrophy may contribute to cAF-induced global atrial dilation, along with changes of the extracellular matrix (with fibrosis and glycogen accumulation). Atrial dilation may itself have important consequences on cellular remodeling and alteration in protein composition and function of the atrial myocytes, as discussed later in this review.

It has recently been shown that atrial myocytes from human tissue sections exhibit extensive t-tubule networks. The presence of t-tubules in the human atria (not detected in isolated human atrial myocytes), may play an important role in determining the spatio-temporal properties of the intracellular CaT. Notably, one can speculate that t-tubules could be subject to remodeling and contribute to perturbed E-C coupling in cAF, as suggested in sheep and dog. However, further investigations will be required to confirm this.

Protein Kinases and Phosphatases

Intracellular CaT is dynamically regulated via phosphorylation by protein kinase A (PKA) and Ca/calcmodulin-dependent protein kinase II (CaMKII) of key Ca²⁺ handling and regulatory proteins, such as L-type Ca²⁺ channels, ryanodine receptors (RyRs), and phospholamban (PLN). In addition, sarcomere proteins and various sarcolemmal ion channels are targets of both PKA and CaMKII. The phosphorylation state of target proteins is also controlled by serine/threonine protein-phosphatases that are differentially regulated in distinct cardiomyocyte microdomains. Thus, altered protein kinase and phosphatase activity may importantly contribute to E-C coupling remodeling in AF. Indeed, CaMKII has been found to be more expressed and more phosphorylated in human cAF. Similar PKA activity was found in cAF vs. sinus rhythm in goats, but El-Armouche et al. detected a higher total activity of type 1 and type 2A phosphatases in human cAF, causing inhomogeneous changes in protein phosphorylation in different cellular compartments. This may specifically amplify PKA and CaMKII effects on certain targets without having significant effects on others (e.g., higher phosphatase activity/lower phosphorylation in thick vs. thin myofilaments, cell membrane vs. SR). Thus there is growing interest in the potential role of CaMKII and protein phosphatase inhibitors in preventing arrhythmogenic remodeling in cAF.

Sarcolemmal Ion Channels

$I_{Na}$

The Na⁺ current ($I_{Na}$) plays a crucial role in cardiac E-C coupling by initiating the AP, and is also a major determinant of the cardiac AP propagation. Bosch et al. reported that $I_{Na}$ density and voltage-dependence of activation were not altered in human AF, the steady-state inactivation was shifted to the right, and no changes were detected in mRNA levels of the Na⁺ channel gene SCN5A. In contrast, Sossalla et al. provided recent evidence that expression of Nav1.5 and peak $I_{Na}$ density is decreased (slightly) in the atrial myocardium of patients with cAF.
Although it is unclear whether altered fast $I_{Na}$ (Fig. 2A, 2nd row) contributes to the electrical remodeling in human AF, it has recently been shown that the late Na$^+$ current component, $I_{NaL}$ (inset), is significantly increased in cAF patients. Sossalla et al. proposed that this increase could be due to the increase in neuronal Na$^+$ channel isoforms (Nav1.1 expression is increased), or mediated by CaMKII, which is increased in AF and known to regulate $I_{NaL}$ or caused by oxidative stress. However, our simulations suggested that an increased $I_{NaL}$ does not contribute significantly to repolarization in cAF, where the overall APD$_{90}$ was still shorter than that in normal healthy cells. On the other hand, an increase in $I_{NaL}$ may cause cellular Na$^+$ and Ca$^{2+}$ overload and lead to contractile dysfunction and electrical instability (via reverse-mode Na$^+$/Ca$^{2+}$ exchange).

$I_{CaL}$

The L-type Ca$^{2+}$ current ($I_{CaL}$) critically regulates E-C coupling by triggering SR Ca$^{2+}$ release, and modulating AP shape and duration, i.e., maintaining the AP plateau. Reduction in $I_{CaL}$ density (-50% vs. sinus rhythm, Fig. 2A, 3rd row) is one of the most consistent electrophysiological features of electrical remodeling in human AF (as seen in (5, 11, 12, 16, 18, 40)). Christ et al. demonstrated that decreased $I_{CaL}$ density in cAF is not accompanied by altered expression of the corresponding $\alpha_{1c}$ and $\beta_{2a}$ channel subunits (although other studies found different results), and proposed that lower basal $I_{CaL}$ is due to decreased channel phosphorylation in AF, which results from an altered ratio of protein kinase/phosphatase activity in favor of increased phosphatase activity. An analogous explanation was proposed for the blunted effect of CaMKII inhibition on $I_{CaL}$ in human cAF. It has been shown that blocking $I_{CaL}$ with nifedipine in normal human atrial cells results in an AP characteristic typically seen in AF with respect to morphology, duration and impaired rate-dependent adaptation, i.e., reduction in $I_{CaL}$ seems to be a critical component of the remodeled atrial electrical phenotype. However, Workman et al. found that nifedipine did not significantly alter ERP in sinus rhythm myocytes (although APD was short-
er), thus supporting the idea that \( I_{\text{CaT}} \) downregulation may not be sufficient by itself to explain the remodeled atrial electrical phenotype.\(^1\)

\( I_{\text{CaT}} \)

There is no evidence of a T-type Ca\(^{2+} \) current (\( I_{\text{CaT}} \)) in human atrial myocytes.\(^42, 43\)

\( I_f \)

The hyperpolarization-activated pacemaker current, \( I_f \) ion channel has been found to be increased in human AF compared to sinus rhythm, at least at the mRNA level,\(^44\) and could contribute to ectopic atrial pacemaker activity. However, functional evidence for \( I_f \) involvement is lacking at present.

\( I_{\text{to}} \) and \( I_{\text{Kur}} \)

The Ca\(^{2+}\)-independent transient outward K\(^+\) current (\( I_{\text{to}} \)) and the ultra-rapid delayed rectifier K\(^+\) current (\( I_{\text{Kur}} \)) dominate the early AP repolarization phase and confer the atrial AP a characteristic triangular shape. Human cAF is associated with strong reduction of \( I_{\text{to}} \) (Fig. 2A, 4th row) density\(^5, 12, 15, 24, 45-47\) and downregulation of its channel \( \alpha \) subunit Kv4.3.\(^35, 48\) \( I_{\text{Kur}} \) (Fig. 2A, 5th row) was reduced in cAF\(^24, 45, 47, 49\) paralleled by diminished expression of Kv1.5.\(^35, 45, 48\) However, others have reported no changes in \( I_{\text{Kur}} \) density.\(^12, 15, 46\) Inconsistent results about \( I_{\text{Kur}} \) function have been commented on previously by Christ et al. and attributed to different strategies for identification of \( I_{\text{Kur}} \) (e.g., pharmacological or with \( I_{\text{to}} \)-activating prepulse), and to a fraction of \( I_{\text{Kur}} \) that is not accounted for by Kv1.5.\(^49\) The reduction in \( I_{\text{to}} \) and \( I_{\text{Kur}} \) explains the slight prolongation in earlier phases of the AP (Fig. 2A, 1st row).\(^16, 50\)

It has been shown that CaMKII (increased in cAF) positively regulates \( I_{\text{to}} \) in human atrial myocytes in acute conditions, as the application of the CaMKII inhibitor KN-93 caused loss of channel function.\(^32\) The authors speculated that, by reducing the extent of inactivation of \( I_{\text{to}} \), upregulation of CaMKII during atrial fibrillation reduces Ca\(^{2+}\) influx and therefore minimizes Ca\(^{2+}\) overload. On the other hand, CaMKII overexpression in cAF may impact channel expression, thus contributing to \( I_{\text{to}} \) downregulation, as recently shown in CaMKII-overexpressing transgenic mice.\(^51\)

Experimental evidence suggests that block of \( I_{\text{Kur}} \) enhances force of contraction of isolated human atrial trabeculae both in patients in sinus rhythm and AF.\(^22, 23, 52\) We have recently predicted that block of \( I_{\text{Kur}} \) results in prolongation and elevation of the AP plateau, which augments the CaT amplitude that would elicit a positive

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**Figure 3:** Altered atrial APs in human ventricular dysfunction. A) Atrial APs from patients with moderate or severe LVSD (bottom) and from patients without LVSD (top) (75). B) Representative AP and response to ACh in isolated atrial myocytes from HF (top) and donor (bottom) hearts at a stimulation frequency of 1 Hz (76). C) Representative APs from a non-dilated (normal, left) and a dilated (right) atrium recorded at a pacing frequency of 1 Hz (80).
inotropic effect.\textsuperscript{16} Taken together, these studies suggest that $I_{\text{Kur}}$ might be a potentially useful atrial-specific target to potentially counteract hypocontractility associated with cAF. A slight AP prolongation associated to $I_{\text{Kur}}$ blockade may also be beneficial.

Caballero et al. have recently looked at differences in current density and AF-induced alterations in the right vs. left human atrium. They found heterogeneity in the repolarizing currents between the atria in sinus rhythm, and demonstrated that cAF reduced the $I_{\text{Kr}}$ amplitude and density more markedly in the left than in the right atrium, thus creating a right-to-left gradient, whereas $I_{\text{Kur}}$ was more markedly reduced in the right than in the left atrium, thus dissipating the left-to-right gradient detected in sinus rhythm.\textsuperscript{24} However, the data concerning intr atrial heterogeneities in repolarizing currents in human atrial myocytes are still limited, and it is unclear whether and how these changes may contribute to the perpetuation of arrhythmia.\textsuperscript{16}

$I_{\text{K}1}$ and $I_{\text{Kr}}$

The delayed rectifier K\textsuperscript{+} currents have proven much harder to record and study in isolated human atrial cells.\textsuperscript{53} Nevertheless, their contribution is likely to be small in cells that lack an appreciable plateau phase (e.g., see current densities in Fig. 2A, 6th and 7th rows).\textsuperscript{54} The block of the rapidly activating delayed rectifier K\textsuperscript{+} current, $I_{\text{Kr}}$, has been shown to prolong human atrial APD in the late phase of repolarization by a small amount,\textsuperscript{23} and to date no experimental evidence has suggested its involvement in AF-induced electrical remodeling.

Recently, Caballero et al. provided the first demonstration that cAF significantly increased the amplitude of the slow delayed rectifier K\textsuperscript{+} current, $I_{\text{Ks}}$, in both atria.\textsuperscript{24} They suggested that $I_{\text{Ks}}$ increase could contribute to cAF-induced shortening of APD and to further promote fibrillatory conduction, especially with current accumulation at high frequencies.

$I_{\text{K1}}$ and $I_{\text{K,ACH}}$

The inwardly rectifying K\textsuperscript{+} current ($I_{\text{K1}}$) primarily controls the resting potential of the cardiac cell, and its much lower density in atrial than in ventricular myocytes\textsuperscript{50} confers the atrial AP a more depolarized resting potential.\textsuperscript{16} In cAF, increases in both current density\textsuperscript{5, 12, 13, 45, 56} and mRNA levels\textsuperscript{5, 13} have been reported (Fig. 2A, 8th row). Increased $I_{\text{K1}}$ causes a more negative resting membrane potential in cAF vs. sinus rhythm human atrial myocytes.\textsuperscript{13, 16, 56}

Patients with chronic AF exhibit agonist-independent constitutive $I_{\text{K,ACH}}$ activity that contributes to the enhanced basal inward rectifier current and may result from abnormal channel phosphorylation by PKC.\textsuperscript{13, 56, 57} Constitutively active $I_{\text{K,ACH}}$ is considered to support the maintenance of AF, together with increased $I_{\text{K1}}$, by stabilizing reentrant activity sustained by rotors (faster activation, less meander).\textsuperscript{58}

Recently, Voigt et al. found significant left-to-right gradients in $I_{\text{K1}}$ and constitutively active $I_{\text{K,ACH}}$ in patients with paroxysmal AF, which were dissipated in cAF, raising the idea that this may contribute to left-to-right dominant frequency gradients that are often more evident in paroxysmal AF vs. cAF.\textsuperscript{56}

$I_{\text{K,ATP}}$

The ATP-sensitive K\textsuperscript{+} ($I_{\text{K,ATP}}$) channels generate an inward rectifying current that activates with a decrease in intracellular ATP concentration.\textsuperscript{59} Gene expression and electrophysiological studies in patients with atrial fibrillation demonstrated reduced mRNA levels of Kir6.2\textsuperscript{48} and current activation,\textsuperscript{60} but increased current was also reported.\textsuperscript{61} Interestingly, a KATP channel mutation has been shown to confer risk for adrenergic atrial fibrillation originating from the vein of Marshall,\textsuperscript{62} and it has been proposed that KATP channel deficit could play a broader role in the pathogenesis of electrical instability.\textsuperscript{63} It is also conceivable that metabolic and mechanosensitive gating of KATP channels could be altered with structural heart disease and atrial dilation, thus providing a substrate for the more common acquired form of atrial fibrillation.\textsuperscript{65}
Ca\textsuperscript{2+} and Na\textsuperscript{+} Handling

$I_{\text{NCX}}$

The Na\textsuperscript{+}/Ca\textsuperscript{2+} exchanger current ($I_{\text{NCX}}$) is the main Ca\textsuperscript{2+} extrusion and Na\textsuperscript{+} influx pathway in cardiac myocytes. It extrudes 1 Ca\textsuperscript{2+} in exchange for 3 Na\textsuperscript{+}, thus generating an inward current that influences cardiac repolarization and arrhythmogenesis.\textsuperscript{29} Increased expression\textsuperscript{18,21,34} and abnormal function of $I_{\text{NCX}}$ protein\textsuperscript{16,18} are implicated in human AF pathophysiology. An increase in $I_{\text{NCX}}$ may be an adaptive response to cellular Ca\textsuperscript{2+} loading and contribute to diminish the Ca\textsuperscript{2+} overload induced by rapid atrial pacing (along with $I_{\text{Ca}}$ downregulation). Indeed, the decay rate of caffeine-evoked CaT (attributable to Ca\textsuperscript{2+} removal by NCX) is shown to be faster in human cAF vs. sinus rhythm myocytes\textsuperscript{16-18}. Note that simulated $I_{\text{NCX}}$ during an AP is smaller in AF than in sinus rhythm (Fig. 2B, 3rd row) because of altered Na\textsuperscript{+} loading in cAF. Intracellular [Na\textsuperscript{+}] changes may contribute to the human cAF phenotype, as we postulated in our modeling study\textsuperscript{16} but have not yet measured.

Ryanodine Receptors

RyRs directly control SR Ca\textsuperscript{2+} release in cardiac muscles, activating contraction during E-C coupling\textsuperscript{29}. Spontaneous Ca\textsuperscript{2+}-release events (Ca\textsuperscript{2+} sparks) and Ca\textsuperscript{2+} waves through leaky RyR channels have been reported in myocytes from cAF patients\textsuperscript{17, 18, 66, 67} despite unaltered SR Ca\textsuperscript{2+} content. One potential contributor to RyR hyperactivity may be oxidative stress, which is known to play a critical role in AF pathophysiology\textsuperscript{38} and increase RyR open probability. Neef et al. suggested that the CaMKII-dependent increase in SR Ca\textsuperscript{2+} leak caused by RyR hyperphosphorylation in AF is a potential arrhythmogenic mechanism,\textsuperscript{17} because elimination of Ca\textsuperscript{2+} via inward $I_{\text{NCX}}$ could lead to cell depolarization and cause DADs. Voigt et al. measured directly single RyRs isolated from cAF patients and demonstrated a higher channel open probability in cAF that responded to CaMKII inhibition\textsuperscript{68}. Thus CaMKII inhibition may reduce the propensity for atrial arrhythmias.

SR Ca\textsuperscript{2+} ATP-ase and PLN

The SR Ca\textsuperscript{2+} ATP-ase (SERCA) is responsible for pumping Ca\textsuperscript{2+} back into the SR after Ca\textsuperscript{2+} release\textsuperscript{29}. The endogenous inhibitor PLN regulates SERCA and releases its inhibition when phosphorylated by either PKA or CaMKII\textsuperscript{29, 30}. A decrease in SERCA activity, associated with smaller SERCA protein expression\textsuperscript{18, 34}, is
evident in human cAF and explains the slower CaT decay compared to sinus rhythm.\textsuperscript{16,18,34} On the other hand, reduced inhibition of SERCA by hyperphosphorylated PLN\textsuperscript{34} in cAF could help to maintain a normal SR Ca\textsuperscript{2+} load despite increased RyR activity.

**Ankyrin-B**

Ankyrin-B (encoded by ANK2) is an adapter protein expressed in excitable cells that targets ion channels (e.g., Na\textsuperscript{+} and Ca\textsuperscript{2+} channels), transporters (e.g., NKA and NCX), and signaling molecules to specific membrane domains. In the heart, ankyrin-B loss-of-function mutations in humans lead to Long QT syndrome, AF, sinus node dysfunction and stress-induced ventricular arrhythmias.\textsuperscript{69} Recently, reduced ankyrin-B expression has been demonstrated in atrial samples of patients with paroxysmal AF, and supported an association between ankyrin-B and AF.\textsuperscript{70} A new potential molecular mechanism underlying ankyrin-associated AF has been proposed involving disrupted Cav1.3 (atrial L-type Ca\textsuperscript{2+} channels) membrane targeting in atrial myocytes.\textsuperscript{70} It will be interesting to further explore the role of ankyrin in cAF.

**Myofilaments**

Altered Ca\textsuperscript{2+} handling (namely, downregulation of the L-type Ca\textsuperscript{2+} channels and increased Ca\textsuperscript{2+} extrusion via NCX) could account for the depressed contractility in remodeled atria, but a reduction of the maximum force generating capacity of the myofilaments and its Ca\textsuperscript{2+}-sensitivity may also be involved. Indeed, recent studies have highlighted the potential role of sarcomeric proteins in the cAF induced hypocontractility,\textsuperscript{9, 34, 71} although results are somewhat controversial. Compared to sinus rhythm myofibrils, cAF myofibrils exhibited reduced maximum rate of tension generation and maximum active tension, reduced passive tension, and increased in myofilament Ca\textsuperscript{2+} sensitivity.\textsuperscript{9} An earlier study did not show significant changes in maximum force and passive force, but did report reduced rate of tension redevelopment in cAF.\textsuperscript{71} One major difference between the two studies is that the former used left atrial samples whereas the latter used right atrial samples.

Altered phosphorylation state of various myofilament proteins was found in cAF vs. sinus rhythm. Phosphorylation of the primary sarcomere target of PKA, cTnI, was not altered in cAF atria.\textsuperscript{9, 34} The expression of the slow β-myosin heavy chain isoform (cMyBP-C)\textsuperscript{9, 34, 71} was upregulated in cAF, and its phosphorylation levels were found significantly increased\textsuperscript{9} or decreased.\textsuperscript{34} It has been suggested that discrepancies between these results may be explained by a decrease in cMyBP-C phosphorylation in cAF reflecting atrial dilation rather than being a component of cAF.\textsuperscript{9} Another potential reason is the use of samples from the left atrium in the former study and from the right atrium in the latter.

Further studies are needed to resolve these inconsistencies. Furthermore, cell shortening data that are currently missing in human atrial myocytes may help in linking these molecular changes to functional alterations.

It is becoming increasingly clear that studies of remodeling of human atrium by chronic AF are frequently and unavoidably influenced in part by multiple confounding clinical variables such as patient age, sex, disease history, and drug treatments. Furthermore, the changes in ion currents and APs should be considered to be associated with, rather than necessarily caused by, the chronic AF. Nevertheless, the concordance between these human chronic AF data and AF/atrial tachypacing-induced changes in animal models (see Table 1 in(72)) supports the view that chronic AF causes atrial electrophysiological remodeling in humans.

**Consequences of Ventricular Dysfunction and Atrial Dilation on Human Atrial AP**
Cardiac dilatation is known to develop frequently during the course of cardiac failure. In trabeculae and myocytes taken from dilated atria the AP was shorter and the plateau was markedly depressed (Fig. 3C) compared to trabeculae and myocytes from non-dilated atria. However, it must be noted that the ventricular dysfunction was not quantified in these patients. AP changes were explained with more severely depressed $I_{\text{Cal}}$ compared to the reduction in total outward current.

Overall, the ionic bases of altered atrial function in patients with ventricular dysfunction, and how it predisposes to more frequent AF episodes culminating in cAF, remains poorly understood.

### Autonomic Changes in Chronic AF and Related Myocardial Diseases

The autonomic nervous system, and particularly the relative activities of the sympathetic (adrenergic) and parasympathetic (cholinergic) branches, have a major influence on the occurrence of AF. Furthermore, chronic AF, and certain predisposing cardiac pathologies, remodel atrial electrophysiological responses to catecholamines and acetylcholine and thus influence the electrophysiological mechanisms of AF. β-adrenergic stimulation increases human atrial $I_{\text{Cal}}$, $I_{\text{Ker}}$, $I_{\text{K,ACh}^*}$, and $I_{\text{Kur}^*}$ has no effect on $I_{\text{Kl}^*}$, $I_{\text{K,ACh}}$ or $I_{\text{to}^*}$ and has markedly different effects on connexin conductance or expression, depending upon their main molecular correlate; i.e. Cx40, Cx43, Cx45. The increased $I_{\text{Cal}}$ and $I_{\text{Kur}^*}$ with lack of effect on other repolarizing currents, results in no net effect of β-stimulation on atrial APD$_{50}$ as predicted by our model, consistent with 5 of 6 reports in human atrial cells or tissues. However, the increased $I_{\text{Cal}}$ markedly elevates the AP plateau and, coupled with increased [Ca$^{2+}]_{i}$ from PLN phosphorylation by adrenergic stimulation, favors non-reentrant activity such as afterdepolarizations.
Human atrial studies of α-adrenergic stimulation are sparse: phenylephrine inhibited $I_{K\text{r}}$ \(^{85}\), $I_{K,ACh}$ \(^{85}\) and $I_{Kur}$ \(^{82}\) also potentially promoting afterdepolarizations. Chronic AF consistently potentiates the effect of β-adrenergic stimulation to increase human atrial $I_{CaL}$ \(^{11,40,43,90}\). While this could, in theory, increase the propensity for afterdepolarizations in the presence of catecholamines, chronic AF also markedly decreases basal $I_{CaL}$ \(^{6}\) and attenuates the effects of α-stimulation on $I_{K1}$ and $I_{K,ACh}$ \(^{85}\). Chronic AF may also cause increased atrial adrenergic innervation, “neural remodeling”, in patients.\(^{91}\) The effects of chronic AF on $[Ca^{2+}]_i$-responses to adrenergic stimulation have yet to be studied in human atrium. Data on effects of myocardial diseases that predispose to AF, on human atrial adrenergic responses, are equivocal: the ability of β-stimulation to increase $I_{CaL}$ was attenuated \(^{92,93}\), unchanged \(^{75}\) or potentiated \(^{77}\) in association with HF or LVSD. An attenuated $I_{CaL}$-increase was also reported in cells obtained from dilated atria from explanted hearts.\(^{79}\) Attenuated β-responses may involve reduced β-receptor density or function.\(^{87}\) Post-operative AF was not predicted by any change in the preoperative atrial $I_{CaL}$ response to β-stimulation.\(^{94}\) Cholinergic elevation and increased levels of acetylcholine activate $I_{K,ACh}$ and also antagonize effects of catecholamines on $I_{CaL}$, both shortening APD and ERP, thus promoting reentry.\(^{95}\) Also, combined adrenergic/cholinergic-stimulation may produce “late phase EADs”,\(^{96}\) possibly by concurrently shortening APD and increasing $[Ca^{2+}]_i$.\(^{97}\) Chronic AF induces a constitutively active $I_{K,ACh}$ in human atrium,\(^{57}\) likely resulting from a PKC isoform switch.\(^{98}\) However, the acetylcholine-mediated increase in atrial $I_{K,ACh}$ \(^{13,57}\) and shortening in atrial APD \(^{13}\) were each attenuated in chronic AF, and the cholinergic receptors GIRK1 and GIRK4 were generally downregulated.\(^{5}\) The attenuation of atrial cholinergic responses by chronic AF may be restricted to the right atrium.\(^{56}\) The ability of acetylcholine to increase $I_{K,ACh}$ and/or shorten atrial APD may be attenuated by HF, as shown in dogs.\(^{99}\) However, corroborative data from human patients with HF or LVSD are sparse and confounded by the presence of chronic AF.\(^{76}\) While much progress has been made, the complex and interacting influences of chronic AF and its predisposing myocardial pathologies on the involvement of the autonomic system in AF are yet to be resolved.

**Oxidative Stress and Inflammation-related Changes in Human AF**

Patients undergoing cardiac surgery often experience post-operative AF. It has been shown that these patients did not exhibit the electrophysiological remodeling seen in patients with cAF as far as $Ca^{2+}$ and $K^+$ currents and AP characteristics are concerned,\(^{94}\) whereas altered atrial $Ca^{2+}$ handling in post-operative AF patients has not yet been studied. However, Van Wagoner et al. showed that patients with the highest $I_{CaL}$ density pre-surgery, were associated with post-operative AF, thus indirectly suggesting a role for $Ca^{2+}$ overload, mediated via oxidative/inflammatory stress, as a possible trigger.\(^{11}\) This is because increased levels of inflammatory markers are often recorded after cardiac surgery, and recent evidence suggests oxidative stress may play an important role in the pathogenesis and perpetuation of post-operative AF.\(^{100}\)

Several studies have shown increased myocardial oxidative stress associated with AF.\(^{38,101}\) In addition, inflammatory markers such as interleukin-6 and C-reactive protein have been found elevated in AF patients.\(^{101,102}\) Evidence suggests that in several pathophysiological conditions inflammation and oxidative stress are highly interrelated, whereby inflammation augments oxidative stress and vice versa, and may be involved in AF pathogenesis. Importantly, oxidant and inflammatory mechanisms may contribute to the described structural, electrophysiological, and contractile remodeling that favors maintenance of AF,\(^{103}\) and thus could be considered as targets for AF-treatment, as

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discussed in more comprehensive reviews on the topic.\textsuperscript{101,104} Inflammatory processes may contribute to atrial injury resulting in myocyte hypertrophy and fibrosis. Furthermore, several Ca\textsuperscript{2+} channels and transporters are the subject of redox modulation.\textsuperscript{105} For example, oxidative stress may play an important role in $I_{Ca,L}$ changes, as it has been shown that S-nitrosylation of the L-type Ca\textsuperscript{2+} channel α subunit is increased in AF, and exogenously applied glutathione partially restores the AF-related $I_{Ca,L}$ reduction.\textsuperscript{106} We also discussed above the potential contribution of oxidation in AF-associated RyR hyperactivity. Several K\textsuperscript{+} channels (e.g., $I_{KATP}$ and $I_{Kur}$) are also sensitive to redox state. Kv1.5 currents are inhibited by oxidation by S-nitrosylation \textsuperscript{108}, which may contribute to $I_{Kur}$ suppression in AF. Redox-dependent modulation of Na\textsuperscript{+} channel activity has also been reported.\textsuperscript{109} Additionally, oxidative stress may affect myofilament protein function \textsuperscript{38} and influence the activity of protein kinases (e.g., CaMKII\textsuperscript{110}) and phosphatases that alter E-C coupling via phosphorylation of target proteins and are also redox sensitive. Suppressing E-C coupling remodeling with anti-inflammatory and antioxidant drugs (such as glucocorticoids and statins) has proven clinically useful in some cases in preventing AF recurrence.\textsuperscript{104} In sum, we are still limited in our understanding regarding how oxidative/inflammatory stress influences E-C coupling, particularly in the context of chronic AF, and further studies are warranted.

**Conclusions**

Chronic AF is associated with altered expression and activity of numerous sarcolemmal ion channels, transporters, Ca\textsuperscript{2+} handling and myofilament proteins. Understanding the ionic mechanisms underlying E-C coupling remodeling in fibrillating human atria, and distinguishing compensatory responses from maladaptive mechanisms, may allow for identification of new therapeutic targets to improve electrical and contractile function in cAF patients.

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Introduction

Catheter ablation for atrial fibrillation (AF) has become the mainstay of interventional treatment of AF and primarily aims at the elimination of AF triggers, which are myocardial muscle extensions (“sleeves”) covering the outside of the pulmonary veins (PV).\textsuperscript{1-3} AF ablation has been mainly performed with the use of radiofrequency (RF) energy creating continuous circumferential lesions by point-by-point ablation. Given the difficulties associated with creating contiguous curvilinear lesions with focal ablation, this technique is challenging and highly dependent on operator dexterity. Therefore, efforts have been directed towards the development of balloon-based systems potentially offering a simpler and less operator dependent means of achieving PV isolation (PVI) by creating a continuous circumferential lesion set with a limited number of energy applications. While such a balloon-based system using cryothermal energy – the cryoballoon (Arctic Front, Medtronic, Minneapolis, MN) – has been commercially used in Europe since 2005, it has only recently received Food and Drug Administration (FDA) approval for the treatment of paroxysmal AF in the United States based on the STOP-AF trial (Sustained Treatment of Paroxysmal Atrial Fibrillation).\textsuperscript{4}

Apart from the efficacy of a novel treatment modality, it is of importance to determine its safety in order to determine the risk-to-benefit profile of a specific procedure. “New” intervention related complications were identified since the beginning of AF ablation using RF energy, such as development of PV stenosis or atrio-esophageal fistula. Although complication rates of cryoballoon ablation of AF have been reported to be similar when compared to radiofrequency ablation (RFA), specific energy and device related complications are probable.\textsuperscript{5,6}

The aim of this article is to review the role of cryoballoon ablation in patients with paroxysmal AF with an emphasis on practical technical aspects, but also limitations and pitfalls based on our clinical experience.

Theoretical Considerations

The basics of cryotherapy on the cellular level have been described in detail.\textsuperscript{7} Briefly, cell in-
Jury due to cryoenergy application is determined by direct cell injury and vascular stasis. The key for irreversible tissue injury is the tissue temperature. At a tissue temperature of -20 °C, ice crystals grow, cells shrink, and membranes and cell constitutions are damaged. Intracellular ice formation occurs at temperatures of -40 °C. With the current cryoballoon system, tissue temperature cannot be measured directly. The cryoconsole monitors the inner balloon temperature from a sensor located in the proximal part of the balloon. Temperature is determined by the overall heat transferred from the myocardium and the surrounding blood. The heat transfer from blood is highly dependent on the blood flow around the balloon. The higher the blood flow, the higher is the amount of heat transferred and consequently the higher the measured inner cryoballoon temperature. Since the surface area of the balloon surrounded by blood is much bigger than the surface area in contact with the tissue, the inner balloon temperature is mainly determined by this convective heating. The influence of the balloon surface area on its temperature can easily be seen when comparing the superior with the inferior PVs or the big and small cryoballoon. Since the small balloon with a diameter of 23-mm has only approximately two thirds of the surface area of a 28-mm balloon, the measured inner cryoballoon temperatures are much lower than for the big balloon.  

Dependent on how the cryoballoon fits into the PV antrum and consequently on the ratio of the cryoballoon surface in contact with the myocardial tissue compared to the area surrounded by blood, the measured temperature is higher or lower. Therefore, temperature measurements during cryoballoon ablation can be used as a surrogate of the contact area with tissue, but should not be used as a measure of the balloon surface temperature or even tissue temperature. 

Due to the design of the nitrous oxide injection into the cryoballoon, the temperature is not homogeneous at the balloon surface. As seen in figure 1, there are 4 cold spots with ice formation on the cryoballoon surface where the jets of nitrous oxide hit the surface. For maximal cooling of the myocardium, the ideal contact with the tissue is at this distal one third of the cryoballoon surface area. Based on these theoretical considerations, central alignment of the cryoballoon with the PV prior to freezing and a 45 degree rotation of the cryoballoon for the second freezing cycle may play a key role to achieve maximal heat transfer from the tissue and consequently create permanent lesions. 

**Technical Aspects**

“Single-shot” techniques for PVI are generally thought to be less dependent on operator dexterity. The cryoballoon produces a large circular ablation zone and is potentially less direction dependent and more stable, as the balloon freezes to the tissue compared to other balloon based ablation technologies. Studies reporting on operator learning curves describe rapidly decreasing procedure- and fluoroscopy times, as well as numbers of energy applications needed to achieve PVI.  

Electrophysiologists performing cryoballoon ablations often have ample experience with left atrial ablations and therefore might have a steep learning curve. However, this might be different if cryoballoon ablation is performed by cardiologists with no or limited experience with left atrial procedures. The cryoballoon is a relatively stiff device requiring a 15 Fr outer diameter deflectable sheath (FlexCath, Medtronic), and even though the problem of creating a continuous lesion with focal RFA may be overcome with the cryoballoon, operator skills in addition to knowledge of the left atrial anatomy are certainly needed to safely maneuver the device. 

Because of the large caliber sheath required for the cryoballoon, proper vascular access is important. At our institution, cryoballoon ablation is usually performed with a three-catheter approach via the right femoral vein using the 28-mm cryoballoon only. In addition to the cryoballoon, a coronary sinus catheter is used as a reference and for pacing a long with a circumferential mapping catheter. While ablating the right PVs one needs to be cautious not to damage the right phrenic nerve. As discussed later in this paper, the latter can be monitored by phrenic nerve pacing from the superior vena cava during cryoballoon ablation. In order to enhance catheter stability in the superior vena cava, we commonly use the coronary sinus catheter for phrenic nerve stimulation instead of an additional non-deflectable catheter.
Access to the left atrium (LA) is gained by performing transseptal puncture. We usually perform two separate transseptal punctures for the cryoballoon and the circumferential mapping catheter because of concerns of persistence of iatrogenic atrial septal defect with passage of two catheters through a single puncture, especially when using a large sheath as required for the cryoballoon. A novel spiral catheter designed for the insertion through the cryoballoon serving as a guidewire and allowing real-time monitoring of PV potentials during cryoablation has been proposed recently and has the potential to overcome the need for a double transseptal puncture. The possibilities and pitfalls of this “through-the-balloon” circumferential mapping catheter will be discussed below.

Anticoagulation is initiated with unfractionated heparin with administration of a loading dose directly after transseptal puncture. Measurement of the activated clotting time is repeated every 30 minutes with more frequent initial measurements and the heparin dose is adjusted in order to achieve a target activated clotting time of 350 seconds. The cryoballoon catheter should be advanced over the wire into the LA in order to prevent inadvertent collateral damage from the relatively stiff tip of the catheter. However, the stiff J-tipped guidewire also needs to be placed with caution since a guidewire-associated dissection of the right inferior pulmonary vein has been described. Once the guidewire is in the targeted vein, the balloon is inflated and positioned against the wall. Central alignment of the sheath should be attained. Contrast injection through the lumen of the catheter into the PV is then performed. In case of good tissue contact along the whole periphery of the balloon, the injected contrast is entrapped in the vein and no para-balloon leaking can be visualized. The catheter is then flushed with saline injection through the balloon catheter and the freezing cycle may be initiated with a standard duration of 5 minutes. We commonly perform two applications (10 minutes of cryoenergy) per PV before inserting the spiral catheter to check for PVI. If PVI cannot be achieved using the cryoballoon alone, we switch to a conventional focal RF catheter. The number of freezing cycles after which a switch to RF is made varies between published studies. We used to perform up to six applications (30 minutes of cryoenergy) if a PV could not be isolated before switching to RF. We now commonly switch to RF after 3 failed isolation attempts.

If PV occlusion is not achieved, special techniques can be applied. Placing the guidewire in different PV branches by deflecting the sheath and the catheter may result in better occlusion and may also correct the central alignment. An inferior gap can frequently be closed with the “pull-down” technique. Freezing is started at the superior PV circumference followed by a gentle pull-down maneuver resulting in better central alignment of the sheath and thus better tissue contact at the
This is especially helpful with ablation at the right inferior PV. The “hockey-stick” technique is a further strategy that has been described for early branching inferior PV to allow balloon-tissue contact at the inferior PV circumference. After placement of the guidewire in the early branching inferior PV the sheath is advanced with maximal bend to the superior-posterior LA. This technique was reported to allow the balloon to be pushed onto the inferior circumference of the PV ostium. However, we experienced incomplete PV occlusion in a relevant number of cases with this technique and commonly use a “modified hockey-stick” technique for the left inferior PV. We keep the sheath low in the LA and the balloon catheter is advanced in the direction of the PV with a slight upward deflection (Figure 2). The ipsilateral PVs may share common fascicles and thus cryoenergy application at the inferior PV may result in isolation of the superior PV, or vice versa, a phenomenon named “cross-talk”. Thus an isolation attempt at the inferior PV is advisable even if complete isolation of the superior PV has not been achieved after two freezing cycles, especially when remaining PV potentials are visible at the inferior circumference of the superior PV.

The lack of real-time monitoring of PV potentials during cryoballoon ablation is a limitation of this technique. A novel spiral mapping catheter (Achieve, Medtronic) that can be inserted through the lumen of the cryoballoon catheter has recently received FDA approval. In addition, it may obviate the need for the separate circular mapping catheter and thus the second septal puncture. This “through-the-balloon” circumferential mapping catheter is available in two fixed diameters (15mm and 20mm). To date, no study investigated whether PVs can be isolated using the novel spiral catheter alone and how reliable it is in confirming complete PVI. With the current design of the cryoballoon, it is our experience that the spiral mapping catheter is frequently positioned too deep in the PV resulting in inadequate signal quality. However, if real-time monitoring of PV potentials can be performed, the time needed to isolate the vein has been demonstrated to predict sustained PVI using the Promap catheter (Prorhythm Inc., Ronkonkoma, NY). This makes monitoring of PV signals during the freezing cycle an attractive tool because unsuccessful freezes can be aborted early. Figure 3 shows real-time PVI of the left inferior PV during cryoablation with the 28-mm balloon using the “through-the-balloon” circumferential mapping catheter.

**Acute Pulmonary Vein Isolation**

Andrade et al. systematically reviewed 23 articles...
using cryoballoon for AF ablation to define its efficacy and safety.\textsuperscript{5} Acute PVI was achieved in 98.81\% of patients (n = 924) and in 98.47\% of targeted veins (n = 3,803). Complete PVI in studies using the cryoballoon alone was achieved in 77.81\% of patients and in 92.64\% of targeted veins compared to concomitant use of focal ablation, either with cryo- or RF energy. Procedure- and fluoroscopy times are significantly longer if a catheter switch is necessary.\textsuperscript{10,16,18}

In our comparative study treating paroxysmal AF patients using the 28-mm cryoballoon, a switch to a focal ablation catheter was required in 28\% of cases to achieve complete PVI.\textsuperscript{13} Similar acute PVI rates are reported by Van Belle et al. (84\%) using both the 23-mm, and 28-mm cryoballoon,\textsuperscript{10} while others report a significantly lower success rate of only 40\%.\textsuperscript{14} Chun et al. and Klein et al. were able to isolate 98\% and 95\% of all PVs, respectively.\textsuperscript{15,19} However, in order to achieve an acute PVI rate of 98\%, up to 45 minutes of cryoenergy on a single PV, and up to 65 minutes in case of the presence of a left common PV was necessary.\textsuperscript{15} We commonly use an irrigated tip RF catheter for “touch-up” ablations but a focal cryoablation catheter is available (Freezor Cardiac CryoAblation Catheter, Medtronic).

To achieve complete PVI using the cryoballoon solely, continuous balloon-tissue contact is necessary. Due to individual anatomy this may be challenging and special techniques may be required, especially at regions of enhanced muscular thickness, such as the left atrial appendage-left PV ridge or inferior segments of the PV, where PV reconduction occurs more frequently.\textsuperscript{13,20} Excessive force in order to achieve complete PV occlusion should probably be avoided for safety reasons, but distortion of the non-compliant balloon may still be seen occasionally. Figure 4 demonstrates a distorted cryoballoon due to push towards the left inferior PV in order to achieve complete PV occlusion. In some patients, PV anatomy may preclude optimal balloon positioning, such as an oval shape of the PV, a common ostium or angulated vein insertions.\textsuperscript{21} Therefore studies defining anatomical variations not suitable for cryoballoon ablation are warranted.

Exchanging catheters in the LA is associated with longer procedure times and carries the potential risk of embolic complications, especially with the large diameter sheaths used with cryoballoon ablation. Therefore, very careful handling of sheaths and catheters is required.

Cryoballoon temperature is monitored continuously during cryoballoon ablation by a thermocouple in the proximal inner balloon and is affected by balloon occlusion of the treated PV because remaining blood flow has a rewarming effect. This can be seen during cryoablation when performing a pull-down maneuver to close a remaining gap at the inferior PV circumference.\textsuperscript{15} In case of complete PV occlusion...
clusion following this maneuver a further temperature drop is frequently observed. Although temperature measurement by the thermocouple does not reflect true tissue temperature achieved during cryoablation ablation, several data suggest a relationship between balloon temperature and acute PVI. In an animal model, the success rate for chronic PVI was higher in the absence of peri-balloon flow leak as evaluated by intracardiac echocardiography and with lower balloon temperatures. However, effective balloon temperatures were below -80 °C, which is not seen in human cryoballoon ablation procedures. In the study by Klein et al. using both the 23-mm and 28-mm balloon, minimal temperatures were similar in the superior or inferior and right or left PVs with a trend for higher minimal temperature in the right inferior PV. The authors report high acute PVI success rate of 95% with a mean minimal temperature below -50 °C during cryoablation, except for the right inferior PV (-49 °C) but the authors provide no data on temperature association with acute PVI success. In the study by Linhart et al. acute success rate was 81% of targeted PVs and the temperature achieved during cryoballoon ablation with either the 23-mm or 28-mm balloon, was not as low as compared to the study by Klein et. al. (-44.6 °C). Acute PVI has been demonstrated to be associated with lower balloon temperature achieved during cryoballoon ablation. A balloon temperature below -51 °C has been shown to be associated with successful acute PVI and balloon temperatures ≥ -36 °C for superior or ≥ -33 °C for inferior PVs 120 seconds after initiating the freezing cycle predicted failed PVI. Thus, balloon temperature may be used to discriminate between successful and failed PVI at various time points during the freezing cycle. However, the same authors report PV conduction recovery during a redo procedure and retrospectively analyzed the minimal balloon temperature achieved during cryoballoon ablation using the 28-mm balloon. The differences in minimal temperatures in those with successful long-term PVI compared to those with recovery of conduction were small and statistically significant for the right superior PV only.

Long-term Outcome

Reported success rates 12 months after cryoballoon ablation of paroxysmal AF, defined as freedom from AF without antiarrhythmic drug therapy vary between 59% and 89%. Patient selection and follow-up differ significantly between studies and may, at least in part, explain the variable success rates. In the systematic literature review by Andrade et al. 1-year freedom from AF recurrence after 3 months blanking period was 72.83% (95% CI 68.79-76.62%), including studies that included patients with persistent AF. To date, no randomized trial compared AF ablation with RF energy and cryoballoon. Non-randomized studies comparing cryoballoon with RFA of paroxysmal AF have reported on similar success rates between the groups.

The only randomized study, the STOP-AF trial...
performed in patients with paroxysmal AF and previously failed antiarrhythmic drug treatment, compared cryoballoon ablation with antiarrhythmic drug therapy and demonstrated a significantly greater treatment success (69.9% vs. 7.3% freedom of AF) and an improvement of quality of life at 12 months in the cryoballoon ablation group. It has to be mentioned, that the STOP-AF trial defined acute procedural success rate as an isolation of ≥3 PVs, a definition not previously used in AF ablation trials. In addition, 19% of patients in the interventional arm underwent a redo procedure with the cryoballoon during the 3-months blanking period.

Pulmonary vein reconnections in patients with recurrent AF following cryoablation undergoing a redo procedure were found in 2.7±0.4 veins per patients. Although the right inferior PV is generally thought to be challenging in terms of complete acute PVI because of anatomical reasons, electrical reconnection for left-sided PVs was demonstrated more frequently.

Reconduction has been demonstrated to occur most often at inferior locations and the anterior aspect of the left atrial appendage (LAA)-PV junction (“ridge”) after cryoballoon ablation with the 28-mm cryoballoon. The PV reconnection site at the inferior circumference seems to be associated with cryoballoon ablation, while following RFA no specific PV reconnection pattern is found, with the exception of the ridge between the LAA and the left superior PV. The reason for the inferior location of PV reconnection may be due to the cranial sheath orientation, resulting in good tissue contact at the superior aspect of the PVs. In contrast to superior PVs where the sheath and the cryoballoon are relatively easily aligned with the PV and the catheter can be pushed towards the PV ostium, complete PV occlusion with inferior PVs are more difficult to achieve. Cryolesions achieved with poor balloon-tissue contact may acutely lead to PVI while being prone to later conduction recovery. Due to the orientation of the refrigerant jets, the deepest temperature at the balloon surface is achieved just in front of the equator. Therefore, despite good occlusion and low temperatures lesions may be inadequate due to a lack of central alignment of the balloon.

PV reconnection is regarded as the most common reason for recurrence in patients with paroxysmal AF after catheter ablation. At our institute, we use RF for repeat procedures in patients with recurrent AF after cryoballoon ablation. The rationale for this approach is that the predilection sites for conduction gaps are likely to apply for the second procedure as well because they are likely due to anatomical factors. This might explain the observation of RFA being more efficient compared to cryoballoon for repeat procedures. In addition, PV respiration with RF energy in conjunction with electroanatomical mapping systems can be achieved with low radiation exposure.

Complications Associated with Cryoablation

Complication rates in patients undergoing RFA have been extensively investigated and were reported in 3.5% to 6% of patients. These include vascular access complications (1.1-1.9%), cardiac tamponade (1.2-1.3%), thromboembolic event (0.2-0.4%), and very rarely atrio-esophageal fistula (0.2%), PV stenosis (<0.01%) or death (0.2%). Complication rates with cryoballoon have been less intensively investigated, but have been reported to be similar compared to RFA. Importantly, the cryoballoon trials included patients during the early learning curve of some operators and therefore there may be potential for complication rates to decrease with increasing operator experience.

Vascular Access Complications

Complication rates related to the vascular access site including haemorrhage, iatrogenic arterial pseudoaneurysm or arteriovenous fistula formation during cryoablation seem to be slightly higher compared to RFA of AF with an incidence of 1.79% vs. 1.2%. The cryoballoon sheath has a larger outer diameter compared to sheaths used during RFA and therefore special attention has to be paid on the adequate puncture technique.

Phrenic Nerve Palsy

With a reported incidence of 2.8% to 13.5% phrenic nerve palsy (PNP) is the most frequent complication of cryoballoon ablation. Owing to the proximity of the right-sided PVs to the right phrenic nerve, PNP occurs during cryo-
ablation of the right-sided PVs, in particular the right superior PV but PNP during ablation of the right inferior PV has been reported. The use of a 23-mm balloon is significantly more often associated with PNP compared to the 28-mm balloon (12.4% vs. 3.5%, p=0.0001). Presumably, although not investigated systematically, the explanation is the more distal ablation site within the PV with the smaller balloon that minimizes the distance between the balloon and the phrenic nerve. In addition, cryoablation deep within the PV might enhance cold transfer due to less convective heating of the balloon by atrial blood flow. Luckily, most PNP are transient and resolve within 14 months with an incidence of PNP of only 0.37% persisting beyond 1 year. However, the morbidity of PNP is considerable. Different measures to avoid PNP have been proposed. Because of the higher incidence of PNP with the 23-mm diameter balloon, caution has to be advised with the smaller balloon size. Phrenic nerve stimulation at a cycle length of 1000 ms during cryoablation of both the right superior and inferior PVs is performed at our institution. Phrenic nerve capture is confirmed by fluoroscopy and manual confirmation before initiation of the freezing cycle and capture should then be assured throughout the freezing cycle by continuous palpation of the abdomen. One member of the electrophysiology laboratory personnel is standing next to the refrigeration console (Cryo-Console, Medtronic) and immediate discontinuation of the freezing cycle in case of loss of phrenic nerve capture or decrease of diaphragmatic contraction is mandatory. Importantly, phrenic nerve damage may be missed if stimulation is performed distal to the potential site of injury. We therefore aim to achieve a stable catheter position in the superior vena cava superior, and demonstration of consistent phrenic nerve capture before initiating the freezing cycle may help to avoid over-diagnosing PNP. To enhance catheter stability, we commonly use the deflectable coronary sinus catheter instead of an additional catheter placed in the superior vena cava (Figure 5). At our institution, AF ablation procedures are performed in conscious sedation and adapting the level of sedation may improve the tolerability of phrenic nerve pacing. PNP has been reported to occur with the larger balloon also. In addition, early termination of cryoenergy application with loss of phrenic nerve capture did not prevent the subsequent occurrence of PNP, including cases of persistent PNP. However, it may be that recovery of phrenic nerve function is due to early termination of the freezing cycle in case of loss of phrenic nerve capture. A small series of cryoballoon ablation using only the 28-mm balloon reported unintentional cryothermal energy application inside the PV with subsequent PNP in patients with large right sided PV ostia. The authors propose calculating the ratio between PV diameter and balloon size and do not advise cryoballoon ablation in patients with a ratio of ≥0.93. In the same series, the balloon pressure decreased during freezing in 1/27 patient with subsequent more distal balloon position inside the right superior PV and transient PNP. From a practical standpoint, it may be advisable to perform ablation of the RIPV first because PNP appears to be exceedingly rare during ablation of the inferior vein. The rationale behind this approach is that if PNP occurs during cryoballoon ablation at the RSPV and the RIPV is not isolated yet, cryoballoon ablation at the RIPV cannot be performed safely because phrenic nerve function cannot be monitored unless recovery of phrenic nerve function is immediate. Pulmonary Vein Stenosis PV stenosis is a complication, associated with catheter ablation of AF using RF energy as a result of energy application inside PVs. Due to differences in the definition of PV stenosis and the rate of screening for this complication reported incidences vary widely from 0% to 38% and the true incidence might be underestimated, as screening for asymptomatic PV stenosis is not performed routinely. Although the precise pathophysiological mechanism is unclear, a progressive vascular reaction leading to replacement of necrotic myocardium by collagen is the most plausible mechanism. In contrast to the beginning of AF ablation in the late 1990’s when investigators were not aware of this potential complication, consensus exists today, that avoiding RF energy delivery within a PV can prevent PV stenosis. PV stenosis has been considered very rare following cryoballoon ablation but concerns rose after presentation of the STOP-AF trial and the first re-
In 9 studies using systematic non-invasive imaging screening for PV stenosis between 1 and 12 months following cryoballoon ablation (773 procedures) the incidence of PV stenosis was 0.90% (7/773). Of note, all cases were observed in the STOP-AF trial, which observed 7 PV stenoses in 228 patients (10/927 PV), resulting in an incidence of 3%. However, STOP-AF used a >75% reduction in cross-sectional area from baseline to define PV stenosis, which corresponds to a 50% reduction of PV diameter. In studies using standard definition based on reduction of the PV diameter >75%, the incidence of PV stenosis was 0%. Thus the reported incidence by the STOP-AF trial may overestimate the real incidence of relevant PV stenosis following cryoballoon ablation due to a more “cautious” definition of PV stenosis.

Reassuringly, the incidence of significant PV stenosis resulting in symptoms or requiring intervention seems to be lower (0.17%) compared to AF ablation with RF energy. However, underestimation of the PV diameter and thus energy application within the PV makes PV stenosis using cryoballoon conceivable.

**Left Atrial Tachycardia and Flutter**

Left atrial tachycardia following RFA of AF is relatively common. This is especially true for patients with persistent AF, who are likely to receive additional linear lesions in the LA, which enhance the likelihood of gaps and thus drive the probability for the occurrence of left atrial tachycardia. The problem of left atrial tachycardia has been described in 0.8% to 1.7% of patients after cryoballoon ablation. This low rate of left atrial tachycardia may be due to the fact that the lesion sets with cryoballoon ablation are circumferential and relatively close to PVs.

**Injury of Adjacent Structures**

No cases of atrio-esophageal fistula have been reported in AF ablation procedures with the cryoballoon. Three studies comprising 116 participants systematically performed upper endoscopy following cryoballoon. In one study, esophageal ulceration was reported in 6/35 patients, whereas two other studies demonstrated no esophageal lesion in 38 and 43 patients, respectively. Luminal esophageal temperature has been showed to decrease during cryoablation, even to subzero temperatures, especially when applying cryothermal energy in the inferior PVs. However, given the relatively small number of patients treated so far in published trials or case series, it may be too early to conclude whether atrio-esophageal fistula formation is of concern following cryoballoon ablation.
Recently, bronchial erosion following cryoballoon ablation with a 23-mm balloon deep inside the left inferior PV and a maximal temperature of -64°C was reported. The patient presented with haemoptysis 4 days after the procedure and thoracic computer tomography imaging revealed no abnormalities. Bronchoscopy showed erosion with blood effusion on the ventral side at the division of the left superior and inferior bronchus, which was located close to the left inferior PV on a computer tomography scan. Van Belle et al. report on 2/57 (3.5%) patients, who presented with haemoptysis that occurred within the first month following the procedure. The authors ruled out PV stenosis with a multislice computer tomography scan but bronchoscopy to exclude bronchial lesion formation was not performed and symptoms did not recur after temporary cessation of anticoagulant therapy. Consequently, following cryoballoon ablation of AF, a high level of vigilance must be maintained because of potential injury of surrounding anatomical structures if patients present with haemoptysis or unspecific symptoms, such as swallowing discomfort, recurrent neurological events, fever and chills, suggestive for bronchial or esophageal injury, respectively.

Thromboembolic Events

Cerebrovascular events associated with the ablation procedure are the most serious complications of RFA of AF with an incidence of 1 to 5% at the beginning of the AF ablation era. Ischemic brain injury was the third most frequent cause of death in a large worldwide retrospective case series of AF ablation with RF over a broad spectrum of electrophysiology laboratories from 1995 to 2005. Improvements of the RF ablation technique, including the use of irrigated tip catheters and a more aggressive procedural anticoagulation regimen have decreased the incidence of stroke to ≤0.5% as demonstrated in recent prospective studies. Comparing the incidence of cerebral microembolic signals in 30 patients during AF ablation using RF 4-mm conventional non-irrigated, 4-mm irrigated tip catheter and the cryoballoon, Sauren et al. found significantly less microembolic signals in the middle cerebral arteries in procedures performed with the cryoballoon and irrigated tip catheter (non-irrigated vs. irrigated-tip vs. cryoballoon: 3,908 ± 2816 vs. 935 ± 463 and 1,404 ± 981). Gaita et al. comparing AF ablation with the cryoballoon, irrigated tip and a multielectrode RF catheter report similarly favorable findings for irrigated tip RF catheters and the cryoballoon regarding silent thromboembolic lesions documented on post-procedural magnetic resonance imaging. A recently published multicenter study prospectively compared the post-procedural incidence of new embolic lesion seen in a magnetic resonance imaging study after AF ablation using conventional irrigated-tip, cryoballoon or a novel multielectrode duty-cycled RF catheter. In the group treated with the multielectrode RF catheter ablation there was a notably higher incidence of subclinical cerebral embolic events (37.5%), while the event rate was lower but not statistically different in the conventional irrigated-tip and cryoballoon catheter group (irrigated-tip vs. cryoballoon: 7.4% vs. 4.3%; p=0.4).

In animal models ablation with the cryoballoon has been shown to reduce thrombus formation compared to RF energy, probably by producing a more homogenous lesion and by keeping the endothelium intact. A systematic review of cryoballoon ablation by Andrade et al. reported a similar incidence of thromboembolic complications of 0.57%, including periprocedural stroke, transient ischemic attack, or myocardial infarction. Of note, the reported myocardial infarctions were related to air embolism because of bubbles inside the sheath. All of the reported periprocedural myocardial infarctions resolved during the procedure without long-term sequelae. The larger outer diameter of the sheath used for cryoballoon ablation compared to sheaths routinely used during RFA might be more prone to air embolism, and thus flushing of the sheath before transseptal puncture and continuous flushing during the procedure is recommended.

Based on the currently available evidence, cryoballoon ablation compares favourably to RF ablation with regards to the risk of systemic embolism associated with AF ablation procedures.

Limitations of Cryoballoon

Balloon based ablation systems are of limited
flexibility. In patients with additional arrhythmias, such as typical isthmus-dependent atrial flutter or persistent AF, who may require linear or focal lesions, we do not use the cryoballoon. Because of this, a relevant number of patients are not considered for cryoballoon ablation at our institution. Of note, the cryoballoon is only approved for ablation of paroxysmal AF in the United States.

Complete PVI depends on adequate tissue contact and individual anatomical variants, for example the presence of a common trunk can make cryoballoon ablation challenging in some patients. A typical PV branching pattern based on the Venice Chart definition (2 left and 2 right PVs) was found to be present in 40% of AF patients only. 31% of patients presented with a common left trunk with an average value of maximal diameter of 33 mm in those with paroxysmal AF. Cryoballoon ablation with the large balloon would inevitably result in energy application deep in the PV in such cases, which should be avoided. An alternative approach would be to ablate at different arcs of the pachymetry at an antral level of a common trunk. However, this technique is not successful in our experience. Thus, although pre-procedural imaging of the LA and PVs is not required for cryoballoon ablation, we routinely perform magnetic resonance imaging or computer tomography in order to obtain anatomical information before the procedure and have recently started not to consider patients for cryoballoon ablation if relevant anatomical variants are found on pre-procedural imaging. In addition, if PVI cannot be achieved with the cryoballoon, additional costs are generated with the inevitable use of an additional catheter. We use an irrigated tip RF catheter for creating such “touch-up” lesions.

Another limitation is that circumferential tissue contact is demonstrated by contrast injection into the PV, which may result in the use of a considerable amount of contrast medium, making this technique problematic in patients with decreased renal function. Alternative modalities to demonstrate adequate tissue contact, such as assessment of the pressure curve obtained at the tip of the catheter or colour Doppler during transoesophageal echocardiography to document PV occlusion have not been widely adopted.

Conclusions

To achieve acute PVI during cryoballoon ablation, complete occlusion of the PV with the balloon and thus good balloon-tissue contact is important. This can be confirmed by contrast injection into the PV. Although the position of the temperature probe in the back of the balloon provides only a rough estimate of tissue temperatures, a rapid temperature decrease and minimal temperatures ≤ -50 °C are indicative for a good tissue contact. In case of PV occlusion failure, special techniques, such as the pull-down maneuver may help to achieve complete PV occlusion during the freezing cycle. If the temperature decrease is insufficient, abotion of the freezing cycle should be considered.

Modifications of the current balloon cooling and of temperature measurement technology in order to lower balloon temperature and to obtain real tissue temperature during the freezing cycle might improve the acute success rate of this technique. In conclusion, the cryoballoon is a novel technology for PVI and is mainly suitable for patients with paroxysmal AF. However, randomized comparisons to radiofrequency catheter ablation are lacking.

References


Epicardial Fat and Atrial Fibrillation: A Review

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Abstract

Atrial fibrillation (AF) is a progressive disorder that increases with age. Obesity is an important risk factor for AF. Pericardial fat is an active adipose tissue in close proximity to the heart and has been shown to be a risk factor for structural as well as coronary artery disease independent of body mass index. Recent studies suggest a role of epicardial fat in atrial remodeling as well as AF burden. This review will summarize the recent evidence linking epicardial fat and AF.

Introduction

Atrial fibrillation (AF) is associated with significant morbidity and mortality.1 Obesity is associated with cardiovascular disease, including AF.2-4 Visceral adipose tissue is thought to play a more central role in the development of cardiovascular disease as opposed to subcutaneous adipose tissue.5 Pericardial fat is an active adipose tissue in close proximity to the heart and has been shown to be a risk factor for structural as well as coronary artery disease independent of body mass index.6, 7 This review will summarize the recent evidence associating epicardial fat with AF.

Anatomical Definitions

The heart is covered by two sacs: The first is the fibrous pericardium, and the second is the serous pericardium which consists of two components: the visceral pericardium and the parietal pericardium. The space between the myocardium and visceral pericardium is the epicardial space and epicardial fat is defined as the fat lying within that space. On the other hand, pericardial fat is fat located within the pericardial sac, which is the border between the pericardial and intrathoracic fat.8 Epicardial fat covers 56-100% of the hearts surface in humans, and mostly is present over the atrioventricular groove, the right ventricular free wall and along the course of the coronary arteries.9 It is hard to dissect the epicardial fat entirely off the myocardium; this is especially true on the atrial surface.10, 11 This is an important limitation of autopsy studies, and most of the description of epicardial fat distribution on the atria comes from imaging studies that measured atrial fat distribution as well as thickness. At the atrial level, the epicardial fat is mostly located near the roof of the left atrium, near the left atrial appendage and lateral to the mitral isthmus, and is more in the superior half of the left atrium compared to the inferior half of the left atrium.12 Given the inability of current imaging modalities to distinguish epicardial from pericardial fat, most of the epidemiological studies as well as the clinical studies focusing on AF in this review have measured pericardial fat,13, 14 which is the fat located within the fibrous pericardial sac. This can lead to overestimation of the epicardial fat volume, an important limitation of all imaging modalities.15 Even though the authors might have measured the adipose tissue volume and thickness within the fibrous pericardial sac in this review, we kept the description terms used by the authors in their original articles.
Measurements of Epicardial Fat

1- Two Dimensional Echocardiography

There are several imaging modalities that measure epicardial fat, with some measuring the thickness and others measuring the total volume. Using two-dimensional echocardiography (2D Echo), Iacabellis et al. measured the epicardial fat thickness as a measure of visceral adiposity.\(^{16-18}\)

**Figure 1:** The PLA view, perpendicular measurements are taken between the RV wall and the visceral pericardium at end systole. Epicardial fat is the hypoechoic area between the myocardium and visceral pericardium (between the yellow arrows).

Most of the epicardial fat is located in the atrioventricular groove and interventricular groove, and is at times unevenly distributed around the atria and ventricles. In an effort to make the measurements more reliable and reproducible, epicardial fat thickness is measured in two standard views, the parasternal long axis (PLA) as well as the parasternal short axis views (PSA views). All measurements are done at end systole (when the aortic valve is open) in three cardiac cycles. In the PLA view, perpendicular measurements are taken between the RV wall and the visceral pericardium (Figure 1). In PSA view, the epicardial fat is measured at the midventricular level between the RV wall and the visceral pericardium. This method has been used in several studies linking obesity and epicardial fat and has excellent intraobserver as well as interobserver variability (ranging from 0.90 to 0.98 and from 0.93 to 0.98 respectively). There is no upper limit of normal that has been formally defined, but in general the epicardial fat thickness ranges between 1 and 23 millimeters (mm). The echocardiographic measurement of epicardial fat thickness has several advantages, including the widespread availability of 2D Echo, its low cost and the measurements are easy and can be done offline. Disadvantages include relying on thickness on two perpendicular views, which doesn’t always account for the variation in the distribution of the epicardial fat. Furthermore, the thickness of the epicardial fat is not uniform in the PLA views, and could vary between end systole and end diastole. Some patients have difficult windows and it is usually hard to distinguish the visceral pericardium, which makes it hard to differentiate between epicardial and pericardial fat. It is our view that this modality suffers from the same limitations that computed tomography and magnetic resonance imaging have when it comes to differentiation between epicardial and pericardial fat, and that most of the measurements used could have easily been for pericardial fat thickness, not epicardial fat thickness, since it is hard to identify the visceral pericardium and it is easier to identify the fibrous pericardial sac.

2-Multidetector Computed Tomography (MDCT)

The Computed tomography offers a more accurate way of measuring both pericardial fat thickness and volume. The pericardial fat is mostly located in the atrioventricular and interventricular grooves, with the thickest area being usually the right atrioventricular groove with a mean thickness of 5.3 ± 1.6 mm. A study by Batal et al measured periatrial fat thickness by having the CT plane in the mid LA and measuring the epicardial fat thickness between the LA and the esophagus (LA-ESO), LA and thoracic aorta (LA-TA) and LA and pulmonary artery (LA-PA). In the total population, including controls, patients with paroxysmal as well as persistence AF, the median LA-PA thickness was 65 mm, the median LA-ESO...
thickness was 40 mm and the mean LA-TA thickness was 58 mm. Using these parameters, the authors found that epicardial fat in close proximity to the esophagus was most significantly associated with AF burden.\textsuperscript{19} In another study on epicardial fat and AF, Tsao et al. measured epicardial atrial fat volume near as well as regional distribution around the left atrium. They found that epicardial fat is unevenly distributed around the LA and is mostly found in three areas: first is within the superior vena cava, right pulmonary artery and right sided roof of the LA (29.8\%), within the aortic root, Main pulmonary artery and LA appendage (26.5\%) and between the left inferior pulmonary vein and the left AV groove (18.1\%).\textsuperscript{12}

Most of the other studies on the association between pericardial fat and coronary artery disease (CAD) and AF focused on calculating total pericardial fat volume. CT studies were performed using a 16 or 64-slice scanner. Gated studies are performed using an electrocardiogram-triggered scanning protocol. To ensure adequate gating and minimal motion artifact, patients in AF could receive beta-blockers and have CT scanning only if the ventricular response was <80 beats/min. The percentage of the R-R interval with the least amount of motion was used for pericardial fat measurements, which are performed offline using a semi-automated technique and dedicated workstation (Figure 2). Contiguous 2.0-mm or thinner slices of the heart extending from the bifurcation of the pulmonary artery to the diaphragm are analyzed. The pericardium is usually manually traced, and pericardial fat consisted of all adipose tissue within the pericardial sac, identified by an image display threshold setting of –190 to –30 Hounsfield Units (HU),\textsuperscript{13} with some studies using a threshold of -200 to -50 HU.\textsuperscript{12} The studies reported excellent intraobserver as well as interobserver variability (ranging from 0.95 to 0.98 and 0.96 to 0.99 respectively).\textsuperscript{12,13} MDCT offers several advantages; it has a great spatial resolution, it allows accurate measurements of LA volume, and it allows for measurements of both thickness and volume of pericardial fat at the same time. However, it is expensive, not always clinically available and is associated with radiation and contrast exposure to the patient. Motion can make it very hard to measure the pericardial fat, and in patients with AF and high ventricular rates, it might be difficult to obtain a good study.

3-Magnetic Resonance Imaging

The only study on pericardial fat and AF to use Magnetic Resonance Imaging (MRI) for measurement is the study by Wong et al. They also looked at ablation outcomes. In this study, MRI at 1.5 T was used and measurements of epicardial fat were done offline as done with CT. The areas of fat were traced on consecutive end diastolic short axis images and multiplied by the thickness to obtain the total volume. Periatrial fat was defined as fat close to the LA, while periventricular fat was defined as fat close to the ventricles. Total pericardial fat is the total fat volume between the myocardium and parietal pericardium. The slices used could be up to 6 mm in thickness. MRI has several advantages including measuring LA volume, left and right ventricular structure and function, and is considered by some to be the gold standard to measure visceral adipose tis-
Epicardial Fat as an Active Tissue

Visceral adipose tissue is metabolically active and is thought to play a more central role in presence and development of cardiovascular disease as opposed to subcutaneous adipose tissue. Epicardial fat is thought to have properties similar to visceral fat. It has twice the capacity of synthesizing fatty acids compared to popliteal fat and it has a higher capacity of fatty acid breakdown. This allows it to maintain the local fatty acid concentration and protects the heart from a toxic level of fatty acids that can depress contractile function.

It acts as a buffer for the heart against hypothermia. In fact this insulating effect is also important during ablation procedures, since epicardial fat is a poor conductor of current. Epicardial fat has very slow electrical conductivity and can impede the passage of the radiofrequency current, making the epicardial ablation lesions ineffective, even when using cooled electrodes. Using mathematical modeling for radiofrequency ablation lesions on the epicardial surface of the atria, Suarez et al. found that as fat thickness increased, the maximum tissue temperature and the lesion depth decreased, regardless if dry or cooled electrodes were used. This could be the reason why 25-30% of the surgical epicardial ablation lesions are non-transmural. The slow conducting properties of the epicardial fat could have a protective effect on the esophagus when delivering endocardial ablation lesions on the posterior wall of the left atrium, but this was not formally studied. Furthermore, epicardial fat can influence the depth and size of ablation lesions delivered on the epicardial surface of both atria and ventricles and can be the cause of the failure of ablation on the epicardial surface of the heart. Epicardial fat is also an active tissue and secretes pro and anti inflammatory mediators including Tumor Necrosis Factor-α (TNF-α), Interleukin-6 (IL-6), Monocyte Chemoattractant Protein-1 (MCP-1), Leptin and Plasminogen activator inhibitor-1. Epicardial fat can also secrete pro and anti-inflammatory cytokines including Tumor Necrosis Factor-α (TNF-α), Interleukin-6 (IL-6), Monocyte Chemoattractant Protein-1 (MCP-1), Leptin and Plasminogen activator inhibitor-1.2005

Epicardial fat and Atrial Fibrillation

Early studies focused on lipomatous hypertrophy of the interatrial septum and its association with atrial fibrillation (AF). Several studies have shown a higher prevalence of inflammatory infiltrates and fibrosis in atrial biopsies of patients with lone AF. Population studies have demonstrated high levels of C-reactive protein (CRP) in patients with AF compared to controls. Furthermore, high CRP levels predict the recurrence of AF after electrical cardioversion. Shin et al. studied 80 patients with atrial fibrillation (40 with persistent AF and 40 with paroxysmal AF) and compared them with 80 controls. Patients with AF had larger LA volumes and larger atrial “epicardial” fat volumes. Adiponectin, IL-6 and TNF-α levels were only measured in AF patients and not in controls. Patients with persistent AF had lower adiponectin levels and higher levels of IL-6 and TNF-α compared to patients with paroxysmal AF. The authors had carefully excluded patients with coronary artery disease. The balance between the pro and anti-inflammatory actions of epicardial fat is not well understood. Whether a critical volume will tip the epicardial fat towards more pro-inflammatory role is unclear and needs to be studied.
<table>
<thead>
<tr>
<th>Year</th>
<th>Authors</th>
<th>N</th>
<th>Imaging modality</th>
<th>Method</th>
<th>Main Findings</th>
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| 2006 | Iacobellis et al             | 50 | 2 D Echo         | Epicardial fat thickness over the Right ventricular free wall in parasternal long and parasternal short axis views | 1- Obese patients had higher epicardial fat thickness compared to controls  
  2- Morbidly obese patients had larger LA and RA diameters and lower diastolic filling parameters  
  3- Epicardial fat thickness correlated with LA and RA diameters, even after correction for BMI |
| 2009 | Fox et al                    | 997| 8 slice MDCT     | Pericardial fat measured as the fat tissue between the myocardium and pericardiac sac. Intrathoracic fat is the total fat in the thoracic cavity including the pericardial fat. | 1- Using univariate analysis, pericardial fat, intrathoracic fat and visceral adipose tissue correlated with LV mass and left atrial dimensions in both genders.  
  2- After multivariate analysis, pericardial fat correlated with left atrial dimensions in men only |
| 2010 | Thanasoulis et al            | 3217| 8 slice MDCT     | Measured pericardial fat volume as fat located between the myocardium and pericardiac sac. Measured intrathoracic fat as the fat within the thoracic cavity (including pericardial fat). Also measured abdominal fat | Pericardial fat volume is independently associated with prevalent AF, but not intrathoracic or visceral fat. Even after correcting for BMI and other clinical variables. |
| 2010 | Batal et al                  | 169| 64 slice MDCT    | Measured periatrial fat thickness in three areas: with LA-ESO, LA-PA, LA-TA and also retrosternal fat | Only LA-ESO is associated with AF burden even after correction with other variables and doing a propensity score. |
| 2010 | Al Chekakie et al            | 300| 64 slice MDCT    | Pericardial fat volume is measured between the myocardium and the pericardial sac | 1- Pericardial fat volume is larger in patients with persistent AF compared to patients with paroxysmal AF and sinus rhythm.  
  2- Pericardial fat volume correlated with measures of LA dimensions, as measured by 2 D Echocardiography and Cardiac CT  
  3- Pericardial fat was independently associated with AF, even after adjusting for other clinical variables and BMI |
| 2011 | Wong et al                   | 130|MRI               | Measured total pericardial fat (fat located between the myocardium and the parietal pericardium. | 1-Pericardial fat is associated with the presence of AF, the severity of AF and left atrial volumes  
  2- Periatrial fat and periventricular fat volumes were also associated with AF burden and LA dimension.  
  3-Pericardial fat is associated with AF recurrence after AF ablation. These associations are both independent of and stronger than more systemic measures of adiposity. |
atrial arrhythmias. Shirani et al. studied 80 patients with lipomatous hypertrophy of the interatrial septum. The thickness of the atrial septum correlated with the thickness of adipose tissue in the atrioventricular groove and 40% of these patients had atrial arrhythmias including atrial fibrillation while 67% of them had coronary artery disease.35 Heyer et al. studied the multislice CT of 1292 patients who underwent CT imaging between 2001 and 2002 in his institution and found that lipomatous hypertrophy of the interatrial septum was found in 28 (2.2%) of patients. Of these 28 patients, 75% of them had increased “epicardial” fat and or intrathoracic fat while 61.9% had atrial arrhythmias including atrial fibrillation.36 However, these two studies didn’t measure the volume of the pericardial fat and were mostly retrospective in design. The association between visceral adipose tissue and left atrial dimensions was examined in several studies. Iacobellis et al. compared left atrial dimensions and measures of diastolic function in 30 patients with morbid obesity body mass index (BMI) > 40 kg/m2 and 20 controls (normal BMI). Epicardial fat thickness was measured at the right ventricular free wall using 2 D Echo in parasternal short and parasternal long axis views. Obese patients had larger LA size, more impaired diastolic filling and higher epicardial fat thickness compared to controls.18 Fox et al. studied 997 participants from the Framingham heart study using MDCT to quantify pericardial fat, intrathoracic fat and visceral adipose tissue and used MRI to quantify left ventricular mass, left ventricular end diastolic dimensions as well as left atrial dimensions. In both genders, pericardial fat, intrathoracic fat and visceral adipose tissue correlated with LV mass and LA dimensions. But after correcting for other variables including BMI and visceral adipose tissue, pericardial fat was only correlated with LA dimensions in men.37 This study did not focus on atrial fibrillation per se, but it is well known that left atrial dilatation is a risk marker for AF. The association between pericardial fat and left atrial dimensions raised interest in studying the association between pericardial fat and atrial fibrillation. Thanassoulis et al. studied 3217 patients in the Framingham Heart study who underwent MDCT between 2002 and 2005. Pericardial fat, intrathoracic fat and visceral adipose tissue volumes were calculated. Of these 3217 patients, only 54 (1.7%) had AF on electrocardiograms or holter monitors obtained prior to the MDCT study. After adjusting for other risk factors including age, gender and body mass index, only pericardial fat and not intrathoracic or abdominal visceral fat was independently associated with AF odds ratio (OR) for 1 standard deviation of volume 1.28, 95% Confidence interval (CI) 1.03-1.58, p=0.04.14 This suggests that the local effects of pericardial fat are more associated with AF than the overall measures of obesity and was the first study to show an association between pericardial fat and AF. Two studies looked at pericardial fat and AF burden. Batal et al. studied 169 consecutive patients who underwent MDCT prior to AF ablation or for assessment of CAD. Epicardial fat thickness was measured in 3 areas near the left atrium: the first was between the LA and esophagus (LA-ESO), the second between the LA and thoracic artery...
undergoing catheter ablation for AF and 20 controls. Wong et al. studied 102 patients to quantify periatrial, periventricular and total fat and ablation outcomes. Using cardiac MRI examined at the association between pericardial fat and ablation outcomes. Two other studies did not study the association between pericardial fat and ablation outcomes. The work by Batal et al. and Al Chekakie et al. did not show such an association. The epicardial fat located near the posterior wall of the LA has a special role due to its proximity to all pulmonary veins or if it has different tissue characteristics is yet to be determined. This study measured periatrial fat thickness in predetermined areas and did not measure periatrial fat volume or total pericardial fat. Al Chekakie et al. studied 300 patients who underwent cardiac CT prior to AF ablation (n=218) or for evaluation for CAD (n=82). Patients with persistent AF have larger pericardial fat volumes (101.6 ± 44.1 milliliters (ml) compared to patients with paroxysmal AF (93.9 ± 39.1 ml) and to patients in sinus rhythm (76.1 ml ± 36.3 ml). This association was independent of BMI and other traditional risk factors of atrial fibrillation. For each 10 ml increase in pericardial fat volume, there is a 13% increase in odds of developing AF (OR 1.13, 95% CI 1.03-1.24, p=0.01) after correcting for BMI and other clinical variables. Furthermore, there was also a correlation between pericardial fat volume and LA dimensions, measured as LA diameter by 2 D Echo (r=0.25, p=0.01), or LA volume using 2 D Echo (r=0.24, p=0.001) or LA volume measured by cardiac CT (r=0.36, p=0.001). The authors measured pericardial fat volume as a continuous variable and did not look at regional differences in pericardial fat (periatrial or periventricular fat). The work by Batal et al. and Al Chekakie et al. did not study the association between pericardial fat and ablation outcomes. Two other studies examined at the association between pericardial fat and ablation outcomes. Using cardiac MRI to quantify periatrial, periventricular and total pericardial fat, Wong et al. studied 102 patients undergoing catheter ablation for AF and 20 control patients without AF. Patients with AF had larger pericardial fat volumes (median 299.9 cm³) compared to patients in sinus rhythm (median 168 cm³). Patients with persistent AF had larger periatrial, periventricular and total pericardial fat volumes than patients with paroxysmal AF or controls. Furthermore, total pericardial fat volume was also associated with LA volume (r=0.46, p<0.001) and ablation outcome, even after adjusting for BMI and LA dimensions (p=0.035 by log rank test). This association was independent of BMI, body surface area and LA size, suggesting that pericardial fat is more specific in identifying risk compared to general measures of obesity. This study was a single center study and was of small sample size, limiting the number of variables that they could adjust for in the model. Tsao et al. also studied the association between epicardial fat and ablation outcomes. They used MDCT to measure epicardial fat volume surrounding the atria and they also measured periatrial fat distribution in 8 areas around the left atrium. A total of 68 patients with AF (43 paroxysmal AF) and 34 controls were studied. Total epicardial fat volume surrounding the LA was significantly increased in AF patients compared to controls (35.2 ± 12.5 ml vs 26.8 ± 11.1 ml respectively). The epicardial atrial fat was mostly located near the roof, near the left atrial appendage and lateral to the mitral isthmus and was significantly increased around the superior half of the LA compared to the inferior half of the LA (21.3 ± 8.9 ml vs 14.2 ± 5.0 ml respectively, p < 0.001). Even after adjusting for other variables, including BMI, age, gender and LA volume and function, total epicardial fat surrounding the LA was independently associated with ablation outcome (p=0.04). There was no difference in epicardial fat volume surrounding the LA between patients with paroxysmal (n=43) and persistent AF (n=23), but this was a small sample size study. The distribution of epicardial fat was uneven in the LA, making the measurement of total volume a more accurate measure of periatrial epicardial fat.

The only study of pericardial fat and AF to include markers of inflammation was the study by Shin et al. This study included 80 patients with AF (40 with Paroxysmal AF) and compared them with 80 controls. Total epicardial fat volume, periatrial and periventricular fat thickness were measured in all patients. Adiponectin, interleukin-6 and
high sensitivity CRP were measured in patients with AF only and not in controls. Compared to controls, patients with AF had larger left atrial volume, (125.4 ± 41.6 ml in AF pts vs 73.3 ± 19.5 ml in control patients, p<0.05) total pericardial fat (83.8± 26.8 ml in AF patients vs 67.2 ± 23.1 ml in controls, p<0.05) and thicker periatrial fat in the AV groove and in the interatrial septum, while periventricular fat thickness was not significantly different (4.0 ±1.2 mm in AF patients vs 3.7 ± 1.2 mm in controls). Furthermore, patients with persistent AF had larger total epicardial fat volume, thicker periatrial fat and lower adiponectin levels compared to patients with paroxysmal AF. Only total epicardial fat volume (p=0.004) and periatrial fat thickness in the interatrial septum (p=0.016) were independently associated with LA volume in patients with paroxysmal and persistent AF after adjusting for other clinical variables. This was the only study to include measures of inflammation and correlate it with AF burden and epicardial fat.34 Table 1 summarized the above studies with the major findings. Currently, there is no known therapeutic intervention that affects the pericardial fat per se. Studies on posterior pericardiectomy in patients undergoing coronary artery bypass surgery focused on the incidence of post-operative pericardial effusion and atrial arrhythmias. Of these studies, two showed a significant decrease in the incidence of post-operative AF38,39 and one failed to show similar results.40 Statins have anti-inflammatory properties and have been shown to reduce the incidence of post-operative AF, but currently there is no study that focused on its effect on pericardial fat volume. The study by Mazurek et al. showed that the local inflammatory milieu didn’t change with the presence of statins; however, this study was not randomized and was of small size and did not measure total pericardial fat volume.29

In animal models, starvation did not decrease epicardial fat thickness.21 A study of 23 patients undergoing bariatric surgery showed that obese patients have higher epicardial fat thickness as measured by 2D Echo compared to age and gender matched controls. Patients in this study had an average weight loss of 40 ±14 kilograms. Epicardial fat change after surgery ranged from a decrease of -5.3 mm to an increase of 1.3 mm. Epicardial fat thickness decreased by an average of 1 mm in 11 patients (48%), and the degree of change was only related to the baseline epicardial fat thickness (r=0.71, p<0.001). There was no relationship between the amount of weight lost and the change in epicardial fat thickness.41 This study was of small size and measured epicardial fat thickness not volume.

Conclusions

Epicardial fat is an active visceral adipose tissue and is associated with left atrial remodeling. Most of the epidemiological studies as well as the clinical studies have measured pericardial fat,13,14 which is the fat located within the fibrous pericardial sac. This can lead to overestimation of the epicardial fat volume, an important limitation of all imaging modalities.15 The association between pericardial fat and AF is strong and well established; however, the exact mechanism(s) are not well defined. Pericardial fat volume and thickness were measured as continuous variables and there was no cut off proposed for upper normal limit in any of the above studies. There is currently no study giving a certain threshold where the balance between the pro and anti-inflammatory properties of pericardial fat is affected one way or the other. There is general agreement that total pericardial fat is associated with AF; however, a study showed that periventricular fat was associated with AF burden and ablation outcome,20 and another study did not.12 Whether periatrial fat plays a more important role than periventricular fat in AF, and whether atrial pericardial fat differs from periventricular fat in tissue characteristics is yet to be determined. More studies are needed to shed light on the effects of weight loss and other therapeutic interventions (including medications) on epicardial fat function, (especially its pro and anti-inflammatory properties) and volume.

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Introduction

Atrial fibrillation (AF) affects approximately 3.03 million Americans in 2005 and is projected to increase to 7.56 million in 2050. These recent estimates based on over 21 million patients from a large national database outpace the estimates from a previous sentinel paper, which additionally noted that AF contributes to approximately 5 million physician office visits and $7 billion USD in expenditures each year. The incidence and prevalence of AF increases with age with a median age of 75, but with the aging population, the projected number of adults with AF will increase markedly in the next few decades.

Risk factors for AF include age, presence of valvular heart disease, increasing left atrial size, coronary artery disease, use of diuretics, systolic blood pressure, plasma glucose, height, high levels of alcohol intake, obesity, and obstructive sleep apnea. New onset AF is most commonly triggered by myocardial tissue that extends onto the pulmonary veins (PVs) of the left atrium either from repetitive firing from a single source or more commonly from episodic reentrant activation from multiple wandering wavelets. Much less commonly, AF can be initiated in non-PV sites or by other supraventricular arrhythmias including atrial flutter. Spectral analysis and mapping has demonstrated that in paroxysmal AF, the PV ostial region was most frequently the source of triggers and AF can be terminated by ablation to those sites in 87% of patients.

New energy catheter energy sources are also being explored.
which allows smaller and more atrial reentry circuits and other electrophysiological changes. Atrial remodeling resulted in several non-PV region triggers with no dominant trigger in longstanding persistent AF. These changes have implications for the timing of catheter ablation in the treatment of AF and its success.

Catheter Ablation of Atrial Fibrillation

In 2011, the American College of Cardiology/American Heart Association Task Force on Practice Guidelines, and the European Society of Cardiology Committee for Practice Guidelines published updated practice guidelines on the management of patients with AF. These updated guidelines continued to define the role of catheter ablation as reserved for antiarrhythmic drug (AAD) therapy failure for the maintenance of sinus rhythm in patients with intolerable symptoms from AF. As a Class I indication, the guidelines suggested that “catheter ablation performed in experienced centers is useful in maintaining sinus rhythm in selected patients with significantly symptomatic, paroxysmal AF who have failed treatment with an antiarrhythmic drug and have normal or mildly dilated left atria, normal or mildly reduced LV function, and no severe pulmonary disease.”

Similarly, the European Society of Cardiology and European Heart Rhythm Association published guidelines for management of AF in 2010 that recommends as Class Ila guidelines that “catheter ablation for paroxysmal AF should be considered in symptomatic patients who have previously failed a trial of antiarrhythmic medication, and “ablation of paroxysmal atrial fibrillation in patients with significant left atrial dilatation or with significant LV dysfunction.”

Other factors to consider include age, LA diameter, and duration of AF. Catheter ablation of AF carries greater risks of cardiac perforation and thromboembolic complications in very elderly patients, lower rates of success in patients with longstanding persistent AF and/or marked dilatation of the LA. Moreover, patients may seek to have AF ablation in the hopes of discontinuing long-term anticoagulation; however, no large prospective randomized clinical trial has been done to establish the safety of discontinuing anticoagulation especially in light of a not insignificant rate of late recurrence of AF post-ablation.

Techniques for AF Ablation

Since approximately 90% of AF trigger foci were localized to the PVs in paroxysmal AF, early efforts at ablation targeted these foci within the PV which resulted in unacceptable rates of PV stenosis secondary to ablation energy. Since these early efforts, PV isolation with radiofrequency catheter (RF) ablation has become the cornerstone for AF ablation with complete electrical isolation as the goal. In a recent survey on methods, efficacy, and safety of catheter ablation for human AF, 48.2% of centers who participated in the survey used Carto-guided LA circumferential ablation and another 27.4% of centers practiced Lasso-guided ostial electric disconnection. Both methods attempt to achieve complete electrical isolation of the PVs. The Lasso-guided ostial electric disconnection method places a “lasso” catheter at the orifice of a PV and multiple electrodes on the catheter determine the precise location of sites of electrical connection which are then ablated. The circumferential ablation method creates confluent ablation lesions that encircle the ostia of the PVs and often include connecting lines to other anatomic landmarks, most commonly the mitral annulus to prevent macroreentrant circuits that can lead to atrial flutter. The comparable efficacy between the two approaches has not been established. Additional ablation lines at the left atrial roof, the posterior wall, and mitral isthmus have been studied and showed increased efficacy.

Other techniques, in descending prevalence, include 3D noncontact ablation, catheter ablation of fragmented atrial electrograms, catheter ablation of the triggering focus, basket ablation, and right atrial compartmentalization.

Efficacy

Cappato et al. in Circulation Arrhythmia and
Electrophysiology also reported the efficacy of AF ablation. This worldwide survey was sent to 521 centers from 24 countries in 4 continents. 67% of centers responded but only 85 centers returned complete interviews. In these centers, 20825 catheter ablations were performed on 16309 patients with AF between 2003 and 2006. 95% of centers reported drug refractoriness as a prerequisite for ablation. All centers performed ablations on paroxysmal AF. 85.9% of centers performed ablations on persistent AF and 47.1% ablated long-lasting AF. Of the 16309 patients followed for an average of 18 months, 70% became asymptomatic without AADs, another 10% became asymptomatic in the presence of previously ineffective AADs. Success rates were significantly higher in those with paroxysmal AF compared to persistent AF which was in turn significantly more successful than ablations of those with long-lasting AF.

Randomized Control Trials Comparing Catheter Ablation and Antiarrhythmics

There have been at least seven randomized clinical trials performed of catheter ablation of AF. Other than one of the studies, enrolled patients had either paroxysmal or persistent AF or a combination of the two, and were refractory to at least one AAD. Patients were randomized and treated with catheter ablation versus second line AADs and followed for 12 months. Each of the seven studies demonstrated a higher freedom from arrhythmia at the end of follow-up for the catheter ablation group. Notably, no study showed an improvement in mortality due to insufficient power.

Risks from Catheter Ablation

The risks of catheter ablation depend on technique used, patient selection, and operator and center experience. In the worldwide survey conducted between 2003-2006 there were 25 procedure-related deaths at a rate of 0.15%. Cardiac tamponade, from catheter perforation, was the most frequent major complication occurring at a rate of 1.31%. However, two other recent studies showed tamponade in 2.4% to 2.9% of procedures. The higher incidence of cardiac tamponade in catheter ablation of AF arises from the need for two or more transseptal punctures and the need for systemic anticoagulation.

The other complications, in descending incidence, included total femoral pseudoaneurysm (0.93%), transient ischemic attack (0.71%), total arterovenous fistulae (0.54%), PV stenosis requiring intervention (0.29%), stroke (0.23%), permanent diaphragmatic paralysis (0.17%), pneumothorax (0.09%), valve damage requiring surgery (0.07%), atrium-esophageal fistulae (0.04%), hemothorax (0.02%), and sepsis, abscesses, or endocarditis (0.01%). All totaled, the rate of major complications including death equaled 4.54%. Iatrogenic flutter resulting from the procedure, not listed as a major complication, occurred at a rate of 8.6%. In comparison to a prior survey conducted between 1995-2002, the number of patients being treated with catheter ablation nearly doubled, and more centers included patients with persistent and longstanding AF. The overall incidence of major complications was 4.5% in the updated survey compared with 4.0% in the former survey. However, iatrogenic flutter was significantly more frequent in the updated survey, 8.6% compared with 3.9%. It is important to also note that given the voluntary nature of the study, the inherent center-to-center variability in safety, and the potentially self-selective reporting of complication rates, the rate of major complications is possibly higher than the reported numbers. Most recently, stiff atrial syndrome and valvular damage have been described and should be considered as potential complications as well.

Transient ischemic attacks and stroke are due to embolism of thrombus or air and are both relatively common and potentially devastating. Other than cerebral compromise, thromboembolic events can cause coronary and peripheral vascular compromise as well. Thromboembolic events tend to occur within 24 hours of the procedure and most events occur within 2 weeks. The risk of embolism in patients undergoing cardioversion of AF without antithrombotic therapy has been reported in a meta-analysis to be 2% while with thrombotic therapy the risk drops to 0.33%. The risk of embolism is due to clots prior to cardioversion and from “myocardial stunning” resulting in de novo clot formation on return to sinus rhythm, which has been described after catheter ablation of AF as well. While the risk is reduced with antithrombotic therapy, even in patients who have undergone 3-4 weeks of antithrom-
botic therapy prior to cardioversion, there is still a minority with persistent clots. Since there is mechanical manipulation of the left atrium during catheter ablation of AF which could dislodge these persistent clots, many operators in the field perform a transesophageal echocardiogram (TEE) to evaluate for a thrombus even in patients who are anticoagulated with warfarin prior to cardioversion. The Venice Chart consensus document and Heart Rhythm Society expert consensus both recommend the employment of TEE in this circumstance. Intra-procedurally, use of increase intensity anticoagulation between an ACT of greater than 300 seconds was associated with reduced incidence of embolic events and using high-dose heparin transseptal sheath flush was associated with decreased thrombus formation on the sheath.

Asymptomatic cerebral lesions have been described by magnetic resonance imaging following AF ablation procedures and were most often smaller than 1 cm with the majority resolving without scarring. While the significance of these lesions are not yet established, they are found more frequently in catheter ablations performed with multielectrode catheter ablation compared with radiofrequency and cryoballoon ablation.

The European Society of Cardiology and the Venice Chart consensus document both suggest 3 months of post-procedural anticoagulation, after which each patient’s requirement for long-term anticoagulation should depend on risk factors of stroke by measures such as the CHADS2 score. There is no evidence that maintenance of sinus rhythm after cardioversion is associated with a reduced risk for thromboembolism. Air embolism causing a transient ischemic attack or stroke is most commonly caused by introduction of air into the trans-septal catheter sheath either during introduction of the infusion line or when catheters are removed. An air embolus could also cause acute inferior ischemia and heart block during a procedure when the embolus enters into the right coronary artery.

Pulmonary vein stenosis is a result of thermal injury and, while incompletely understood, a progressive replacement of necrotic myocardium by collagen has been suggested. The incidence of pulmonary vein stenosis has fallen dramatically due to the increased recognition of this complication, better imaging modalities, and avoidance of ablation within the pulmonary vein. Pulmonary vein stenosis manifests as chest pain, dyspnea, cough, hemoptysis, and recurrent lung infections but even severe pulmonary vein stenosis can be asymptomatic.

A rare but dreaded complication in catheter ablation is esophageal injury and development of an atrial-esophageal fistula. It often presents as fever, chills, and recurrent neurological events and leads to mediastinal infection, stroke, and most often death. While it is thought that decreased power delivery, delivery time, and tissue contact pressure, along with pre-procedure or real-time visualization with modalities such as intra-cardiac echocardiography would decrease the rate of esophageal injury, the rarity of this complication has made it hard to study the efficacy of these interventions. Energy delivery in the left atrial posterior wall has also been proposed as the cause of acute pyloric spasm and gastric hypomotility described as abdominal bloating and discomfort thought to be due to periesophageal vagal plexi damage. For two of the four patients described in the series, the symptoms were self-limiting. Another case series described two patients undergoing circumferential pulmonary vein ablation for atrial fibrillation who developed symptoms of endocarditis 3-5 days after the procedure and subsequently developed gaseous and/or septic embolic. An atrial-esophageal was found in both patients. The employment of intra-procedural transesophageal echocardiography, lower energy settings, and duration of power delivery, have been suggested to decrease esophageal involvement.

Phrenic nerve injury is a rare complication of AF, most often involving the right phrenic nerve with ablation near the right superior pulmonary vein and superior vena cava. Symptoms include dyspnea, hiccups, atelectasis, pleural effusion, cough and thoracic pain and can be diagnosed by unilateral diaphragmatic paralysis by radiography. The phrenic nerve can recover function as quickly as 1 day and as long as 12 months; however, there have been reports of permanent phrenic nerve injury.

Recurrent arrhythmia occurs in about 45% of patients during the first 1-3 months of follow-up despite AADs. While early AF prognoses treatment failure, immediate re-ablation is unnecessary as up to 60% of cases are self-limiting. Age
Pulmonary hypertension (PH) secondary to left atrial dysfunction, also called stiff atrial syndrome, has been recognized as a possible new complication of AF radiofrequency ablation. Gibson et al. reported in a study that out of 1380 patients, 19 (1.4%) developed new onset dyspnea and pulmonary hypertension after AF ablation. Of these 19 patients, 53% developed mild PH, 32% had moderate PH, and 15% had severe PH. Pulmonary vein thrombosis and pulmonary vein occlusion were excluded with computer tomography or magnetic resonance imaging. In this study LA dysfunction was recognized as a potential cause of pulmonary hypertension due to AF ablation. Although the incidence of this complication was low, it is important to keep it in mind when patients follow up.

Valvular damage such as mitral valve trauma may occur in AF radiofrequency ablation usually when a circular electrode catheter is positioned into the ventricle with a counterclockwise rotation. This may result in the entrapment of the circular catheter into the mitral valve apparatus which may require surgical removal; as with attempts to free the catheter, there is the possibility of tearing the mitral valve.

General anesthesia has been proposed to reduce fluoroscopy and procedure time and increase cure rate in catheter ablation of AF when compared to conscious sedation. However, general anesthesia carries its own complications including malfunction of gas delivery equipment, adverse respiratory events, burns, awareness during anesthesia, and nerve injury. Contact force monitoring during catheter ablation of AF has also been recently explored for its efficacy and safety but its comparative benefit has not been established.

The risks and complications of catheter ablation of AF are numerous and at times life-threatening. The radiation exposure for such a complex procedure is also higher than that of simpler catheter ablation procedures, and carries with it increased acute and sub-acute skin injury and increased lifetime risks of malignancy. However, improvements in complication rates, other than an increase of iatrogenic flutter, has followed the increasing experience with catheter ablation of AF. In another report of a retrospective study of 517 patients undergoing 641 catheter ablations for AF at a single institution between 2001 and 2007, complication rates were found to be higher (9%) in the first 100 cases than during the subsequent 541 (4.3%), again suggesting the role of experience and volume in the reduction of complication rates. The same study also showed that age >70 and female gender were predictors of major adverse events.

Catheter Energy Selection and Safety

Radiofrequency energy is the dominant energy source in catheter ablation of AF in 98.8% of cases, either with irrigated, cooled, 8-mm standard, or conventional 4-mm tip. There have been small trials studying the comparative efficacy irrigated tip and large tip versus conventional catheters showing their increased efficacy, but there have been no large trials exploring their comparative safety.

As for other energy sources in catheter ablation, cryoablation is the most common. In the STOP-AF trial, 245 patients with paroxysmal AF were randomized to catheter ablation or to AADs. In terms of safety, the overall incidence of adverse events in the cryoablation arm was 6.1%; stroke was 2.5%, transient ischemic attacks 1.8%, myocardial infarctions 1.2%, tamponade 0.6%, and death 0.6%. On the other hand, the German Ablation Registry reported low incidence of in-hospital complication (1.4%) for 776 patients who underwent cryoballoon ablation. The lower reported incidence could be due to the voluntary nature of the registry. The complication rates observed in the Updated Worldwide Survey where radiofrequency was the dominant energy source totaled 4.5%.

Other less-explored alternative energy sources
include high-frequency ultrasound, microwave, and laser energy. These energy sources are more prevalent in surgical ablation of atrial fibrillation and are applied on the epicardial surface. A review of surgical literature suggest several theoretical safety benefits and risks of each of these energy sources in comparison with radiofrequency energy.\textsuperscript{89–91} In epicardial high-frequency ultrasound, ultrasound waves can be focused at certain depths without dissecting epicardial fat and in theory without concern for coronary artery injury. In microwave energy, the generated electromagnetic energy is independent of current flow from ablation catheter to tissue, and therefore is not influenced by contact pressure, orientation, and tissue desiccation. However, the unfocused heat energy can cause collateral injury. Finally, laser energy has the advantage of making deep, uniform, and narrow lesions at low temperatures. But, unlike radiofrequency energy where impedance rises at increased temperatures, serving as a protective mechanism, laser energy does not have this benefit. In a recent first-in-human study, 30 patients with paroxysmal atrial fibrillation underwent pulmonary vein isolation with laser energy. Adverse events include one case of cardiac tamponade, one stroke, and one asymptomatic phrenic nerve palsy.\textsuperscript{92} In another recent study, high-intensity focused ultrasound was employed to achieve pulmonary vein isolation with esophageal temperature guided safety algorithm. However, in 28 patients, major complications occurred in six cases including an unexplained death and another lethal atriomesenteric fistula.\textsuperscript{93}

Recently, several robotic navigation systems have been developed for catheter ablation of atrial fibrillation. From single-center experiences with small numbers of patients, feasibility has been demonstrated. Robotic navigation systems may have the potential to reduce fluoroscopy time without compromising efficacy of the ablation. The comparative complications are yet to be elucidated\textsuperscript{94–96}.

**Future Directions**

While the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) trial showed in AF patients high risk for stroke and death, it also showed that there were no significant differences in all-cause death between rhythm using the most effective AAD and rate control.\textsuperscript{97} A subsequent on-treatment analysis showed that sinus rhythm is associated with survival but that AADs are not associated with improved survival, suggesting that the beneficial effects of being in sinus may be offset by the adverse effects of AADs.\textsuperscript{98} In one study evaluating symptom control in patients with paroxysmal atrial fibrillation, rhythm control was associated with better quality of life scores.\textsuperscript{99}

Several large trials are underway to investigate catheter ablation of AF as first line therapy for maintaining sinus rhythm. The Catheter Ablation versus Antiarrhythmic Drug Therapy for Atrial Fibrillation (CABANA) trial is currently enrolling patients and will compare drug therapy (rate and rhythm control) with catheter ablation in AF and also compare the cost of care and their impact on quality of life.\textsuperscript{100}

The First Line Radiofrequency Ablation versus Antiarrhythmic Drugs for Atrial Fibrillation Treatment (The RAAFT Study) has completed enrollment and is ongoing and will compare pulmonary vein isolation catheter ablation of AF with conventional AAD therapy in order to investigate the role of catheter ablation as first line therapy for AF.\textsuperscript{101}

Medical Antiarrhythmic Treatment or Radiofrequency Ablation in Paroxysmal Atrial Fibrillation (MANTRA-PAF) again is another study that is ongoing comparing catheter ablation versus AAD therapy with a longer 24-month follow-up in patients with paroxysmal Af without prior antiarrhythmic drug therapy.\textsuperscript{102}

**Conclusions**

In summary, catheter ablation of AF remains reserved for selected patients with intolerable symptomatic AF refractory to AAD or for younger individuals for paroxysmal lone AF who have failed AAD therapy. Updated guidelines set forth by ACC/AHA/ESC in 2011 more specifically defined its role for symptomatic paroxysmal AF, symptomatic persistent AF, and paroxysmal AF with significant left atrial dilatation or with significant LV dysfunction.\textsuperscript{12} Successful catheter ablation of AF should not be an indication for discontinua-
tion of previously indicated long-term anticoagulation of AF with high risk of stroke and transient ischemic attacks. As for any complex procedure, the safety and efficacy of catheter ablation is often operator and institution dependent, and improves with their increasing experience. Major complications occur at least at a rate of 4.5%, with tamponade as the most common complication. Operators and institutions should be aware of the risks of catheter ablation of AF and be prepared to optimally manage complications as they occur. New energy source, catheter designs, and pre-procedure and real-time imaging modalities are being explored as are several large studies exploring the role of catheter ablation as first line therapy for rhythm control in lieu of AADs.

References


41. Hocini M., Jais P., Sanders P., Takahashi Y., Rotter M.,


N., 2000, “Comparison of effectiveness of an 8-mm versus a 4-mm tip electrode catheter for radiofrequency ablation of typical atrial flutter,” Am J Cardiol, 86(9), pp. 1029-1032, A10.
Introduction

Chronic kidney disease (CKD), defined by the presence of either reduced estimated glomerular filtration rate (eGFR) and/or albuminuria/proteinuria, affects currently about 30 million patients in the US. Upon these, more than 530,000 CKD patients suffer from end-stage renal disease (ESRD) requiring renal replacement therapy, over 370,000 receive chronic dialysis. As the population ages, the incidence for CKD and its risk factors, such as hypertension and diabetes mellitus, and the prevalence for CKD, ESRD, and its concomitant diseases will further increase and become a global challenge. Despite this unfavorable epidemiological development, data about associated risks and treatment strategies in CKD are limited yet and left many open issues. This concerns especially the most common arrhythmia in CKD which is atrial fibrillation.

Cardiovascular Events and CKD

It is well known that patients with CKD are more prone to develop coronary heart disease, chronic heart failure, peripheral artery disease, and venous thromboembolism independent of other risk factors. CKD is also a key risk factor for cardiocerebrovascular events as stroke, and is associated with other important stroke risk factors such as diabetes mellitus, myocardial hypertrophy, hypertension - and atrial fibrillation. Other key players which are altered by CKD, such as the renin-angiotensin-aldosterone system and sympathetic activation, have also been found to trigger AF.

Atrial Fibrillation

In general, the prevalence of AF increases with age: whereas about 0.4 - 2.0% in the general pop-
ulation suffer from atrial fibrillation, the prevalence rises up to 15% in patients over 80 years.\textsuperscript{10,11} Regarding solely hemodialysis patients, the prevalence of AF is significantly higher: thus, possibly 7% up to 27% of ESRD patients suffer from AF.\textsuperscript{12-17} (Figure 1).

One recent epidemiological study with 26,917 US patients who were categorized by renal function demonstrated that CKD, regardless of its stage, was associated with a higher risk for AF: the prevalence for AF in patients with CKD stage 1 to 2 (eGFR $\geq$ 60 ml/min/1.73 m$^2$ with albuminuria), CKD stages 3 (eGFR 30 to 59 ml/min/1.73 m$^2$) and CKD stage 4 to 5 (eGFR < 30 ml/min/1.73 m$^2$) was 2.8%, 2.7% and 4.2%, respectively, compared to only 1.0% in patients without CKD.\textsuperscript{18}

Soliman et al.\textsuperscript{19} reported a prevalence for AF of more than 25% in CKD patients 70 years and older, but found no association of the development of AF with hypertension or diabetes. Another retrospective study with 1,010 consecutive CKD patients from two community-based hospitals found also a much higher prevalence for AF even at mild renal impairment: 17.9% of patients with CKD stage 2 (eGFR 60 to 89 ml/min/1.73 m$^2$), 25.2% of CKD stage 3 patients (eGFR 30 to 59 ml/min/1.73 m$^2$) and 20.8% of CKD stage 4 patients (eGFR 15 to 29 ml/min/1.73 m$^2$) had AF.\textsuperscript{20}

Interestingly, CKD appears to increase the risk of new onset of AF as well as AF increases the risk of developing renal disease. This bidirectional association was described for a large prospective community-based observational cohort study of 235,818 individuals in Japan. Therein, the hazard ratio for the development of AF were 1.32 for patients with eGFR of 30 to 59 ml/min/1.73 m$^2$, and 1.57 for patients with eGFR <30 ml/min/1.73 m$^2$ compared to patients with an eGFR $>60$ ml/min/1.73m$^2$. Vice versa, in patients with atrial fibrillation at entry, the hazard ratio for the development of kidney dysfunction was 1.77. Interestingly, both associations remained significant independent of any existence or treatment of the concomitant comorbidities hypertension or diabetes mellitus.\textsuperscript{21} The bidirectional association between CKD and AF cannot simply

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*Figure 1: Prevalence of atrial fibrillation is shown in the general population, and in patients with different stages of chronic kidney disease (CKD) including end-stage renal disease (ESRD). In some studies, different stages are pooled together which is indicated by wider rectangles above the CKD stages.*

CKD stage 1: eGFR $\geq$ 90 ml/min/1.73 m$^2$; CKD stage 2: eGFR 60-89 ml/min/1.73 m$^2$; CKD stage 3: eGFR 30-59 ml/min/1.73 m$^2$; CKD stage 4: eGFR 15-29 ml/min/1.73 m$^2$; CKD stage 5: eGFR <15 ml/min/1.73 m$^2$
be explained by increased mechanical stress in the atrium as a result of hypertension and high atrial pressure. There have to be other pathophysiologic processes which play a role in the development and perpetuation of both CKD and AF, e.g. inflammatory processes, and the renin-angiotensin-aldosterone system activation.

**Thromboembolic Risk**

Patients with AF have an increased risk for thromboembolism and therefore for transient ischemic attacks as well as ischemic strokes. Blood stasis in the left atrium and its appendage, endothelial injury of the vessel wall, and hypercoagulation, known as Virchow’s triad, contribute to thrombogenesis and the risk for thromboembolism. Patients with renal impairment but with no AF are also at increased risk for thromboembolic events because of altered hemostasis, atherosclerosis and endothelial damage, altered protein C metabolism, increased levels of lipoprotein(a) and therefore inhibition of plasmin, as well as defects in the expression of glycoprotein GPIb. Therefore, patients with AF and CKD are even more at advanced risk for stroke, and treatment with oral anticoagulation represents an important therapeutic option.

**Stroke**

Stroke is the major complication in patients with AF, and especially in CKD, too. Its incidence increases as kidney function declines. A Japanese community-based longitudinal observational study with 1,977 individuals showed that the hazard ratio for first symptomatic stroke was 1.9 for patients with creatinine clearance (CrCl) between 40 and 70 ml/min and 3.1 for patients with CrCl < 40 ml/min compared to patients with CrCl > 70 ml/min.[24]. The US Renal Data System report the stroke incidence to be 15.1% in hemodialysis patients and 9.6% in patients with less severe CKD compared to 2.6% in patients without CKD.[25]

The association of CKD with increasing risk of stroke was also proven by another Japanese study of 11,780 individuals. In patients with normal eGFR (≥ 90 ml/min) stroke occurred in 4.3% of men and 2.4% of women, whereas in patients with CKD, characterized by an eGFR < 60 ml/min, 13.1% of men and 7.6% of women experienced a stroke event. Men had a higher risk of hemorrhagic stroke and women of ischemic stroke. Furthermore, regular alcohol consumption markedly increased the rate of hemorrhagic stroke both in men and in women with CKD (5.3% and 6.1%, respectively) compared to never-drinkers with CKD (0.7% and 1.7%, respectively) and never-drinker without CKD (1.1% and 1.5%, respectively). This is an important finding, since the amount of consumed alcohol was substantially lower than the current recommendation suggests for cardiocerebrovascular protection. Thus, in patients with CKD, mild to moderate alcohol consumption was associated with a higher risk for hemorrhagic stroke, at least in the Asian population. A strict alcohol prohibition for Asian patients with eGFR < 60ml/min might reduce the rate of hemorrhagic stroke.[27] Whether CKD independently increases the risk for ischemic stroke in patients with AF was investigated by Go et al. in the ATRIA study.[28] None of the included patients was treated with anticoagulation. With decreasing eGFR a graded, increased risk of stroke was proven: after adjustment for known risk factors for stroke, the hazard ratio was 1.16 for patients with eGFR between 45 and 59 ml/min/1.73m² and 1.39 for patients with eGFR < 45 ml/min/1.73m² compared to patients with eGFR ≥ 60 ml/min/1.73m².

In a meta-analysis of 21 articles, the relative risk for incident stroke was 1.43 (95% CI 1.31-1.57, P<0.001) among patients with an eGFR < 60 ml/min/1.73 m² compared to patients with normal baseline eGFR.[29] Vazques et al.[30] described a 9.8 fold increased risk for ischemic stroke in hemodialysis patients suffering from AF compared to hemodialysis patients who maintained sinus rhythm. In the Rotterdam study,[31] risk of hemorrhagic stroke was elevated with decreasing GFR, but not the risk of ischemic stroke.

In contrast, an Italian study with 476 hemodialysis patients did not find any significant differences in stroke rates regardless of AF or sinus rhythm.[32] Differences in the various study results may be explained by different ages of the studied population, different length of follow-up, differences in the type and documentation of detected AF and anticoagulation treatment.[23]
Mortality

The direct impact of atrial fibrillation on the mortality rate of CKD patients is difficult to assess since there is a strong association between AF with structural heart disease. In CKD patients, the risk of death increases as renal function declines. In the large Kaiser Permanente Renal Registry, the adjusted hazard ratio for death was 1.2 fold higher in patients with eGFR between 45 and 59 ml/min/1.73m² compared to patients with eGFR >59 ml/min/1.73m² and rose to a 5.9 fold increase in patients with eGFR < 15 ml/min/1.73m².

Patients on hemodialysis suffering from AF were reported to have an annual mortality of 5% compared with only 2% in those without AF. One other longitudinal, single-center study with 190 individuals reported a dramatically increased four-year mortality rate of 81% in patients with AF and ESRD compared to 29% in patients without AF. After a stroke, the cumulative two-year mortality rate for patients with CKD or ESRD is raised to 55% and 74%, respectively, whereas patients without

<table>
<thead>
<tr>
<th>Study (year, design)</th>
<th>Included CKD stages</th>
<th>Number of patients</th>
<th>Average follow-up</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>2001, retrospective study [47]</td>
<td>Hemodialysis patients</td>
<td>430 patients overall 61 (14.2%) with chronic AF 96 (22.3%) on warfarin or aspirin for various reasons</td>
<td>Study covers a 22 year period</td>
<td>Overall incidence for stroke in dialysis patients was 3.78/100 patient-years. In patients on antithrombotic therapy (aspirin or warfarin) the overall rate of stroke was 8.33/100 patients-years compared to patients without antithrombotic therapy (2.6/100 patients-years, p=0.0002). Patients with AF and on warfarin or aspirin had a higher risk for stroke (4.46/100 patient-years) than AF patients without anticoagulation (1.0/100 patient-years).</td>
</tr>
<tr>
<td>2003, retrospective cohort study using data of USRDS DMMS Wave II [48]</td>
<td>Dialysis patients</td>
<td>3,374 patients overall 123 (3.6%) with newly diagnosed AF during follow-up 198 (5.9%) on warfarin, 10 of those for AF treatment</td>
<td>2.92 ± 1.14 years</td>
<td>Baseline use of warfarin was associated with a lower risk of mortality after hospitalization for AF.</td>
</tr>
<tr>
<td>2003, retrospective study [36]</td>
<td>Hemodialysis or peritoneal dialysis patients</td>
<td>240 patients overall 29 (12.1%) on coumarin derivatives (warfarin), 7 of them with AF</td>
<td>20 month for coumarin subgroup 21 month for non-coumarin subgroup</td>
<td>The relative risk for bleeding under coumarin was 2.36 (95% CI, 1.19-4.27) compared to the non-coumarin subgroup. The risk for bleeding in the coumarin subgroup was mainly in the digestive tract, no bleeding event was fatal.</td>
</tr>
<tr>
<td>2007, retrospective study using data from ANZDATA [49]</td>
<td>Hemodialysis patients</td>
<td>155 patients overall 40 (25.8%) with AF, 5 of them taking warfarin 11 (27.5%) on warfarin, 5 of them for AF treatment</td>
<td>25.5 ± 8.4 months</td>
<td>No statistical significant difference in the incidence of cerebrovascular events or major hemorrhage between 1. patients taking warfarin and patients off warfarin. 2. the AF and the non-AF subgroup. Incidence of major hemorrhage was over three times that of cerebrovascular events in the whole population as well as in the AF and non-AF subgroup.</td>
</tr>
<tr>
<td>2008, prospective multi-center study [32]</td>
<td>Hemodialysis patients</td>
<td>476 patients overall 127 (26.7%) with preexisting AF 31 (24.4%) of the AF patients taking anticoagulation (warfarin) at enrollment</td>
<td>3 years</td>
<td>No difference in stroke incidence in patients with AF compared to no-AF patients (15.4% vs. 12.4%, P=0.4)</td>
</tr>
<tr>
<td>Year</td>
<td>Study Type</td>
<td>Population</td>
<td>Follow-Up</td>
<td>Outcomes</td>
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<td>--------------------------------------------------------------------------</td>
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<tr>
<td>2009, retrospective study</td>
<td>[41] 1,671 Hemodialysis patients</td>
<td></td>
<td>1.6 years</td>
<td>Warfarin doubles the risk for stroke (HR = 2.00; 95% CI 1.34-2.99, P = 0.001) compared to non-warfarin use. There was a positive relationship between increasing INR and increasing risk of stroke, which is highest for patients with no INR monitoring.</td>
</tr>
<tr>
<td>2009, observational retrospective study [37]</td>
<td>399 CKD stage 3 patients, 232 CKD stage 4 patients, 78 CKD stage 5 patients</td>
<td>31 ± 34 months</td>
<td></td>
<td>Warfarin significantly reduced the incidence of new thromboembolic stroke in all investigated CKD stages and hemodialysis patients (CKD stage 3: 10% on warfarin vs. 20% without warfarin, P&lt;0.05; CKD stage 4: 5% vs. 21%, P&lt;0.05; CKD stage 5: 10% vs. 37%, P&lt;0.001; hemodialysis: 10% vs 38%, P&lt;0.005).</td>
</tr>
<tr>
<td>2010, retrospective study using data from DOPPS [42]</td>
<td>17,513 Hemodialysis patients</td>
<td>Not reported</td>
<td></td>
<td>Warfarin use was associated with significantly higher stroke risk in patients &gt; 75 yrs (HR = 2.17; 95% CI=1.04-4.53, P&lt;0.04).</td>
</tr>
<tr>
<td>2011, prospective single-center observational cohort study (INVOR)[46]</td>
<td>235 Incident dialysis patients</td>
<td>2.84 years</td>
<td></td>
<td>No stroke or fatal bleeding events occurred in patients under sufficient oral anticoagulation. The mortality risk for AF patients on warfarin was slightly, but not significantly lower than for patients without AF and without anticoagulation therapy (reference group). AF patients with contraindication for warfarin had a significantly higher mortality risk compared to the reference group (HR: 3.9, 95% CI=2.16-7.04, P&lt;0.001)</td>
</tr>
</tbody>
</table>

USRDS DMMS indicates United States Renal Data System Dialysis Morbidity and Mortality Study; ANZDATA, Australia and New Zealand Dialysis and Transplant Registry; DOPPS, Dialysis Outcomes and Practice Patterns Study; AF, atrial fibrillation; INVOR, Incident Dialysis Patients in Vorarlberg; HR, hazard ratio; CI, confidence interval;
**Table 2: Trials of oral anticoagulation in CKD**

<table>
<thead>
<tr>
<th>Drug</th>
<th>RE-LY [38]</th>
<th>ROCKET AF [39]</th>
<th>ARISTOTLE [40]</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Study design</strong></td>
<td>Phase 3, multicenter, prospective, open-label randomized trial: 18,113 patients with AF and one additional risk factor for stroke</td>
<td>Phase 3, multicenter, double-blind, double-dummy randomized trial: 14,264 patients with AF and elevated stroke risk</td>
<td>Phase 3, multicenter, double-blind, double-dummy randomized trial: 18,201 patients with AF and at least one additional risk factor for stroke</td>
</tr>
<tr>
<td><strong>Dosage</strong></td>
<td>110 mg resp. 150 mg dabigatran etexilate twice daily versus warfarin adjusted to an INR of 2.0 to 3.0</td>
<td>20 mg rivaroxaban per day resp. 15 mg/day rivaroxaban for patients with CrCl 30-49 ml/min versus warfarin adjusted to an INR of 2.0 to 3.0</td>
<td>5 mg apixaban twice daily resp. 2.5 mg apixaban twice daily for patients with serum creatinine ≥ 1.5 mg/dl (approx. CrCl ≤ 50 ml/min) versus warfarin adjusted to an INR of 2.0 to 3.0</td>
</tr>
<tr>
<td><strong>Antiplatelet agents</strong></td>
<td>Aspirin ≤100 mg per day Clopidogrel Ticlopidine Dipyridamole ASA/Dipyridamole</td>
<td>Aspirin ≤100 mg per day</td>
<td>Aspirin ≤165 mg per day Clopidogrel</td>
</tr>
<tr>
<td><strong>Investigated CKD stages</strong></td>
<td>CrCl &lt; 50 ml/min CrCl 50 - 79 ml/min CrCl ≥ 80 ml/min</td>
<td>CrCl 30 - 49 ml/min CrCl ≥ 50 ml/min</td>
<td>CrCl ≤ 30 ml/min CrCl 30 - 50 ml/min CrCl ≤ 30 ml/min CrCl 30 - 50 ml/min</td>
</tr>
<tr>
<td><strong>Exclusion criteria with regard to creatinine clearance</strong></td>
<td>&lt;30 ml/min &lt;30 ml/min &lt;25 ml/min</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Study Outcomes</strong></td>
<td><strong>Primary efficacy outcome</strong></td>
<td><strong>Primary safety outcome</strong></td>
<td><strong>Secondary efficacy outcome</strong></td>
</tr>
<tr>
<td></td>
<td>Stroke • Systemic embolism • Major hemorrhage • Stroke • Systemic embolism • Death • Myocardial infarction</td>
<td></td>
<td></td>
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<tr>
<td><strong>Secondary efficacy outcome</strong></td>
<td><strong>Composite of stroke and systemic embolism</strong> • Composite of major and non-major clinically relevant bleeding events • Composite of stroke, non-central nervous system systemic embolism, cardiovascular death, myocardial infarction</td>
<td><strong>Ischemic or hemorrhagic stroke</strong> • Systemic embolism • Major hemorrhage • Death • Myocardial infarction</td>
<td></td>
</tr>
<tr>
<td><strong>Study Results</strong></td>
<td><strong>Primary efficacy outcome</strong></td>
<td><strong>Primary safety outcome</strong></td>
<td><strong>Secondary efficacy outcome</strong></td>
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<td></td>
<td>Dabigatran 110 mg: 1.53%/yr&lt;sup&gt;a&lt;/sup&gt; 150 mg: 1.11%/yr&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Rivaroxaban 15 mg: 2.32%/yr 20 mg: 1.57%/yr</td>
<td>Apixaban 1.27%/yr&lt;sup&gt;a&lt;/sup&gt; 1.60%/yr&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Warfarin 1.69%/yr</td>
<td>Warfarin 2.77%/yr 2.00%/yr</td>
<td>Warfarin 2.13%/yr 3.09%/yr</td>
</tr>
<tr>
<td></td>
<td>Dabigatran 110 mg: 2.71%/yr&lt;sup&gt;a&lt;/sup&gt; 150 mg: 3.11%/yr</td>
<td>Rivaroxaban 15 mg: 17.82%/yr 20 mg: 14.24%/yr</td>
<td>Apixaban 3.52%/yr 3.94%/yr</td>
</tr>
<tr>
<td></td>
<td>Warfarin 3.36%/yr</td>
<td>Warfarin 18.28%/yr 13.67%/yr</td>
<td>Warfarin 3.52%/yr 3.94%/yr</td>
</tr>
<tr>
<td></td>
<td>Mortality Rate:</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Dabigatran 110 mg: 3.75%/yr 150 mg: 3.64%/yr</td>
<td>Rivaroxaban 15 mg: 5.58%/yr 20 mg: 3.55%/yr</td>
<td>Apixaban 3.52%/yr 3.94%/yr</td>
</tr>
<tr>
<td></td>
<td>Warfarin 4.13%/yr 4.16%/yr</td>
<td>Warfarin 6.54%/yr 4.16%/yr</td>
<td>Warfarin 3.52%/yr 3.94%/yr</td>
</tr>
<tr>
<td><strong>Outcome with regard to CKD</strong></td>
<td><strong>No significant difference in the treatment effect could be observed in patients with renal impairment</strong></td>
<td><strong>Patients with moderate renal impairment (CrCl &lt;50 ml/min) have higher rates of stroke and bleeding under both rivaroxaban and warfarin compared to patients with normal renal function. No superiority or non-inferiority of rivaroxaban versus warfarin could be demonstrated for patients with CrCl 30-49 ml/min</strong></td>
<td><strong>Patients with moderate to severe renal impairment (CrCl ≤50 ml/min) showed an even greater reduction in major bleeding events under apixaban compared to warfarin.</strong>*</td>
</tr>
</tbody>
</table>

RE-LY: Randomized Evaluation of Long-Term Anticoagulation Therapy; 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; ARISTOTLE: Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation; INR: international normalized ratio; CrCl: creatinine clearance.

Numbers in bold represent significant differences of the investigated medication compared to warfarin. a: for non-inferiority; b: for superiority.
Major risk factors

<table>
<thead>
<tr>
<th>Major risk factors</th>
<th>Clinically relevant non-major risk factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior stroke or TIA or thromboembolism</td>
<td>Heart failure or moderate to severe LV dysfunction (LV EF ≤ 40%)</td>
</tr>
<tr>
<td>Age ≥ 75 years</td>
<td>Hypertension</td>
</tr>
<tr>
<td>Mitral stenosis or prosthetic heart valves</td>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td>Age 65-74 years</td>
<td>Female sex</td>
</tr>
<tr>
<td>Vascular disease (prior myocardial infarction, peripheral artery disease, complex aortic plaque)</td>
<td></td>
</tr>
</tbody>
</table>

TIA: transient ischemic attack; LV: left ventricular; EF: ejection fraction

Outcomes with Oral Anticoagulation Depending on CKD Stage

CKD stage 2 and 3 (eGFR between 90 and 29 ml/min/1.73 m²): To our knowledge there are no studies investigating the risk for stroke under warfarin versus placebo or versus antiplatelet medication in patients with light to moderate renal impairment and AF.

There is only one study which examines the incidence of thromboembolic stroke in patients with all (including the above) stages of CKD and AF treated with or without warfarin \(^{37}\) (Table 1). Independent of CKD stage, therein thromboembolic stroke occurred in 9% of patients treated with warfarin and 26% of patients without anticoagulation (P<0.001). The incidence of stroke in patients with CKD stage 2 and 3 under warfarin was half that of patients without warfarin (10% resp. 20%, P<0.05). Major bleeding was slightly but insignificantly increased in patients under warfarin treatment.

Three recent phase 3 studies compared new anticoagulant drugs to warfarin concerning safety and efficacy (Table 2). In the RE-LY trial, the direct thrombin inhibitor dabigatran was given at two different doses (110 mg and 150 mg) twice daily; AF patients with CrCl of at least 30 ml/min were included. The lower dose was associated with comparable rates of stroke, systemic embolism, and major bleeding events to those under warfarin. The higher dabigatran dose was superior to warfarin in preventing stroke. Concerning patients with CrCl < 50 ml/min, between 50 and 79 ml/min, and ≥80 ml/min, there was no significant difference in the treatment benefit of the studied anticoagulants. \(^{38}\)

Rivaroxaban, a novel factor Xa inhibitor, was
tested at two different doses depending on creatinine clearance against warfarin in the ROCKET-AF study. Patients with AF and CrCl ≥ 30 ml/min were included. The efficacy results showed that slightly but not significantly less stroke and systemic embolism events occurred in the rivaroxaban groups than in the warfarin group. Compared to warfarin there was no excess bleeding on rivaroxaban.

In the ARISTOTEL trial, another direct factor Xa inhibitor, apixaban, was studied versus warfarin in AF patients with CrCl of at least 25 ml/min. Apixaban was superior to warfarin in reducing stroke, systemic embolism events, and major hemorrhages. Especially patients with severe or moderate renal impairment suffered from significantly less major bleedings under apixaban than under warfarin (apixaban group: 3.2% versus warfarin group: 6.4%; P=0.03 for interaction).

Data from the Dialysis Outcomes and Practice Patterns Study (DOPPS), showed that warfarin given to hemodialysis patients with AF increased their stroke risk especially for elderly patients over 75 years (hazard ratio 2.17, 95% CI 1.04 – 4.53).

Controversially, Lai reported a reduced stroke incidence in patients on warfarin compared to patients off warfarin: 10% of hemodialysis patients and 10% of patients with eGFR < 15 ml/min/1.73 m² under warfarin treatment experienced a thromboembolic stroke versus 38% respectively 37% of patients without warfarin.

A retrospective analysis of 5,858 ESRD patients examined the long-term survival after cardiac valve surgery. Patients received either mechanical prosthetic valves requiring lifetime anticoagulation or bio prosthetic valves with no medical need for subsequent anticoagulation. Although all dialysis patients had a poor long-term survival after cardiac surgery, there was no difference in the survival of the 4,944 patients with mechanical valves compared to that of the 848 patients with tissue valves. This is remarkable, since patients receiving mechanical valves need permanent anticoagulation whereas most of the patients with tissue valves probably did not take anticoagulation although there are no data given in the study.

CKD stage 4 (eGFR between 15 and 29 ml/min/1.73 m²): Only few trials with small numbers of CKD patients with eGFR between 15 and 29 ml/min/1.73 m² are available. Limdi et al. evaluated the influence of kidney function on warfarin dosage. With decreasing kidney function patients require significantly lower warfarin doses and are at higher risk for over-anticoagulation. Further, patients with severe CKD (eGFR < 30 ml/min/1.73m²) had a 2.4-fold increased risk of major hemorrhage.

As mentioned above, a recent retrospective study with 399 patients with CKD stages 3, 4 and 5 and AF investigated the incidence of thromboembolic stroke under treatment with or without warfarin. The incidence of thromboembolic stroke in patients with CKD stage 4 was only about a fourth of those in patients without anticoagulation (5% versus 21%, P<0.05). Vazquez conducted a small observational study with 240 patients on hemodialysis, of whom 29 had received oral anticoagulant warfarin derivatives for a period of at least one month. Although the relative risk of bleeding with anticoagulation was more than 2-fold enhanced, none of the bleeding incidences, mainly in the digestive tract, was fatal.

Recently, two retrospective studies of hemodialysis patients with AF suggest that warfarin is associated with increased risk of stroke. In a retrospective cohort analysis of 1,671 hemodialysis patients the use of warfarin increased the risk for new stroke by 1.93 compared with nonuse. Furthermore, patients on warfarin who received no INR monitoring in the first 90 day had an even more advanced risk for stroke (hazard ration 2.79). On the other hand, there was no statistically significant increase in all-cause mortality or hospitalization under warfarin use.

Data from the Dialysis Outcomes and Practice Patterns Study (DOPPS), showed that warfarin given to hemodialysis patients with AF increased their stroke risk especially for elderly patients over 75 years (hazard ratio 2.17, 95% CI 1.04 – 4.53).

Controversially, Lai reported a reduced stroke incidence in patients on warfarin compared to patients off warfarin: 10% of hemodialysis patients and 10% of patients with eGFR < 15 ml/min/1.73 m² under warfarin treatment experienced a thromboembolic stroke versus 38% respectively 37% of patients without warfarin.

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Therapeutic Strategies

In general, oral anticoagulation is an effective therapy to prevent stroke in AF patients. Whether patients with impaired renal function benefit to the same extent from an anticoagulant therapy, is the issue of only few studies so far. The problem with anticoagulation in CKD patients is their also increased risk of bleeding due to altered hemostasis. In consequence, with worsening kidney function, both the risk of stroke and the risk of bleeding events rise markedly.

To determine the risk of stroke in the general population, several stroke risk stratification algorithms have been developed. The simplest and most common risk assessment scheme, the CHADS2-score, is based on a point system in which one point is assigned for recent cardiac failure, hypertension, age > 75 years, and diabetes and two points are assigned for history of stroke or transient ischemic attacks (TIA). In routine care of the general population, oral anticoagulation is recommended for patients with a CHADS2-score ≥2.1 Lately, the CHADS2-score has been modified to the CHA2DS2-VASc-score, giving two points to age > 75 years and an additional point for vascular disease, age 65-74 years, and female gender.4 Thus, more risk factors for stroke are considered in the CHA2DS2-VASc-score. Again, oral anticoagulation is recommended for patients with a CHA2DS2-VASc-score of two or greater.45

In CKD and especially in ESRD, affected patients suffer from a prothrombotic state which is the result of a high risk for thromboembolism and a coagulopathy with an increased tendency for bleeding.9 The management of chronic hemodialysis patients with AF is therefore difficult, and so far no current stroke risk stratification schemes consider the situation in CKD or ESRD patients.23 An individual algorithm considering risk factors and persistent medication, as suggest by us previously,9 might currently represent the most suitable approach for CKD patients until data from randomized trials will be available. Going briefly through this algorithm, all CKD patients with permanent, persistent, and paroxysmal atrial fibrillation should be considered to be prone to an increased risk for ischemic stroke. Based on the ESC guidelines11 for atrial fibrillation, the patient’s major and clinically relevant non-major risk factors (Table 3) should be assessed and the CHADS2- or CHA2DS2-VASc-score could be calculated. Since all the patients evaluated in this context have CKD as an additional but yet not concerned risk factor, there is wide consent that their true ischemic risk must be classified to be higher. If a patient has definitely no or only one moderate risk factor, anticoagulation with antiplatelet drugs, e.g. low-dose acetylsalicylic acid (ASS), can be considered as an efficient therapy.

Otherwise, for patients with two or more risk factors an oral anticoagulation therapy should be considered. If the patient has already taken oral anticoagulation for more than 3 months, there is evidence that he probably represents a positive selection with a lower risk for bleedings.9 Nevertheless, the bleeding risk is higher in CKD patients; therefore during long-term treatment the INR should be controlled at least every 14 days and be adjusted within a precise target range of 2.0-2.5.

In patients without current oral anticoagulation or beginning of this therapy within the last 3 months, risk factors for bleedings e.g. previous hemorrhage, dementia, cancer, eGFR<30 ml/min/1.73 m² or recurrent falls, should be carefully considered. If the decision towards oral anticoagulation is made, than the titration phase should be started carefully, with lower starting doses of the anticoagulant and small-meshed INR controls during the first 4 weeks, during which the highest bleeding rates in all patients especially those with increased risks occur. If the bleedings risk appears to be too high, then at least administration of antiplatelet drugs should be considered, even more if other vascular manifestations are present (coronary, peripheral or carotid artery disease).

Conclusions

Although it is well known that CKD and ESRD patients are at a markedly increased risk for cardiovascular events and mortality, only limited and conflicting data are available about treatment strategies in many fields. As a consequence, CKD patients are often undertreated compared to patients with normal renal function. Thus, the unfavorable prognosis of CKD and ESRD...
patients with AF is in part due to poor treatment which is the consequence of the poor data basis. In so far, CKD patients are hit twice: they suffer from a higher morbidity and are often treated worse.

With regard to atrial fibrillation, there is a great insecurity whether the standard therapy which is oral anticoagulation provides any benefit in patients with renal impairment and AF. CKD patients with AF who are closely monitored as seen in a recent study appear have a comparable survival rate to patients without AF and without anticoagulation. Also, the stroke incidence can be dramatically reduced if an INR between 2.0 and 3.0 was achieved. Other, non-randomized, retrospective studies did not support these positive findings. More studies evaluating CKD patients especially with CKD stages 4 and 5 and AF are strongly recommended to improve the medical therapy and to develop widely accepted risk stratification and treatment guidelines.

References


Introduction

Congestive heart failure (CHF) remains a major public health burden affecting an estimated 5.7 million people in the United States, and accounting for over 250,000 deaths annually. Over the past few decades, data from randomized trials have led to a dramatic increase in the use of pharmacological therapies that improve outcomes for patients with heart failure due to systolic dysfunction. In addition to these medical therapies, implantable cardiac devices provide additional therapeutic benefits for patients with congestive heart failure and depressed left ventricular systolic function.

Cardiac resynchronization therapy (CRT) has been shown to improve quality of life, prevent hospitalizations, and reduce mortality for patients with CHF.

Abstract

Cardiac resynchronization therapy (CRT) has evolved as an effective therapy for patients with congestive heart failure (CHF) and ventricular dyssynchrony, currently defined as a wide QRS on the electrocardiogram. While multiple randomized controlled trials have confirmed the favorable effects of CRT on mortality and heart failure symptoms for patients in sinus rhythm, only recently observational studies have begun to suggest a similar benefit for patients with atrial fibrillation (AF) and dyssynchrony. Yet, implementing effective biventricular pacing in patients with AF can be problematic due to competing intrinsic AV conduction. For patients with depressed ejection fractions needing AV node (AVN) ablation to control fast ventricular rates, biventricular pacing has been shown to be superior to right ventricular pacing alone. When consistent pacing (over 90% of the time) cannot be achieved in AF patients due to a rapid ventricular response despite pharmacological therapy, AVN ablation should be considered. The additional benefit of performing AVN ablation to promote biventricular pacing in patients without rapid ventricular rates remains uncertain. A randomized controlled trial is needed to test the incremental benefit of AVN ablation to promote biventricular pacing in heart failure patients with AF and wide QRS.
achieving effective biventricular pacing can be challenging. The use of rate-controlling medications or programming higher pacing rates may be ineffective or result in undesired side effects. As such, AV node (AVN) ablation has become an important therapeutic option to eliminate intrinsic AV conduction and ensure a high percentage of biventricular-paced beats. Here we review the data relevant to CRT in patients with AF and the potential role of AVN ablation in improving outcomes for these patients.

Atrial Fibrillation and Heart Failure

AF and CHF often coexist together, and each portends a worse prognosis for patients with heart disease. The prevalence of AF varies with the severity of heart failure, from less than 10% of those with class I symptoms to as high as 50% of those with class IV symptoms. In a community-based cohort study, 17% of patients with CHF were subsequently diagnosed with AF over a mean follow-up of 4.2 years, which is associated with an increased risk of death or hospitalizations. AF contribution to worsening heart failure can be secondary to loss of AV synchrony, faster ventricular rates, or more ventricular rate irregularity. It is also possible that AF is simply a marker of a worse disease process in this patient population.

The presence of structural heart disease and CHF complicates the management of AF. Options for antiarrhythmic medications for rhythm control are limited due to potential toxicities of these drugs. Most recent guidelines recommend only dofetilide or amiodarone as antiarrhythmic options in this population, yet limitations still exist, such as limited efficacy, exclusion due to comorbidities, potential harmful drug interactions, and concern about long-term side effects. Finally, pulmonary vein isolation for AF has developed as an important therapy and is highly effective, yet procedural success may be lower in the presence of severe structural heart disease.

In view of the limited efficacy of antiarrhythmic agents, clarity on optimal therapeutic strategies was necessary. The AF-CHF study, a large randomized multicenter study that enrolled 1376 patients, found no significant difference in outcomes for patients randomized to a rate-control versus rhythm-control strategy. However, it may be difficult to achieve acceptable rate-control for all patients with AF and heart failure using medications alone.

For patients unable to achieve adequate rate-control, AVN ablation and implantation of a pacemaker may be performed. However, when pacing is required, patients with structural heart disease tend to do poorly over the long term as a consequence of the detrimental effects of RV apical pacing. In the DAVID trial, 506 patients with standard ICD indications were randomized to backup VVI pacing at 40 bpm, or DDD pacing at 70 bpm. The trial was designed with the hope of demonstrating that DDD pacing was superior, as it would allow up titration of CHF medications, mainly beta-blockers, and therefore improve outcomes. Yet the opposite was observed, as the group randomized to the DDD arm had a significant increase in mortality and hospitalizations for CHF, prompting for the early termination of the study. Since then, and after analysis of other prior studies, RV apical pacing is considered detrimental to patients with CHF due to systolic dysfunction and is best avoided.

CRT for Patients with Atrial Fibrillation and Heart Failure

Cardiac resynchronization therapy has been shown to improve quality of life and survival for patients in sinus rhythm with depressed left ventricular systolic function, wide QRS, and class III or IV heart failure symptoms. Left ventricular reverse remodeling was evident with CRT including improved ejection fraction, decreased left ventricular volume, and diminished mitral regurgitation. The initial randomized trials of CRT tended to exclude patients with AF, but emerging data now suggests that heart failure patients with AF also benefit.

Leclerq, et al. first observed an improvement in left ventricular ejection fraction and exercise tolerance in a small group of patients with AF and wide QRS who received a CRT device. In an observational study including 60 patients, the response to CRT was noted to be similar in patients with AF compared to those with sinus rhythm. Subsequently, multiple observational studies, some that included several hundred patients, have found similar outcomes after CRT.
for patients with AF compared to those in sinus rhythm, although one study noted worse survival for those with AF. The improvement in heart failure outcomes was even observed in one study in which no AVN ablation was performed.

The mechanism of improvement in cardiac function in patients with AF is likely multifactorial. For patients in sinus rhythm, CRT may enhance atrio-ventricular synchrony, interventricular synchrony, and intraventricular synchrony leading to reverse remodeling. In addition to the aforementioned benefits, in patients with AF, CRT might also allow for optimal ventricular rate control. Implantation of a CRT device may allow more aggressive rate-controlling drugs to be administered to prevent rapid ventricular rates. Also, a number of patients in these studies were noted to have undergone AV node ablation.

**AV Node Ablation as a Rate-Controlling Strategy**

A major potential contributor to heart failure symptoms for patients with AF and wide QRS may be uncontrolled ventricular rates. AV node ablation and permanent ventricular pacing have shown to improve symptoms of heart failure in patients with AF regardless of ejection fraction. This “ablate and pace” strategy appears to be highly effective in relieving symptoms from rapid AF with no significant detrimental effect on mortality compared to pharmacological rate control, even when right ventricular pacing is utilized. However, these short term benefits are tempered by the potential detrimental effects of right ventricular apical pacing over the long term, especially in the presence of underlying structural heart disease, mainly systolic dysfunction, as demonstrated in the DAVID trial.

More recent data suggest that biventricular pacing with a CRT device is superior to right ventricular pacing after AVN ablation, especially in patients with structural heart disease. In the PAVE study, randomization to biventricular pacing resulted in greater improvements in six minute walk test, especially for those patients with depressed left ventricular ejection fraction. Furthermore, in patients with AVN ablation who have documented CHF and low systolic function, upgrading from a right ventricular to a biventricular pacing device leads to reduced heart failure symptoms and improved left ventricular ejection fraction. More recently, Brignole and colleagues reported their results of a randomized study they conducted involving 186 patients assigned to CRT or RV apical pacing alone after AVN ablation. After a median follow up of 20 months, biventricular pacing resulted in fewer hospitalizations or worsening heart failure symptoms, regardless of ejection fraction and QRS width before the procedure.

These data support the use of AVN ablation and biventricular pacing for patients with palpitations and heart failure symptoms that are attributed to uncontrolled rapid or irregular ventricular rates. Yet, not all patients deteriorate with RV apical pacing, especially those with no evidence of structural heart disease at baseline. Since CRT therapy is associated with higher costs and complication rates than RV apical pacing alone, additional data is required in order to understand who would be the best candidates for CRT after AVN ablation when the ejection fraction is preserved as the outcome after AVN ablation might not be only dependent on ejection fraction but also other mechanisms, such as the autonomic tone. When the ejection fraction is impaired, CRT therapy appears to be superior. Alternatively, not all heart failure patients with AF suffer from rapid ventricular rates, yet they may have ventricular dysynchrony as evident by a wide QRS, for which cardiac resynchronization may be beneficial.

**Assessment of Effective Cardiac Resynchronization**

A concern for CRT recipients with AF is whether effective biventricular pacing is being delivered. Rapid or irregularly conducted beats may inhibit pacing such that ventricular dysynchrony persists. A commonly used measure of the amount of CRT delivered is the percentage of biventricular pacing recorded by the CRT device counter. However, these counters can be misleading as they are unable to assess whether paced beats are fully captured because there is often fusion with intrinsic AV conduction.

Kamath and colleagues used 12-lead Holter monitoring to evaluate patients with AF and CRT.
They demonstrated that the CRT device pacing counters do not accurately quantify the amount of effective biventricular pacing administered to patients with AF; it was often the case that many of the paced beats did not capture or only partially captured due to fusion with the conducted intrinsic complex. In fact, nonresponders to CRT demonstrated a higher percentage of fusion and pseudofusion beats, while responders had a higher percentage of fully paced beats (over 90%). These data suggest that ineffective biventricular pacing due to intrinsic AV conduction may be an important cause for lack of response to CRT in AF patients. Furthermore, the presence of ineffective biventricular pacing may be unapparent from device interrogation alone, and Holter evaluation would be required.

The CRT device may be programmed to a faster pacing rate to ensure biventricular pacing, but these faster rates may be undesirable in some patients, such as those with coronary artery disease and angina. Rate-controlling medications such as beta-blockers, calcium channel blockers, digoxin, or even amiodarone could be administered, but these might be ineffective or the side effects not tolerated. AVN ablation therefore is often considered, as the creation of heart block is naturally the most effective tool in preventing intrinsic AV conduction and augmenting the percentage of effective biventricular pacing in those who require it.

**AV Node Ablation to Promote Biventricular Pacing**

There are no randomized trials that test the effect of AVN ablation on outcomes for heart failure patients with AF who are receiving CRT for wide QRS. Several recently published observational studies provide some insight into the potential role of AVN ablation for these patients (Table).

Gasparini, et al. described the outcomes of consecutive patients with AF and heart failure with a wide QRS who received CRT devices at two centers in Europe. Those patients who had less than 85% biventricular pacing on device interrogation underwent AVN ablation. Compared to patients in sinus rhythm with CRT devices, those in AF who underwent AVN ablation had similar improvements in echocardiographic parameters and functional capacity. Interestingly, those who did not have AVN ablation performed were significantly less likely to respond to CRT with no significant change in left ventricular ejection fraction. In a subsequent analysis of multicenter registry data, similar results were observed. Those heart failure patients with a CRT device and AF who were treated with negative chronotropic drugs had a higher mortality rate compared to patients who underwent AVN ablation.

Consistent with the above results, Ferriera, et al. found that AVN ablation performed after CRT in patients with AF was associated with lower mortality and a higher CRT response rate. There was also a higher rate of hospitalization for heart failure for those patients who did not have AVN ablation performed. Most recently, Dong et al. analyzed the outcomes after CRT-D implant in 154 patients with heart failure, QRS greater than 120 msec, AF and depressed ejection fraction. They observed improved survival and greater improvement in NYHA class for those patients who received AVN ablation compared to those who did not have ablation performed. It is noted that in this study, those patients who did not receive AVN ablation still had a median percentage of biventricular pacing of 96%, although only device counters were used. More effective biventricular pacing in this group might account for the similar improvement in echocardiographic parameters that was observed for AF patients after AVN ablation compared to those in normal sinus rhythm in this study. The observational nature of these studies limits the interpretation of the results, as selection bias or unmeasured confounding variables may have influenced the differences in outcomes between those who did or did not have AVN ablation performed. Specifically, patients who did not receive AVN ablation in the multicenter registry tended to have lower ejection fraction and wider QRS duration at baseline, suggesting they had more severe cardiac disease. Also, the effectiveness of biventricular pacing in AF patients was generally measured using the CRT device counters, which have been shown to overestimate the percentage of effective biventricular pacing. Those patients with less effective biventricular pacing would be expected to more likely benefit from AVN ablation. Furthermore, large-scale randomized trials are necessary to reproduce the effect of the procedure on global outcome over the long-term for
this population.

**Potential Limitations**

The disadvantages of AVN ablation should be considered before pursuing this procedure on all patients. The procedure itself carries a small risk of complications at the venous access site or damage to cardiac or vascular structures. Ventricular fibrillation and sudden death have been observed following AVN ablation, although this complication may be prevented by initially programming the pacemaker to a higher pacing rate. In fact, sympathetic nerve activity increases after AVN ablation, which might contribute to the incidence of post-ablation arrhythmia. Interestingly, sympathetic nerve activity is decreased if patients are programmed to faster rates after the ablation. Patients are generally rendered pacemaker dependent after AVN ablation, and as such there is the potential for life-threatening bradyarrhythmia to occur in the event of pacemaker malfunction. Oversensing of diaphragmatic myopotentials has been observed in pacemaker-dependent patients with CRT devices, notably with integrated bipolar right ventricular leads, which has resulted in inhibition of pacing, inappropriate shocks, and potentially death. As such, dedicated bipolar lead systems should be considered in these instances. When AVN ablation results in a slower ventricular escape rhythm, this was associated with worse outcomes in one study. In the event of device complications or infections, prolonged hospitalizations may be required for treatment before a new device can be implanted.

Not all patients with heart failure and electrical dyssynchrony benefit with CRT, and some patients may become worse. By promoting more biventricular pacing, AVN ablation could be detrimental for these nonresponders. Suboptimal left ventricular lead positions, notably anterior or apical positions, are associated with worsening heart failure in CRT recipients. An increase in ventricular tachyarrhythmia has been reported with biventricular pacing and may be a significant problem in patients who do not respond to CRT. In addition, some patients in AF may return to sinus rhythm after CRT is implemented such that AVN ablation is no longer required.

An important question that remains is what is the optimal percentage of pacing that leads to clinical benefits? Although there is consensus that at least 90% capture on Holter should be achieved, it is not clear whether an even higher number (such as over 95%) would be superior and therefore considered as a target. Additional data would be required to answer this and other questions.

**Conclusions**

Cardiac resynchronization therapy remains an effective treatment for patients with heart failure and wide QRS whether they are in sinus rhythm or AF. The presence of AF may prove to be an obstacle to effective biventricular pacing in these patients, as intrinsic conduction can preclude

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**Table 1:** Observational studies of CRT patients with atrial fibrillation for whom AVN ablation was or was not performed

<table>
<thead>
<tr>
<th>Reference</th>
<th>Number of patients</th>
<th>Findings associated with AVN ablation compared to no AVN ablation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Molhoek et al. 2004</td>
<td>17</td>
<td>Similar improvement in NYHA class</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Similar improvement in LVEF</td>
</tr>
<tr>
<td>Gasparini et al. 2006</td>
<td>114</td>
<td>Improved LVEF Improved NYHA class</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Improved functional capacity score</td>
</tr>
<tr>
<td>Delnoy et al. 2007</td>
<td>21</td>
<td>Not reported</td>
</tr>
<tr>
<td>Gasparini et al. 2008</td>
<td>117</td>
<td>Improved survival</td>
</tr>
<tr>
<td>Ferreira et al. 2008</td>
<td>26</td>
<td>Greater improvement in NYHA class</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fewer HF hospitalizations</td>
</tr>
<tr>
<td>Tolosana et al. 2008</td>
<td>19</td>
<td>Fewer HF hospitalizations</td>
</tr>
<tr>
<td>Dong et al. 2010</td>
<td>45</td>
<td>Improved survival greater improvement in NYHA class (No difference in improvement in LVEF)</td>
</tr>
</tbody>
</table>

+AVN Abl, AVN ablation was performed; -AVN Abl, AVN ablation was not performed; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; HF, heart failure; CRT, cardiac resynchronization therapy.
the patient from achieving the high percentage of pacing required to achieve full benefit from CRT. An accurate assessment of the effectiveness of CRT may not be apparent from the device interrogation alone, as fusion and pseudofusion would not be detected. AVN ablation is effective in ensuring a high percentage of biventricular pacing in most patients with AF. Observational studies have shown that the performance of AVN ablation in patients with heart failure and AF with a CRT device is associated with improved survival and a higher CRT response rate, although selection bias and unmeasured confounding variables may limit the interpretation of these results. A randomized controlled trial testing the effect of AVN ablation on clinical outcomes for patients with AF who are candidates for CRT is indicated. Until the results of such trial are available, the decision to perform AVN ablation must be made on an individual basis, but strong consideration must be given to patients with AF and CHF who fail to respond to CRT and who have less than optimal percentage of biventricular pacing as demonstrated by Holter monitoring.

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Cardiac resynchronization therapy (CRT) is now a well established treatment for selected patients with advanced chronic heart failure (CHF), having shown to reduce morbidity and mortality when combined with optimal pharmacotherapy. \(^1\) Since the prevalence of atrial fibrillation (AF) parallels the severity of CHF (from 10% in patients in New York Heart Association (NYHA) class II up to 50% in NYHA class IV), \(^2\) it is not surprising that many candidates for CRT have AF. Indeed, patients with AF make up 20-30% of CRT recipients in clinical practice. \(^3, 4\) The development of AF in the CHF patient also heralds a worse prognosis, nearly doubling the risk of death, \(^5\) even though there is no consensus as to whether AF is an independent risk factor or just a marker of more advanced disease. Nevertheless, and despite the high prevalence of this arrhythmia among patients eligible for CRT, almost all the randomized clinical trials that validated the benefit of resynchronization therapy excluded patients with preexisting AF. In this review, we examine the available evidence on the benefits and limitations of CRT in patients with AF and discuss recent data that narrowed the knowledge gap on this topic.

Why is Atrial Fibrillation Relevant for Patients Receiving CRT?

AF poses a number of challenges for adequate CRT delivery. Patients with AF have no AV synchrony, precluding coordinated AV pacing with appropriately programmed AV intervals. Moreover, these patients often have highly irregular and fast ventricular rates, particularly during exertion. In these circumstances, spontaneous ventricular rate tends to override biventricular pacing rates, causing a reduction of paced beats precisely when patients most need it. \(^8\) Special programming features have been developed to overtake spontaneous rhythm in these circumstances, \(^9\) including Ventricular Rate Regularization™, Ventricular Sense Response™, and Conducted AF Response™. However, some of these programming features increase biventricular pacing at the expense of higher ventricular rates,
and their benefits remain to be proven. So, the net result of rhythm irregularity and fast ventricular rates is a decrease in biventricular pacing delivery, the cornerstone of resynchronization therapy.

How Important is the Percentage of Biventricular Pacing?

Our knowledge on the relationship between the percentage of biventricular pacing and the clinical benefit of CRT had recent advances. Earlier studies arbitrarily defined adequate biventricular pacing as >85% capture,10,11 but it soon became apparent that an even greater degree of biventricular pacing might be required for optimal results. This conclusion stemmed from several observational studies showing that near-maximal biventricular capture is required to realize all the benefits of CRT, both in sinus rhythm and in atrial fibrillation.12-17

The largest of these studies followed up a cohort of more than 30,000 patients in a remote-monitoring network.17 Higher percentages of biventricular pacing were associated with lower mortality and fewer heart failure symptoms. The optimal cut-point that divided the patient population into two pacing groups with maximally different survival patterns was 98.5%. Interestingly, this high cut-point value was also valid for patients with AF (defined here as >0.5% of atrial sensed beats at rates greater than 180 beats/min). This study raised the goal of biventricular pacing even further by showing that subjects with a biventricular pacing percentage above 99.6% experienced a 24% reduction in mortality compared with other quartile groups, while those with <94.8% had a 19% increase in mortality. The reasons behind this brisk decline in CRT benefit when biventricular capture rates drop below near-maximal values are still unclear, but this high threshold emphasizes the need to achieve biventricular pacing as close to 100% as possible. It is interesting to note that both AF and low biventricular pacing rates are independently associated with worse outcomes,14,17 thus suggesting that AF may have a dual impact on prognosis, both as a component of more advanced cardiomyopathy and as a determinant of poor biventricular pacing rates that hamper response to therapy.

An important limitation of these analyses (and also a common difficulty in clinical practice) is that even when pacing is delivered, many ventricular complexes may be fused or pseudo-fused, making pacing capture percentages retrieved from CRT devices inaccurate and an overestimate of effective pacing capture.13,18 It is also possible that the loss of biventricular pacing may be a marker of deteriorating cardiac function, since it may be caused by other factors associated with worse outcome, such as nonsustained ventricular tachycardia and premature ventricular contractions. This could help explain why very small reductions in the percentage of biventricular pacing relate to poorer outcomes.19 Studies in which the actual cause for decreased biventricular pacing can be ascertained and the degree of fusion and pseudofusion accurately quantified are needed to settle these issues.

What is the Impact of AF on the Benefit of CRT? Does AF Preclude Clinical Response to CRT?

Large-scale randomized clinical trials have validated the use of CRT in patients with significant systolic dysfunction, symptomatic CHF despite optimized medical therapy, prolonged QRS duration, and sinus rhythm. The established benefits include improvements in symptoms, exercise capacity, left ventricular systolic function, and ultimately, prognosis.1,20-24 Whether or not these benefits can be extended to patients with AF has been a matter of study and debate in these last few years, encouraged by initial reports showing a beneficial acute effect of CRT on hemodynamic parameters.25,26 In the absence of randomized controlled trials of CRT vs. no CRT in patients with AF, our knowledge on this subject comes essentially from surrogates such as observational studies and comparisons between patients in AF vs. patients in sinus rhythm among CRT recipients. Their findings on mortality and responsiveness to CRT are summarized in Table 1.

A recent meta-analysis of 23 observational studies including a total of 1,912 CRT recipients with a history of AF suggests that, while patients with AF benefit from CRT, they are at increased risk for adverse outcomes when compared to similar patients with sinus rhythm.27 AF was a predictor of all-cause mortality (pooled RR 1.50; 95% CI 1.08-2.09) and was also associated with an increased risk of nonresponse to CRT (pooled relative risk [RR] 1.32; 95% confidence interval [CI] 1.12-1.55), even though the definition of response to CRT...
differed widely among studies. The effects of CRT on softer endpoints have also been reported in several observational studies including patients with AF. Quality of life was assessed in seven studies reporting changes in the Minnesota Living with Heart Failure (MLWHF) score. All showed improved scores in CRT recipients with AF, even though the pooled mean reduction was 4.1 points less than in those without AF (95% CI 1.7 - 6.6). The same was true for exercise capacity, where patients with AF experienced a weighted mean improvement in 6-minute walking distance of 63m, which was 14.1m smaller (95% CI 0.0 - 28.2) than in those without AF.

Data on hospitalizations for CHF are only available from four studies. Three of these suggest that CRT in patients with AF decreases hospitalization rates, while another one suggests that patients with AF not submitted to ablation of the atrioventricular junction (AVJ) are at increased risk for hospitalization compared to patients in sinus rhythm. Finally, most studies show significant improvements in left ventricular ejection fraction (LVEF) which seem independent from heart rhythm, with no consistent difference in LVEF change between patients with AF and patients with sinus rhythm.

So, there is some evidence that, even though their prognosis is poorer, patients with AF do benefit from CRT in terms of symptomatic improvement and, possibly, mortality. Nevertheless, it remains unclear whether the worse prognosis of CRT recipients with AF is the result of reduced response to CRT or merely the reflection of greater baseline risk. There are also reasons why CRT might work particularly well in patients with AF, provided that biventricular pacing delivery is assured. Rhythm regularization, rate slowing, simpler programming and the need for less leads are among those reasons. More importantly, the extent to which the benefits of CRT depend upon performing ablation of the atrioventricular junction (AVJ) is still uncertain.

**What is the Role of Atrioventricular Node Ablation?**

Perhaps the most controversial issue regarding CRT in patients with AF is whether optimal rate control should be achieved pharmacologically...
or nonpharmacologically by ablation of the AVJ. The potential benefits of AVJ ablation include rhythm regularization by optimizing the alternation of systolic and diastolic phases of the cardiac cycle, lower heart rates favoring diastolic performance, and the avoidance of rate control drugs with potential deleterious effects and, of course, the nearly complete biventricular capture. The main arguments against AVJ ablation are lifelong pacemaker dependency and the possible restoration of sinus rhythm with prolonged CRT.

Six observational studies followed 675 patients with atrial fibrillation and assessed the response to CRT according to the use of AVJ ablation (Table 2). AVJ ablation was performed in 49% of the patients (ranging from 25% to 70%) based on different criteria. Only one small study found no benefit of AVJ ablation. The remainder reported improvements in functional capacity and left ventricular function. One of the largest studies suggested that only patients submitted to AVJ ablation had significant benefit as far as left ventricular ejection fraction (LVEF), left ventricular end-systolic volume and exercise tolerance were concerned. AVJ ablation was also independently associated with a survival advantage in three of these studies. A recent meta-analysis further underlined the importance of AVJ ablation, associating it with a lower risk of non-response to CRT (pooled RR 0.40, 95% CI 0.28–0.58; P<0.001). These findings, taken together with the increasingly recognized importance of near-maximal biventricular capture, suggest that the threshold for performing AVJ ablation should be low. Nevertheless, robust randomized clinical trials are needed to confirm these results and help us understand who should undergo AVJ ablation and when. Meanwhile, it seems reasonable not to perform AVJ ablation systematically at the time of CRT implantation, but instead to perform it a few weeks later if biventricular pacing is suboptimal (<95-99%) despite adequate pharmacological optimization of ventricular heart rate. Holter monitoring and exercise testing can provide accurate and useful information on biventricular pacing rates in order to make informed decisions. The situation is somewhat clearer for patients with AF and CHF who require conventional pacing for other reasons, including those undergoing ablation of the atrioventricular junction (AVJ) for rate control purposes. The benefit of biventricular pacing in these circumstances has been demonstrated in several randomized clinical trials. Finally, a rhythm control strategy with pulmonary vein isolation should also be considered. There is some evidence that sinus rhythm is desirable in patients with heart failure and that catheter ablation is effective in achieving it and improving the patient’s overall condition. The future may hold a greater role for ablation, as new technology allows faster, more efficient, and safer procedures. For the time being, a recent meta-analysis of AF catheter ablation in patients with systolic left ventricular dysfunction showed significant improvement in LVEF, albeit with considerable heterogeneity among the analyzed studies regarding the

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of AF patients</th>
<th>Number submitted to AVJ ablation (%)</th>
<th>Criteria for AVJ ablation</th>
<th>Timing of AVJ ablation</th>
<th>Benefits of AVJ ablation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Molhoek</td>
<td>30</td>
<td>17 (57)</td>
<td>Not reported</td>
<td>18 ± 6 months pre-CRT</td>
<td>Reduced risk of non-responsiveness</td>
</tr>
<tr>
<td>Gasparini</td>
<td>159</td>
<td>114 (70)</td>
<td>BiV &lt;85%</td>
<td>2 months post-CRT</td>
<td>Improvement in functional class and echocardiographic parameters restricted to AVJ ablation group</td>
</tr>
<tr>
<td>Ferreira</td>
<td>53</td>
<td>26 (49)</td>
<td>Low BiV or ICD shock due to AF</td>
<td>Pre-, at, or post-CRT</td>
<td>Independently associated with less risk of non-responsiveness, hospitalization and cardiac death</td>
</tr>
<tr>
<td>Gasparini</td>
<td>243</td>
<td>118 (49)</td>
<td>BiV &lt;85%</td>
<td>2 months post-CRT</td>
<td>Independently associated with less risk of death (particularly due to HF)</td>
</tr>
<tr>
<td>Schutte</td>
<td>36</td>
<td>9 (25)</td>
<td>BiV &lt;90%</td>
<td>Not reported</td>
<td>No effect</td>
</tr>
<tr>
<td>Dong</td>
<td>154</td>
<td>45 (29)</td>
<td>Not reported</td>
<td>Median -13 days</td>
<td>Independently associated with less risk of death; Improvement in functional class</td>
</tr>
</tbody>
</table>

Table 2: Observational studies assessing CRT response according to the use of AVJ ablation. BiV: percentage of biventricular pacing.
extent of this improvement. More specifically, the PABA-CHF study was a randomized controlled trial comparing pulmonary vein isolation (PVI) with the combination of AVJ ablation and biventricular pacing for patients with symptomatic AF and an ejection fraction of 40% or less. Catheter ablation of AF was superior to CRT with AVJ ablation regarding improvements in LVEF, exercise capacity and quality of life. These results suggest that PVI may be a third option for patients with AF receiving CRT, apart from AVJ ablation and pharmacological therapy. A randomized controlled trial assessing these three alternatives would be most welcome.

Conclusions

Current evidence suggests that CRT is effective in patients with AF, even though its benefits may be less pronounced than in patients without AF. Near-maximal biventricular pacing rates seem crucial to attain the best possible outcome, but these are often difficult to achieve in AF patients unless AVJ ablation is performed or sinus rhythm is restored. Prospective randomized studies to confirm the benefit of CRT in AF patients and assess the roles of AVJ ablation and pulmonary vein isolation are needed.

Acknowledgements

The authors thank Dr. Diogo Cavaco and Dr. Francisco Morgado for their critical review of the manuscript.

References


Introduction

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia and is difficult to treat.\(^1\) It may present with a variety of symptoms ranging in severity from mild to disabling.\(^2\) While some patients get diagnosed at the time of a routine visit and are not aware of their arrhythmia, others may present with palpitations, chest discomfort, dyspnea and syncope. Atrial fibrillation is commonly associated with cardiac and extra cardiac conditions such as valve disease, left ventricular dysfunction, hypertension, diabetes, pulmonary and thyroid disease.\(^3\)

Patients with AF and structural heart disease or hypertension are at a particularly high risk of developing significant functional impairment or frank congestive heart failure.\(^4\) This is related to diastolic dysfunction whereby patients depend heavily on the atrial ‘kick’ and a controlled regular heart rate for ventricular filling. If these conditions are not met, the filling pressure briskly rises leading to pulmonary congestion.

As part of an adaptation response, left atrium may dilate to be able to accommodate a larger volume of blood, compensate for lack of atrial contraction, and moderate the increase in pulmonary pressures. In turn, left atrial enlargement may signify increased atrial scarring and promote atrial fibrillation by providing a suitable electromechanical substrate for reentry.\(^5\)

Unfortunately, AF is not unique to patients with other comorbidities. Patients without any discernable heart disease or systemic conditions may have so called ‘lone’ atrial fibrillation accounting for about 3\% of patients with AF.\(^6\) The definition of lone atrial fibrillation varies between publications and typically excludes patients with AF and significant structural heart disease defined as left ventricular ejection fraction less than 40\%, moderate or severe aortic or mitral valvular insufficiency or stenosis, or history of prior heart surgery. According to the guideline definition, patients with thromboembolic risk factors of hypertension, diabetes or prior stroke should be excluded along with patients suffering from congestive heart failure, significant pulmonary or thyroid disease.\(^7\) Given accumulating body of evidence linking obstructive sleep apnea (OSA) and atrial fibrillation, patients suffering from OSA should be excluded.\(^8\) Finally, given known association between AF and left atrial enlargement, those with left atrial size greater than normal may be qualified as having plausible etiology for their arrhythmia. It is certainly plausible that myocardial fibrosis in the left atrium and left atrial dilatation may also be the result rather than the cause of AF in some patients. At the same time, based on the purported explanations for the maintenance of AF which include multiple wavelet reentry, it is known, that greater myocardial

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**Risk of Arrhythmia Recurrence After Successful Ablation of Lone Atrial Fibrillation**

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mass and larger atria form better substrate for re-entry. Atrial fibrillation may be more prevalent in taller people who also happen to have larger atria. While that does not mean that the relationship of larger atria and atrial fibrillation is always causative, it certainly suggests that it is true in many instances and as such may form the basis for AF in these patients. While determining left atrial volume index may be the preferred method for identifying such patients, this measurement is frequently lacking in clinical practice leaving the clinicians with left atrial diameter, typically measured during transthoracic echocardiography procedures in the long parasternal axis.

Atrial fibrillation is present in as many as 10% of the octogenarians. Advanced age among patients with AF (greater than 65-75 years of age) is an independent risk factor for embolic events. Accordingly, patients over 75 are not typically classified as having lone arrhythmia.

**Treatment Options**

Our options for managing atrial fibrillation have improved tremendously over the years. Domains of care for these patients include treatment of co-existent conditions, prevention of thromboembolic events, medical or interventional control of the ventricular response rate and symptom relief, which typically involves conversion to sinus rhythm and its long-term maintenance.

The latter can be achieved medically in some patients using antiarrhythmic medications. Unfortunately, all of these are fraught with side effects, frequently outweighing the benefits of their use, and are not very effective. The best yet most toxic antiarrhythmic drug, amiodarone, provides rhythm control up to 60% of the time at best.

Discovery of the pulmonary vein ectopic events initiating atrial fibrillation has lead to a revolution in AF management, whereby ablative therapy initially aimed at elimination of the sources of ectopic activity, ostial isolation of the pulmonary veins and, more recently, isolation of the pulmonary vein antra, can now be offered to patients suffering from AF who cannot or prefer not to take antiarrhythmic medication.

Ablation is particularly important to consider as an option in patients with lone atrial fibrillation. These patients are typically at low risk of an embolic event, do not have other comorbidities requiring management, and are frequently young, anxious and highly symptomatic for palpitations and functional impairment as a result of their arrhythmia. While some prefer antiarrhythmic drug therapy, when given the opportunity, most of these patients choose ablation, stating unwillingness to be on long-term medication or medication side effects, particularly lack of energy related to the use of most drugs in this class.

**Evidence to Date**

There is little published literature addressing outcomes of catheter ablation in patients with lone atrial fibrillation. Most of the literature addresses surgical therapy in these patients. Patients with lone AF in the surgical literature are typically defined as those who do not require any other surgical intervention beyond a modified Maze procedure for their arrhythmia. While there is some overlap between these patients and patients undergoing catheter ablation, few young and otherwise healthy patients choose to undergo surgical therapy for their arrhythmia as a stand-alone procedure and many patients thus treated are older and have other comorbidities. Discussion of surgical AF therapy for lone AF is outside of the scope of this review.

Rather than examine outcomes among patients with lone AF vs others, most of the literature on catheter ablation divides patients into those with paroxysmal or non-paroxysmal arrhythmia, and further stratifies patients by age and other comorbid conditions. We identified only three prior publications focusing specifically on the outcomes of catheter ablation in patients with lone atrial fibrillation. All arrhythmia recurrences are defined as any episode of atrial fibrillation of at least 30 seconds in duration.

In the first paper, Khaykin et al. defined lone AF patients based on absence of left ventricular dysfunction (ejection fraction < 40%), moderate or worse aortic or mitral valvular insufficiency or stenosis, or prior history of heart surgery. This is the largest reported cohort of patients with lone atrial fibrillation undergoing ablation at 194 patients. Lone AF patients in this study were young (54±12 years), but had relatively large left atria at
### Table 1: Baseline Characteristics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Lone PAF (n=60)</th>
<th>Non-Lone PAF (n=398)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>47 ± 8.7</td>
<td>60 ± 9.9</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Male</td>
<td>42</td>
<td>272</td>
<td>0.80</td>
</tr>
<tr>
<td>BMI</td>
<td>27 ± 4</td>
<td>29 ± 6</td>
<td>0.02</td>
</tr>
<tr>
<td>AF duration (yrs)</td>
<td>6.0 ± 5.1</td>
<td>7.4 ± 6.2</td>
<td>0.14</td>
</tr>
<tr>
<td>#Failed AADs</td>
<td>1.4 ± 0.9</td>
<td>1.7 ± 1.1</td>
<td>0.04</td>
</tr>
<tr>
<td>Failed amiodarone</td>
<td>11 (18)</td>
<td>142 (36)</td>
<td>0.008</td>
</tr>
<tr>
<td>LA size (mm)</td>
<td>36.8 ± 2.97</td>
<td>41.7 ± 4.93</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

|                        |                |                      |         |
| Hypertension            | 218 (55)       |                      |         |
| Diabetes                 | 48 (12)        |                      |         |
| Structural Heart Disease | 166 (42)       |                      |         |
| Valve disease           | 73 (18)        |                      |         |
| Significant coronary artery disease | 59 (15) | |         |
| Cardiomyopathy¹          | 34 (8)         |                      |         |
| History of Prior Heart Surgery | 16 (4) | |         |

Data are expressed as mean ± SD or number (%) of patients. ¹Left Ventricular Ejection Fraction less than 40%, clinical diagnosis of hypertrophic or dilated cardiomyopathy

### Table 2: Procedural Details

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Lone PAF (n=60)</th>
<th>Non-Lone PAF (n=398)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Irrigated catheter</td>
<td>28 (47)</td>
<td>145 (36)</td>
<td>0.13</td>
</tr>
<tr>
<td>Concurrent atrial flutter ablation</td>
<td>5 (8)</td>
<td>55 (14)</td>
<td>0.24</td>
</tr>
<tr>
<td>Fluoroscopy time (min)</td>
<td>73 ± 28</td>
<td>74 ± 24</td>
<td>0.87</td>
</tr>
<tr>
<td>Procedure time (min)</td>
<td>206 ± 61</td>
<td>212 ± 89</td>
<td>0.63</td>
</tr>
<tr>
<td>RF time (min)</td>
<td>89 ± 34</td>
<td>89 ± 38</td>
<td>0.93</td>
</tr>
<tr>
<td>Statins post ablation</td>
<td>8 (13)</td>
<td>167 (42)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>ACEi post ablation</td>
<td>2 (3)</td>
<td>113 (28)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Data are expressed as mean ± SD or number (%) of patients

### Table 3: Repeat Ablation Procedures

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Lone PAF (n=60)</th>
<th>Non-Lone PAF (n=398)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Procedures</td>
<td>1</td>
<td>40 (67)</td>
<td>272 (68)</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>17 (28)</td>
<td>102 (26)</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>3 (5)</td>
<td>22 (6)</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>0 (0)</td>
<td>2 (0.5)</td>
</tr>
</tbody>
</table>

Data are expressed as number (%) of patients
44±24 mm in diameter; 3.5% of the patients were in NYHA II-III functional class. They had previously failed 3.2±1.1 antiarrhythmic drugs. Only 58% of these patients had paroxysmal AF. Patients in this study underwent pulmonary vein antrum isolation (PVAI) guided by a circular mapping catheter. Intracardiac echocardiography was used during the majority of procedures. The authors presented long-term follow-up of 18±7 months. During that time 16% had a late recurrence beyond the three-month blanking period, 2% were controlled on antiarrhythmic drugs and 14% of the patients had repeat procedures. The rate of significant complications was 4.1%, in line with that reported in other contemporary studies.

In a series of patients undergoing AF ablation reported by Calvo et al., their 107 patients had lone AF, defined as arrhythmia in patients under 60 years of age and without hypertension, thyroid disease, clinical or echocardiographic evidence of cardiopulmonary disease. Left atrial size in these patients was normal at 39±6 mm. Paroxysmal AF was present in 74% of the patients studied.

Patients in this study underwent circumferential pulmonary vein ablation (CPVA) using the CARTO (Biosense Webster, Diamond Bar, CA) 3D mapping system and incorporating a left atrial roof line, posterior line and a mitral isthmus line in the lesion set. Isolation of the posterior left atrium but not block across the mitral isthmus line was verified by the operators. One year following the procedure, 59% of the patients with lone AF were free of recurrent arrhythmia. The rate of complications among these patients was similar to the study reported by Khaykin et al. at 4.3%.

Another study evaluated first-line cryoballoon ablation with pulmonary vein isolation verified using a circular mapping catheter and insured with focal radiofrequency ablation as necessary in 18 patients with paroxysmal lone AF defined as AF in the absence of structural heart disease. One of the patients had diabetes; left atrial size was normal at 39±4 mm among study patients. After a mean follow-up of 14±9 months, 89% of the patients were free from recurrent AF off antiarrhythmic drugs. One of the patients in this study developed transient phrenic palsy and another had to have surgical repair for a pseudoaneurysm at a vascular access site.

A study reported by De Potter et al., compared outcomes of AF ablation in patients with and without reduced left ventricular ejection fraction (LVEF). In this study, 56% of the 36 patients without depressed LVEF (defined as LVEF ≥ 50%) did not have recurrent AF after a median follow-up of 16±13 months following CPVA performed using the same approach as that reported by Calvo et al. In all of these studies, the likelihood of freedom from recurrent AF was similar among patients with and without lone atrial fibrillation.

Our Perspective

Between February 2004 and May 2011, 458 patients with paroxysmal atrial fibrillation underwent PVAI...
Having defined lone AF as AF in patients under 75 years of age, without structural heart disease, any of the CHADS-2 score components or left atrial enlargement beyond 40 mm, 60 of the ablation patients qualified as having lone AF (13%). Table 1 compares baseline characteristics of patients with lone AF vs others. Apart from the difference in factors defining lone AF, these patients had a lower BMI and have previously failed fewer antiarrhythmic drugs. Fewer lone AF patients failed amiodarone.

As seen in Table 2, procedural characteristics were similar between the two groups of patients. Following ablation, however, patients with lone atrial fibrillation were far less likely to be treated with statins or ACE inhibitors as would be expected based on their selection criteria. Patients with lone AF were followed for 1.8±1.5 years on average compared to 2.0±1.6 years for the other patients (p=0.3). Eighteen patients (30%) with lone AF had an early recurrence during the 3 month blanking period following the procedure compared to 173 (43%, p=0.05 vs lone AF) patients with non-lone AF. Twenty-six patients with lone AF (43%) had a late recurrence beyond the blanking period vs 195 (50%, p=0.34) patients with non-lone AF. There was a trend to longer time to late recurrence among patients with lone AF with a mean time to late recurrence of 13±16 months vs 10±10 months in the other group (p=0.1). The difference in the rate of AF recurrence over time reached statistical significance in Kaplan-Meier analysis (p<0.05, Figure 1) with curves representing survival free of recurrent arrhythmia separating after 6 months of follow-up. Patients with lone AF were just as likely to have repeat ablation procedures following the initial procedure as illustrated in Table 2.

Conclusions

The definition of lone atrial fibrillation in the literature is inconsistent between studies. Based on the guidelines, lone AF should be defined as atrial fibrillation in patients under 75 years of age without structural heart disease, including left atrial enlargement and without any of the CHADS-2 risk factors for thromboembolic events. We believe that this definition should also exclude patients with history of heart surgery or any comorbidities known to be associated with AF, such as pulmonary and thyroid disorders as well as obstructive sleep apnea, based on available evidence. Patients with lone atrial fibrillation may present with either paroxysmal or persistent arrhythmia.

Prevalence of lone AF among patients presenting for ablation is significantly higher than what is reported in the medical literature. This may be expected since many lone AF patients would prefer ablative therapy to long-term medical management.

Surprisingly, regardless of the ablative approach used, outcomes in patients with lone atrial fibrillation are similar to those in patients who have risk factors for thromboembolism or other comorbid conditions known to associate with AF, although based on our data, time to recurrence of AF following ablation is longer among patients with lone paroxysmal AF compared to other paroxysmal AF patients, presumably secondary to a healthier left atrial substrate. One-year success rate of ablation among lone AF patients ranges from 56% to 89% depending on the study, definition of lone AF and approach used with little data on long-term follow-up in this group of patients.

Experience at our center suggests that lone AF patients do derive a greater long-term benefit compared to other patients presenting for AF ablation. At the same time cost effectiveness of ablation in this group of patients is suspect based on some published estimates and the rate of procedural complications, while similar to the general AF population, is excessive given their low baseline risk.

Further epidemiological studies are necessary to better define the prevalence of lone AF among patients treated with ablation as well as procedural cost effectiveness. These studies should also pay close attention to the risks of ablation in this otherwise low-risk group of patients.

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23. De Potter, T., A. Berruezo, L. Mont, M. Matiello, D. Tamborero, C. Santibanez, B. Benito, N. Zamorano, and J. Brugada, Left ventricular sys-


Atrial fibrillation (AF) is the most common supraventricular arrhythmia with an approximative prevalence of 1% in the general population and above 6% in the elderly. After a first AF diagnosis, the hospitalization rate is markedly increased. Management of a first AF episode is different depending on the clinical status of patients. Practical guidelines developed in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society are available for the management of these patients. A four-step decisional scheme must be followed in the management of a first recent AF episode: need for a short- and long-term anticoagulation, define a rhythmologic strategy (rhythm or rate control), select the weapon (drug, device or ablation) and reconsider the strategy if needed. After a first uncomplicated paroxysmal AF episode, guidelines recommend that prescription of antiarrhythmics must be avoided and anticoagulation is optional. After a first persistent AF episode, guidelines recommend either respect or reduce the arrhythmia. Prescription of antiarrhythmics and anticoagulation is also optional depending on the patient's condition. In case of the AF reduction decision, anticoagulation must be tailored preliminary to this reduction. AF recurrence rate varies depending on the patient's condition, and the risk of stroke assessed by the CHA\textsubscript{2}-DS\textsubscript{2}-VASc score might be similarly considered for both paroxysmal and persistent AF. However, there are still some obscurities in these recommendations that we will be discussed below based on the nature of paroxysmal or persistent AF.

Epidemiology of First Episode of AF

AF affects approximately 1% of the general population and accounts for more than a third of hospitalizations in the United States for heart rhythm disorders. First detected episode of AF represents 11% of all types of AF. Because AF may be asymptomatic (silent AF) and as a result undiagnosed, the “true” prevalence of AF is probably closer to 2% of the population.

New onset AF often spontaneously reverts to normal.
mal sinus rhythm, with the incidence of reversion related to the duration of the arrhythmia. Spontaneous conversion to sinus rhythm occurs in almost 70% of patients presenting with atrial fibrillation of less than 72 hours duration, and presentation with symptoms of less than 24 hours duration is the best predictor of spontaneous conversion in a large prospective observational study. After the initial diagnosis of AF, the likelihood of hospitalization increases during the first year of AF. Advancing age, greater body mass index, hypertension, paroxysmal AF (vs permanent/persistent AF) at initial diagnosis, history of myocardial infarction, valvular heart disease, peripheral or carotid artery disease, stroke, diabetes mellitus, chronic renal disease, and chronic obstructive pulmonary disease are significant independent predictors of hospitalisation after a first detected episode of AF. The main causes of hospital admission are AF related congestive heart failure, coronary or peripheral arterial causes, and thromboembolic events. A first detected episode of AF appears a marker for underlying cardiac diseases. Moreover, new onset of AF is associated with an increased mortality.

Patients with AF have an increased risk of stroke, often with more severe form, and with a higher rate of recurrence. Stroke in AF is often severe and can result in long-term disability or death. Undiagnosed silent AF is a likely cause of some “cryptogenic” strokes. Furthermore, it is important to know that regardless of the type of AF (paroxysmal or permanent), the embolic risk is comparable. Hence, patients with paroxysmal AF should be regarded as having a stroke risk similar to those with persistent or permanent AF, in the presence of risk factors detailed below. Moreover, cognitive impairment may be related to AF, through silent embolic events. Finally, if AF can affect patients without underlying heart disease (also called “idiopathic AF” or “lone AF”), it occurs mainly in patients with a structural cardiomyopathy secondary to hypertension, valvular or coronary artery disease. A small sample observational study, but with a 12 year follow-up, confirms the favourable prognosis of newly-diagnosed lone AF. However, development of an underlying heart disease and arrhythmia progression are risks factors of cardiovascular events, including stroke.

Types of Atrial Fibrillation

According to recent European Society of Cardiology (ESC) guidelines, five types of AF based on the clinical presentation and duration of the arrhythmia can be described: first diagnosed paroxysmal, persistent, long-standing persistent, and permanent AF (Figure 1).

1. First Diagnosed AF is every AF identified for the first time by an electrocardiogram (ECG) or other electrocardiographic rhythm recording device, irrespective of the duration of the arrhythmia or the presence and severity of AF-related symptoms.

2. Paroxysmal AF is self-terminating in less than 7 days, usually within 48 h.

3. Persistent AF is present when an AF episode either lasts longer than 7 days or requires termination by cardioversion (CV), either with drugs, or direct current cardioversion (DCC).

4. Long-Standing Persistent AF lasts for one year or more when it has been decided to adopt a rhythm control strategy.

5. Permanent AF is considered to be present if the arrhythmia lasts for more than one year and cardioversion either has not been attempted or has failed, or if the arrhythmia is accepted by the patient (and physician).

The pathogenesis of AF underlines the importance of slowly developing structural changes preceding a newly documented episode of AF episode. The idea that “AF begets AF” through complex electrophysiological and structural remodeling of the atria suggests that early treatment of AF should be considered associated with early, aggressive intervention on factors such as hypertension, obesity or sleep apnoea, in an attempt to prevent atrial remodeling, and so AF recurrences. A prospective study on 106 patients with first AF showed that half of the patients had no further recurrence after 5 years, but that patients with comorbidities are at higher risk for rapid progression to permanent AF.
Paroxysmal AF recurrences vary markedly from one patient to another. Silent AF (asymptomatic) is common even in symptomatic patients. It may look like any of the temporal forms (paroxysmal, persistent or permanent) of AF. It may also manifest as an AF-related complication (ischaemic stroke or tachycardiomyopathy) or may be diagnosed by an opportunistic ECG. A recent meta-analysis showed that, in patients with an implanted device (pace-maker or internal defibrillator) asymptomatic atrial tachyarrhythmias, without clinical atrial fibrillation, were associated with a significantly increased risk of ischemic stroke or systemic embolism. This has important implications for management of therapies aimed at preventing AF-related complications.

Several instruments are useful to assess AF episode recurrence, their duration or ventricular response rates. Continuous ambulatory ECG recording for 24 hours to 7 days or more, or event recorders are used to identify the arrhythmia if it is intermittent and not captured on routine electrocardiography. Finally, AF can occur under specific conditions such as acute coronary syndrome, hyperthyroidism, valve replacement, fever, etc. For instance, new onset of AF occurring during acute myocardial infarction is a risk factor of stroke and prescription of OAC dramatically decreases the rate of stroke. Among patients with severe sepsis, patients with new-onset AF were at increased risk of in-hospital stroke and death compared with patients with no AF and patients with preexisting AF. In hyperthyroid patients who presented with new-onset AF, there was an increased risk of ischemic stroke during the initial phase of presentation.

Management of a First Detected Episode of AF

A complete history and physical examination should be performed in all patients with new onset AF. There should be an assessment for an underlying cause, such as heart failure, pulmonary disease, alcohol, fever, or hyperthyroidism. Therapy for a precipitating cause should be initiated prior to cardioversion in stable patients and may result in reversion to sinus rhythm. Antithrombotic treatment will be discussed below.

Time to onset of the episode should be accurately established. It’s also important to weigh the risk/benefit ratio of these potential therapeutics in reducing morbidity and mortality of these patients with a first episode of AF to answer the following questions:

-Should I prevent complications related to the AF, including embolic?
-Does the patient have symptoms? If so, should I remove them?
-Should I prescribe an anti-arrhythmic (AA) treatment?

Thus, a 4-point strategy decision must be proposed in the context of this first episode:

-Discuss the need for a prescription of anticoagulant or anti-aggregation
-Choose rate versus rhythm control strategy

![Figure 1: Different types of AF. First-onset AF may be the first of recurrent attacks or already be deemed permanent. (from [2])](https://www.jafib.com)
- Select a therapeutic weapon: AA, rate slowing drugs
- Consider a new strategy in case of failure

By asking these four questions, we barely just have to follow the ACC/AHA/HRS and ESC 2011 guidelines on management of a first episode of AF and apply these according to history and clinical status of the patient.\textsuperscript{1,2} We will detail below those recommendations based on the nature of paroxysmal or persistent AF.

### Table 1: Risk factor-based approach expressed as a point based scoring system, with the acronym CHA2DS2-VASc (maximum score is 9 since age may contribute 0, 1, or 2 point) (from [2])

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congestive heart failure, LV dysfunction &lt;40%</td>
<td>1</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1</td>
</tr>
<tr>
<td>Age &gt; 75</td>
<td>2</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1</td>
</tr>
<tr>
<td>Stroke/TIA/thrombo-embolism</td>
<td>2</td>
</tr>
<tr>
<td>Vascular disease</td>
<td>1</td>
</tr>
<tr>
<td>Age between 65 and 74</td>
<td>1</td>
</tr>
<tr>
<td>Female sex</td>
<td>1</td>
</tr>
</tbody>
</table>

### Management of the First Episode of Paroxysmal AF

#### Stroke Risk Assessment

As already said, the thrombo-embolic risk in paroxysmal AF does not differ from persistent or permanent forms, and is present especially in case of underlying cause of AF.\textsuperscript{19-21} Therefore, every patient with paroxysmal AF should be assessed carefully for the risk of stroke and should be screened to receive oral anti-thrombotic therapy (anticoagulation or anti-aggregation) according to their risk score.

The previously used CHADS\textsubscript{2} score does not include many stroke risk factors, and other “stroke risk modifiers” are considered in a comprehensive stroke risk assessment resulting in a new risk factor-based approach for patients with non-valvular AF, also expressed as an acronym, CHA\textsubscript{2}DS\textsubscript{2}-VASc (Table 1).\textsuperscript{22} “Major” risk factors are prior stroke, transient ischemic attack (TIA) or thrombo-embolism, and older age (≥75 years). The presence of some types of valvular heart disease (mitral stenosis or prosthetic heart valves) would also categorize such “valvular” AF patients as “high risk” and require oral anti-coagulation (OAC). “Clinically relevant non-major” risk factors are heart failure, hypertension, or diabetes, female sex, age between 65 and 74 years, and vascular disease (myocardial infarction, complex aortic plaque, peripheral artery disease). Risk factors are cumulative, and the simultaneous presence of two or more “clinically relevant non-major” risk factors would vindicate a stroke risk that is high enough to require anti-coagulation. In patients with a CHA\textsubscript{2}DS\textsubscript{2}-VASc score of ≥2, chronic OAC therapy (vitamin K antagonists), is recommended in a dose adjusted to achieve an INR value in the range of 2–3, unless contraindicated. New OAC drugs, such as dabigatran, may ultimately be considered.\textsuperscript{23}

In patients with a CHA\textsubscript{2}DS\textsubscript{2}-VASc score of 1, we may consider OAC or aspirin, after evaluation of the risk of bleeding complications, ability to safely sustain adjusted chronic anticoagulation, and patient preferences. In patients with a CHA\textsubscript{2}DS\textsubscript{2}-VASc score of 0, it is recommended to consider no anti-thrombotic therapy rather than aspirin (Table 2).

However, these recommendations are not so concerning about the anticoagulation after a first isolated episode of paroxysmal AF, because of the remote risk of embolism (admittedly rare) due to atrial stunning post-AF reduction.\textsuperscript{24}

### AA Treatment

In the situation of a first episode of paroxysmal AF, the issue of rate versus rhythm control is not standing here because of the self-terminated AF episode by definition. The only question is wheth-
Management of the First Episode of Persistent AF

Stroke Risk Assessment

Persistent AF is present when an AF episode either lasts longer than 7 days or requires termination by cardioversion. For most patients in whom the duration of new onset AF is suspected to be more than 48 hours (or when the duration is unknown), the risk of embolization is substantially increased, and it is preferable to anticoagulate and use transesophageal echo (TEE) to rule out left atrial thrombi before attempting cardioversion. This recommendation includes patients with a low CHADS² score (0 or 1). Because of delayed return of atrial mechanical function (atrial stunning) after cardioversion, it could increase the risk of a thromboembolic event after this approach with cardioversion. Even with the lower CHADS² score, oral anticoagulation is recommended for at least 4 weeks after cardioversion that is electrical, chemical or even more after catheter ablation. An alternative approach to four weeks of OAC therapy is to perform a transesophageal echocardiography (TEE) to rule out the presence of left atrial thrombi before cardioversion.

Another study proposed a cryoballoon ablation as first-line treatment of lone paroxysmal AF, with good results on short-term AF recurrence. 

First detected AF is the most symptomatic type of AF, with paroxysmal AF. The lack of control of heart rate is possibly responsible for the more symptomatic nature of the first episode of AF. Palpitations, chest pain and shortness of breath must not justify an AA prescription, even in the presence of either a minimal, either a significant underlying heart disease, but we should take into account patients comorbidities such as age or diabetes. Conversely, if critical symptoms occur at the time of the AF episode, such as anginal pain, hypotension or heart failure, that are usually observed in the setting of an advanced or unstable underlying cardiomyopathy, the prescription of an AA treatment is undoubtedly recommended. This rhythm control strategy is based on different antiarrhythmic drug therapy such as dronedarone, sotalol, flecainide, propafenone or amiodarone. The choice of the first line AA therapy should take into account whether or not the patient has significant underlying heart disease. Catheter ablation could be an alternative to AA drugs as a first-line therapy of AF, because of patient preference or contra-indication to AA drugs. A recent study showed that ablative therapy performed at an earlier stage of the disease was associated with a significantly higher success rate and with a decreased need for repeat procedures. Another study proposed a cryoballoon ablation as first-line treatment of lone paroxysmal AF, with good results on short-term AF recurrence.

Table 2: Approach to thromboprophylaxis in patients with AF according to their CHA2DS2-VASc score (from [2])

<table>
<thead>
<tr>
<th>CHA2DS2-VASc Score</th>
<th>Recommended Antithrombotic Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 2</td>
<td>OAC</td>
</tr>
<tr>
<td>1</td>
<td>Either OAC or aspirin</td>
</tr>
<tr>
<td>0</td>
<td>Either aspirin or no antithrombotic therapy</td>
</tr>
</tbody>
</table>
ene of any thrombi prior to cardioversion. The recent ACUTE trial has compared both strategies. ACUTE directly compared a TEE-guided strategy to the conventional strategy in patients with AF of more than 48 hours duration who were undergoing electrical cardioversion. In addition, assessments of quality of life have not shown significant differences between the two in most studies. However, after a first episode of persistent AF, owing to the natural time course of AF and its consequences, a rhythm control strategy should reasonably be chosen first with a set routine, with the exception of patients who are completely asymptomatic, and particularly those who are very old (>80 years). Indeed, in patients with multiple comorbidities, the risk of undergoing cardioversion or using AA drugs may outweigh the benefits of restoring sinus rhythm. The rhythm control strategy uses the same drugs as described above (Figure 2).

Rate Versus Rhythm Control

Before considering rate or rhythm control strategy, an important question should be discussed: is there a need for urgent or emergent cardioversion? In four critically clinical situations this matter must considered:

- Active ischemia (symptomatic or electrocardiographic evidence)
- Evidence for organ hypoperfusion
- Severe manifestations of heart failure
- Presence of a preexcitation syndrome, which may lead to an extremely rapid ventricular rate due to the presence of an accessory pathway

In a patient with any of these indications for urgent cardioversion, the need for restoration of sinus rhythm takes precedence over the need for protection from thromboembolic risk. Intra-venous anticoagulation with heparin should be started, but it should not cause a delay in emergent cardioversion.

In the absence of urgent cardioversion, most patients who present with AF will require slowing of the ventricular rate to improve symptoms. Then a decision regarding the long-term approach to the management of the rhythm disturbance (rhythm versus rate control) should be made. Two studies, AFFIRM and RACE, show evidence that rhythm and rate control strategies are associated with similar rates of mortality and serious morbidity, such as embolic risk. In addition, assessments of quality of life have not shown significant differences between the two in most studies. However, after a first episode of persistent AF, owing to the natural time course of AF and its consequences, a rhythm control strategy should reasonably be chosen first with a set routine, with the exception of patients who are completely asymptomatic, and particularly those who are very old (>80 years). Indeed, in patients with multiple comorbidities, the risk of undergoing cardioversion or using AA drugs may outweigh the benefits of restoring sinus rhythm. The rhythm control strategy uses the same drugs as described above (Figure 2).

Rate slowing drugs are generally started before rhythm control strategy in patients with either excessive heart rate or disabling symptoms and are sometimes continued in patients who remain are sinus rhythm (in the event of AF recurrence). The rate control strategy generally uses drugs that slow conduction across the atrioventricular (AV) node, such as beta blockers, rate slowing calcium channel blockers, or digoxin.

Finally, in case of failure in the reduction of a first episode of persistent AF, before abandoning the idea of reduction of the AF, a new shock after antiarrhythmic impregnation could be performed with a high-energy biphasic antero-posterior thoracic shock (300 Joules). Several AA drugs have proved their efficacy in facilitating cardioversion, such as ibutilide, amiodarone, and propafenone. Moreover, continuous use of Class Ic drugs or amiodarone appears to be an independent predictor of sinus rhythm at 1-year follow-up after cardioversion. In case of recurrent symptomatic, persistent AF, with major symptoms, or AF-related LV dysfunction, a left atrial (LA) catheter ablation could be proposed. There is evidence that patients with heart failure benefit from LA ablation as the ejection fraction and exercise tolerance may improve significantly. However, in such patients, successful ablation is more difficult to achieve, and often requires several attempts. The procedure can be long and technically challenging, and is associated with greater risk than pulmonary vein isolation alone. Hence, major symptoms should be present to vindicate those procedures.
Conclusions

Management of a first detected episode of AF is driven by US and European recommendations, but there are certain specific conditions, particularly with anti-thrombotic drugs, where a determined attitude is impossible. The first episode of AF can occur with a infraclinic preexisting atrial remodeling, which may move to recurrence, or persistent AF, with their well-known adverse outcomes. Thus, it is essential to focus on detection of AF and treatment of underlying heart disease, considering the use of upstream therapy. 39 Regarding the antiarrhythmic therapy, our attitude must be tailored to each patient according to its symptoms, its land, its embolic risk and we must not hesitate to challenge the published recommendations according to evolution of AF.

References


Introduction

Atrial fibrillation (AF) is the commonest sustained cardiac arrhythmia and is associated with increased morbidity and mortality due to stroke and thrombo-embolism. In patients with AF, strokes are usually more severe, resulting in longer hospital stays, worse disability and considerable healthcare costs. The prevention of stroke therefore is crucial in the management of AF. Stroke risk stratification tools can be used to determine patients at higher risk of stroke, and if no contraindications are present oral anticoagulation (OAC) therapy can be initiated. Despite the strong evidence for the benefit of OAC in stroke prevention in patients with AF, the use of thromboprophylaxis remains inadequate. The key measures to prevent stroke in patients with AF include: adequate stroke risk assessment and thrombo-prophylaxis; prompt initiation of OAC and avoidance of interruptions; earlier detection of AF; and education to overcome the under-usage of OAC in elderly patients.

Preventative Measures of Stroke in Patients With Atrial Fibrillation

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Abstract

Atrial fibrillation (AF) is the commonest sustained cardiac arrhythmia and is associated with increased morbidity and mortality due to stroke and thrombo-embolism. In patients with AF, strokes are usually more severe, resulting in longer hospital stays, worse disability and considerable healthcare costs. The prevention of stroke therefore is crucial in the management of AF. Stroke risk stratification tools can be used to determine patients at higher risk of stroke, and if no contraindications are present oral anticoagulation (OAC) therapy can be initiated. Despite the strong evidence for the benefit of OAC in stroke prevention in patients with AF, the use of thromboprophylaxis remains inadequate. The key measures to prevent stroke in patients with AF include: adequate stroke risk assessment and thrombo-prophylaxis; prompt initiation of OAC and avoidance of interruptions; earlier detection of AF; and education to overcome the under-usage of OAC in elderly patients.

Newer drugs such as dabigatran, a direct thrombin inhibitor and rivaroxaban, a direct factor Xa inhibitor are anticipated to soon replace warfarin altogether, negating the need for regular dose monitoring and adjustment.18

This review is targeted at clinicians who are exposed to patients with atrial fibrillation, including general practitioners, general physicians and cardiologists. Although this is not a systematic review, information was obtained through literature search engines such as PubMed, from current guidelines on the management of atrial fibrillation and from recent review articles. Examples of search terms used included “atrial fibrillation”, “AF”, “stroke prevention”, “oral anticoagulation”, “oral anticoagulants”, “OAC”, “warfarin”, “barriers to anticoagulation”, “stroke risk assessment”, “bleeding risk assessment”. Prevention of stroke in atrial fibrillation is a vast topic with a wealth of literature. This article does not attempt to evaluate all the evidence in this area, but rather to give an overview of some of the new developments and measures to prevent stroke in patients with AF.
Atrial Fibrillation and Stroke

AF occurs in approximately 1-2% of the general population. The prevalence of AF increases with advancing age and is expected to increase by 2.5-fold over the next fifty years, as the population ages. AF is associated with increased morbidity and mortality as a result of stroke and thromboembolism. Patients with AF are five times more likely to develop a stroke than patients in sinus rhythm, and when stroke occurs it is more likely to be severe. AF related strokes have higher mortality and morbidity, with longer hospital stays and increased disability, as well as considerable healthcare costs. In the United Kingdom AF accounts for almost 1% of total National Health Service expenditure, estimated at £459 million excluding costs of nursing care and hospitalizations where AF is a secondary diagnosis.

Stroke Risk Stratification

Given the adverse implications of stroke, both to the patient and to the healthcare system, the prevention of stroke in AF should therefore be a key component of the management of AF. As the risk of stroke in AF is not homogeneous, all patients diagnosed with AF should undergo a stroke ‘risk assessment’.

The risk of stroke in AF is variable and dependent on multiple risk factors, which are cumulative in adding to the overall stroke risk. Various risk stratification models exist to try and identify patients at higher risk of stroke, namely the CHADS2 score (see Table 1, C = Congestive heart failure, H = Hypertension, A = Age over 75 years, D = Diabetes, S = Prior Stroke or transient ischaemic attack) and more recently, the CHA2DS2-VASc score which is more inclusive of common stroke risk factors (see Table 2, as per CHADS2 plus additionally V = Vascular disease, A = Age 65-75 years, Sc = Sex category female). Patients are given a score which is a total of the individual risk factors and then, could be (perhaps artificially) stratified into low, intermediate or high risk strata.

Guidelines recommend OAC therapy (such as warfarin) or aspirin in patients with an intermediate risk of stroke, and OAC in those with a high risk of stroke. Patients with a low risk of stroke may not need any anticoagulation. The CHADS2 scoring system is well known and readily used, as it is simple and easy to remember, and based on the original validation of this scheme, patients with a score of 0 are low risk, 1-2 are intermediate risk and ≥3 are high risk. However there is concern that with CHADS2, the risk of stroke is under-estimated as this scheme does not include many common stroke risk factors, and secondly, far too many patients are placed within the “intermediate risk” category whereby ambiguity exists as to whether these patients should receive aspirin or warfarin.

The CHA2DS2-VASc stratification tool includes more risk factors than CHADS2 and has been shown to be superior at identifying the “truly low risk” patient and secondly, to minimise stratification to the “intermediate risk” category. In a Danish study of 73,538 patients with non-valvular AF, the rates of thrombo-embolism per 100 person-years in “low risk” patients were found to be 1.67 (95% confidence interval [CI] 1.47-1.89) with CHADS2 and 0.78 (0.58-1.04) with CHA2DS2-VASc at 1 year follow up. The study also demonstrated that the risk of thrombo-embolism depended on the specific risk factor, with age ≥75 years and previous thrombo-embolism posing the greatest risk.

The European Society of Cardiology recommends the CHADS2 stratification tool as a quick initial screening, and patients with a score ≥2 should be given OAC unless contraindicated. In patients with a score of 0 or 1 a more detailed risk assessment is required by way of the CHA2DS2-VASc score. In patients with a score of 0 (ie a “truly low” risk of stroke) no anticoagulation is preferred. In patients with a CHA2DS2-VASc score of 1, aspirin or OAC is recommended and OAC (whether with well-controlled warfarin or one of the new oral anticoagulant drugs, see later) is preferred.

Oral Anticoagulation Therapy

Traditional oral anticoagulants include vitamin K antagonists such as warfarin or phenindione.
Warfarin requires dose-adjustment according to the international normalized ratio (INR), which should be maintained between 2 and 3. An INR greater than 3 confers a greater risk of bleeding whilst an INR less than 2 confers greater risk of thromboembolism. Extensive studies have demonstrated the benefit of vitamin K antagonists. A meta-analysis showed that adjusted-dose warfarin and antiplatelet agents reduce stroke by 64% [95% CI 49-74] and 22% [95% CI 6-35%], respectively. Dose-adjusted warfarin was found to be more efficacious than antiplatelet therapy with a relative risk reduction of 39%. The disadvantages of using warfarin include the increased bleeding risk, the need for intensive monitoring of INR and the potential drug and food interactions. Studies have shown that patients receiving OAC remain in therapeutic range approximately 60% of the time, and in clinical practice less than 50% of the time. Furthermore a 10% rise in time out of the desired INR range was associated with a significant increased risk of mortality (odds ratio (OR) 1.29, p<0.001), ischaemic stroke (OR 1.10, p=0.006) and other thrombo-embolic events (OR 1.12, p<0.001).

**Bleeding Risk Assessment**

The main concern with OAC is the risk of intracranial haemorrhage which is greatest in patients of advanced age and those with hypertension. In a systematic review, other factors associated with higher risk of bleeding complications include: history of myocardial infarction or ischaemic heart disease, cerebrovascular disease, anaemia or a history of bleeding, and the use of antiplatelet therapy. The HAS-BLED score (H = Hypertension, A = Abnormal renal/liver function, S = Stroke, B = Bleeding history or predisposition, L = Labile INR, E = Elderly, D = Drug/alcohol concomitantly, see Table 3) is a new and easy-to-use bleeding risk assessment tool that predicts patients at high risk of bleeding.

Patients are given a score of 1 for

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**Table 1. CHADS<sub>2</sub> Stroke Risk Stratification Tool**

<table>
<thead>
<tr>
<th>CHADS&lt;sub&gt;2&lt;/sub&gt; risk factor</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congestive heart failure</td>
<td>1</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1</td>
</tr>
<tr>
<td>Age ≥ 75 years</td>
<td>1</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1</td>
</tr>
<tr>
<td>Stroke/transient ischaemic attack</td>
<td>2</td>
</tr>
<tr>
<td>Maximum</td>
<td>6</td>
</tr>
</tbody>
</table>

**Table 2. CHA<sub>2</sub>DS<sub>2</sub>-VASc Stroke Risk Stratification Tool**

<table>
<thead>
<tr>
<th>CHA&lt;sub&gt;2&lt;/sub&gt;DS&lt;sub&gt;2&lt;/sub&gt;-VASc risk factor</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congestive heart failure</td>
<td>1</td>
</tr>
<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>Stroke/transient ischaemic attack/thromboembolism</td>
<td>2</td>
</tr>
<tr>
<td>Vascular disease (previous myocardial infarction, peripheral arterial disease, aortic plaque)</td>
<td>1</td>
</tr>
<tr>
<td>Age 65-74 years</td>
<td>1</td>
</tr>
<tr>
<td>Sex category (female)</td>
<td>1</td>
</tr>
<tr>
<td>Maximum</td>
<td>9</td>
</tr>
</tbody>
</table>
Hypertension = systolic blood pressure >160 mmHg, Abnormal kidney function = chronic dialysis or renal transplantation, or serum creatinine >200 μmol/L, Abnormal liver function = chronic hepatitis disease (e.g. cirrhosis) or biochemical evidence of significant hepatic derangement (e.g. bilirubin > 2 x upper limit of normal, in association with aspartate aminotransferase/alanine aminotransferase/alkaline phosphatase > 3 x upper limit normal), Bleeding = previous bleeding history and/or predisposition to bleeding e.g. bleeding diathesis, anaemia, Labile INR = unstable/high INR or <60% duration within therapeutic window, Drugs/alcohol = concomitant use of drugs e.g. antiplatelets, non steroidal agents, or alcohol abuse. INR = international normalized ratio. Adapted from ESC guidelines for the management of atrial fibrillation. 

### Table 3. HAS-BLED Bleeding Risk Tool

<table>
<thead>
<tr>
<th>HAS-BLED risk factor</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>1</td>
</tr>
<tr>
<td>Abnormal liver/renal function (1 point each)</td>
<td>1 or 2</td>
</tr>
<tr>
<td>Stroke</td>
<td>1</td>
</tr>
<tr>
<td>Bleeding</td>
<td>1</td>
</tr>
<tr>
<td>Labile INR</td>
<td>1</td>
</tr>
<tr>
<td>Elderly (age&gt;65 years)</td>
<td>1</td>
</tr>
<tr>
<td>Drugs/alcohol (1 point each)</td>
<td>1 or 2</td>
</tr>
<tr>
<td>Maximum</td>
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Anticoagulation Services

The standard and availability of anticoagulation services are key in the management of OAC in patients with AF. Well-managed anticoagulation involves strict adherence to the recommended INR ranges, quick identification and response to out-of-range INR levels and a service that is readily used by clinicians. Some studies show that patients with access to anticoagulation services have better anticoagulation control when compared to patients managed in the community. In one study they found...
that patients who self-manage their anticoagulation spend a greater amount of time within the therapeutic INR range compared to those who did not although this was not statistically significant. In a recent meta-analysis patients who self-test or self-manage (self-adjust dosing) their OAC were found to have a significantly reduced risk of thrombo-embolism (Peto odds ratio [OR] 0.58 [95% CI 0.45 – 0.75]) and mortality (Peto OR 0.75 [95% CI 0.63-0.87]), with no increased risk of bleeding (Peto OR 0.89 [95% CI 0.75-1.05]). Of the twenty two trials analysed only five were deemed high quality and the rate of randomization was less than 50%.

Barriers to Anticoagulation

Despite the strong evidence of the benefit of OAC in patients with AF, the use of thromboprophylaxis still remains inadequate. In the UK it is estimated that only 56% of patients eligible for OAC are actually receiving it. A recent literature review reports the following as barriers for the use of OAC in patients with AF: age, risk of bleeding, risk of falls, co-morbidities including cognitive impairment and alcohol use, and the patient’s ability to comply with treatment. Physicians were found to be less likely to use OAC in patients aged over 70 years compared to those aged less than 70 years, despite having no contra-indications to warfarin. In two studies, 50 to 60% of physicians agreed that the benefit of anticoagulation therapy outweighed the risks in elderly patients with AF.

The reluctance of physicians to use OAC in elderly patients with AF is an important barrier in the prevention of stroke. Evidence exists to support the use of warfarin in elderly patients with AF as they have the highest risk of stroke. In fact the benefit of warfarin has been shown to increase with advancing age, and the risk of intracranial bleeding to be not significantly different in patients receiving warfarin compared to antiplatelets.

Novel Oral Anticoagulants

Novel therapies have been developed to overcome the limitations of vitamin K antagonists. These include dabigatran etexilate, a direct thrombin inhibitor and rivaroxaban, a direct factor Xa inhibitor.

Dabigatran is available orally in doses of 110mg or 150mg twice daily, and peak plasma concentrations are achieved 2-3 hours following oral administration. There are few drug/food interactions and dose monitoring is not required. However there are a few limitations: currently no antidote exists to reverse its effect in patients with massive haemorrhage; its half life is 12 – 17 hours which means that patients who miss doses may not be adequately anticoagulated; it is mainly excreted renally and should be used cautiously in patients with renal failure; its absorption is dependent upon pH which is reduced in patients taking proton pump inhibitors.

Dabigatran has recently been approved in the USA, Canada, Japan and Europe for stroke prevention in AF. The Randomized Evaluation of Long Term Anticoagulant Therapy (RE-LY) trial demonstrated non inferiority of dabigatran as compared to warfarin. 113 patients with AF were randomized to receive either a fixed dose of dabigatran (110mg or 150mg twice daily) or dose adjusted warfarin. Patients were followed up for 2 years where the primary outcome was stroke or systemic embolism. The study showed patients receiving dabigatran 110mg twice daily had similar rates of stroke and systemic embolism as patients receiving warfarin (1.69%, 1.53% respectively, relative risk with dabigatran 0.91; 95% CI 0.74-1.11, p<0.001 for non-inferiority), but lower rates of major haemorrhage (2.71%, 3.36% per year respectively). Patients receiving dabigatran 150mg twice daily had similar rates of stroke or systemic embolism when compared to patients receiving warfarin (1.11%, 1.53% respectively, relative risk 0.66, 95% CI 0.53 – 0.82, p<0.001 for superiority), and similar rates of major haemorrhage (3.11%, 3.36% per year respectively). A recent study has shown that dabigatran can be used in patients undergoing cardioversion.

Rivaroxaban, an oral direct inhibitor of factor Xa has been shown to be a potential alternative to warfarin in patients with non valvular AF. Rivaroxaban does not require dose adjustment and has little food or drug reaction. It is primarily excreted via the liver and therefore should be used.
cautiously in patients with hepatic impairment. In the Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET AF), a randomized double blind study, 14,264 patients were randomized to receive oral rivaroxaban (20mg daily) or dose adjusted warfarin. They found that the occurrence of stroke or systemic embolism in patients taking rivaroxaban and warfarin was comparable (1.7%, 2.2% per year respectively, hazard ratio in the rivaroxaban group 0.79; 95% CI 0.66-0.96; p<0.001 for non inferiority). Furthermore the rates of intracranial bleeding were significantly lower in patients taking rivaroxaban compared to warfarin, (0.5% v 0.7% per year; hazard ratio 0.67; 95% CI 0.47-0.93, p=0.02) although major gastrointestinal bleeding was higher in patients taking rivaroxaban (3.2%, 2.2%, p<0.001).

**Earlier Detection of Atrial Fibrillation**

Patients with AF are commonly asymptomatic and may only be diagnosed during presentation related to complications of AF, including heart failure, stroke or thrombo-embolism. An irregular pulse should raise the suspicion of AF and a 12 lead electrocardiogram (ECG) should be performed to confirm the diagnosis. Often AF begins with paroxysms that are short and rare, which progress to longer and more frequent attacks which may become continuous. In paroxysmal AF about 1 in 12 paroxysms are actually symptomatic. Studies of patients with pacemakers confirm that the burden in AF can vary between patients and that many paroxysms are asymptomatic. Theoretically earlier detection of AF allows for earlier risk stratification and use of thromboprophylaxis and hence reduction in risk and occurrence of stroke; However, this is difficult to put into practice.

Screening patients following ischaemic stroke with holter monitoring has been found to detect new onset AF or atrial flutter in 5% of patients. Performing a 12 lead ECG would detect AF in 6.7% of patients, a 24 hour holter would detect 10.6% and a 7 day event loop recorder would detect 15.6%. In the UK, incentivized screening programmes in primary care were piloted and 1.4% of patients were found to have a new diagnosis of AF through opportunistic pulse palpation.

**Earlier Initiation of OAC and Avoiding Interruptions**

Once patients have been identified as requiring OAC, it is recommended that treatment should be initiated promptly. However in the UK, it is common practice for non-specialists to refer to a specialist clinic for a decision on appropriate anticoagulation. This creates unnecessary delays and places patients at a higher risk of stroke and thrombo-embolism. A survey of accident and emergency consultants in the UK found that half were reluctant to make a decision on appropriate anticoagulation, and preferred to refer to a medical or cardiology team.

Patients receiving OAC may need to undergo surgical procedures for which interruption of therapeutic anticoagulation is essential. Although evidence is lacking in the absolute risk of stroke following interruption of anticoagulation in patients with AF, it is recommended that the interval without anticoagulation should be kept to a minimum and that anticoagulation should be re-started on the evening of (or the morning after) the surgery assuming there is adequate haemostasis. Furthermore it has been recognized that not all procedures will require anticoagulation therapy to be stopped.

**Anti-Arrhythmics and the Role for Catheter Ablation**

Rhythm control can be achieved with pharmacological, electrical or more invasive means such as catheter ablation. The rhythm-control strategy has been largely reserved for symptomatic patients, and furthermore catheter ablation is generally considered for symptomatic patients with paroxysmal AF who are resistant to at least one anti-arrhythmic agent.

Restoring sinus rhythm in a patient with AF will theoretically reduce the risk of stroke. However studies to date comparing the rhythm versus rate control strategy, such as the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) study and the Atrial Fibrillation and Congestive Heart Failure (AF-CHF) study, show...
no significant difference in mortality or stroke risk. Patients undergoing catheter ablation often require more than one procedure, and remain at risk of recurrence.

Current studies are under way to evaluate the role of catheter ablation in the treatment of AF. The Catheter Ablation versus Anti-arrhythmic Drug Therapy for Atrial Fibrillation (CABANA) trial is a randomized, parallel, open label trial evaluating percutaneous left atrial catheter ablation for the purpose of elimination of atrial fibrillation, as compared with current state-of-the-art therapy with either rate or rhythm control drugs [CABANA; clinicaltrials.gov; identifier NCT00911508]. The primary outcome is mortality and secondary outcomes include stroke, bleeding, cardiovascular hospitalization, arrhythmias and recurrent AF. It is expected to complete in 2015.

The Early treatment of Atrial Fibrillation for Stroke prevention Trial (EAST) is a randomized, prospective, open label study that is expected to complete in 2017 [EAST; clinicaltrials.gov; identifier NCT01288352]. EAST hopes to test the hypothesis that early, structured rhythm control therapy based on anti-arrhythmic drugs and catheter ablation can prevent AF related complications when compared to usual care (following the 2010 ESC guidelines for the management AF). The primary outcomes include stroke, bleeding, cardiovascular hospitalization, arrhythmias and recurrent AF. It is anticipated that these large trials will help establish a role for catheter ablation in the management of AF.

Special Considerations

OAC Following Stroke

1. Acute Infarct

OAC following a minor stroke or TIA is more effective than aspirin in prevention of further ischemic events and therefore current guidelines recommend that unless there are clear contraindications, long-term OAC should be initiated following ischemic stroke. However, OAC will increase the risk of developing intracerebral hemorrhage (ICH) which can potentially have devastating effects to the patient causing increased mortality and morbidity. The main factors that increase the risk of ICH include dose intensity, advanced age and hypertension. Other possible factors include size of infarct, associated cerebrovascular disease, concomitant antiplatelet therapy, tobacco or alcohol consumption, ethnicity, dialysis and vascular abnormalities detected by cerebral imaging (amyloid angiopathy, leukoaraiosis or microbleeds). Guidelines therefore recommend appropriate management of uncontrolled hypertension, and cerebral imaging, such as computed tomography or magnetic resonance imaging (MRI) to exclude ICH prior to initiation of OAC. Unfortunately no robust evidence exists as to the optimal timing of OAC; however most guidelines recommend that in the absence of ICH, anticoagulation should begin after 2 weeks. The American Heart Association/American Stroke Association (AHA/ASA) guidelines for the prevention of stroke in patients with stroke or transient ischemic attack recommend delaying OAC (more than 2 weeks) in patients with larger infarcts, hemorrhagic transformation and uncontrolled hypertension.

2. Hemorrhagic Transformation

In an acute infarct there is a risk of hemorrhagic transformation which may be a complication of thrombolysis treatment or indeed a natural course of the stroke. Hemorrhagic transformation may or may not give rise to neurological deterioration depending on its type, and one case series suggests that OAC may be safe in selected patients. Current guidelines differ in their guidance in situations where hemorrhagic transformation has occurred. The ESC and NICE guidelines state that OAC should be stopped. The AHA/ASA guidelines recommend that the decision for OAC should be made on a case-by-case basis depending upon various factors including size of hemorrhage, status of the patient and the indication for anticoagulation. Furthermore the introduction of OAC should be delayed by more than 2 weeks.

3. Intracerebral Haemorrhage

Unfortunately no robust evidence exists as to the risks and benefits of oral anticoagulation in
patients who have had an intra-cerebral hemorrhage, and randomized controlled trials would not be ethical. Eckman et al. applied a decision-analysis model to evaluate the role of anticoagulation in patients following intra-cerebral hemorrhage. They determined that OAC should largely be avoided in survivors of ICH, and only considered in patients with a deep hemorrhage (affecting the thalamus or basal ganglia), with a particularly high risk of thromboembolism or low risk of ICH recurrence.

The ESC and NICE guidelines recommend that OAC should not be given in the presence of an intracranial hemorrhage, although they do not elaborate as to whether there would be any situations where OAC may be considered. The AHA/ASA guidelines recommend that for patients who develop ICH, anticoagulants and antiplatelets should be discontinued during the acute period for 1 to 2 weeks, and clotting abnormalities may be corrected. However the decision to restart anticoagulation depends upon balancing the risk of recurrent ICH against the risk of ischemic stroke. Furthermore if anticoagulation is to be restarted this should be done within 7-10 days.

4. Patients who Develop a Stroke Despite Adequate Anticoagulation

In patients who have developed an ischemic stroke despite adequate anticoagulation (ie INR between 2-3) current guidelines agree that it may be re-instated with a higher target INR range of 3-4. However, this recommendation is not evidence-based. As mentioned previously an INR greater than 3 will increase the risk of bleeding. Adding in an antiplatelet agent is discouraged as there is no evidence to suggest this would be beneficial, as there is an increased risk of ICH.

It is evident that managing patients with AF who have developed strokes (whether ischemic or hemorrhagic) is challenging and clinicians are advised to use their clinical judgement to try and balance the risks of bleeding with OAC against the risk of thromboembolism without. Each decision should be case-based and patients should be evaluated carefully.

OAC in Acute Coronary Syndromes and/or Percutaneous Intervention

The management of OAC in patients with AF and acute coronary syndrome (ACS) and/or percutaneous intervention (PCI) can be difficult for clinicians.

In patients without AF, dual antiplatelet therapy (aspirin and clopidogrel) is recommended for 1 year in ACS and along with stenting (clopidogrel for 4 weeks with a bare metal stent, 6-12 months following a drug eluting stent). In patients with AF a combination of OAC and antiplatelet therapy may be needed. Although this combination is known to increase bleeding risk, it will need to be balanced with the protective effects of antiplatelets in ACS and PCI.

In ACS (with or without PCI), the ESC guidelines recommend triple therapy with warfarin, aspirin and clopidogrel for 3-6 months or longer in selected patients with a low bleeding risk, followed by long term warfarin and clopidogrel (or aspirin and gastric protection). In elective PCI, drug eluting stents (DES) should be limited to clinical and/or anatomical situations where the greatest benefit will be seen. Patients with bare metal stents (BMS) should receive triple therapy for 4 weeks, followed by warfarin and clopidogrel (or aspirin and gastric protection) for one year and warfarin alone thereafter. Patients with DES should receive triple therapy for a minimum of 3 months (with a sirolimus/everolimus/tacrolimus-eluting stent) or 6 months (with paclitaxel-eluting stent), followed by warfarin and clopidogrel (or aspirin and gastric protection) for 6 months and warfarin alone.

In the ESC guidelines, triple therapy is recommended post PCI (BMS 4 weeks, DES 6-12 months) then VKA + antiplatelet, avoid DES, in stable CAD monotherapy (no acute event or PCI in preceding year).

Conclusions

Stroke and thrombo-embolism are important consequences of AF, causing considerable morbidity, mortality and associated healthcare costs.
The prevention of stroke is an essential component of the management of AF. Patients with irregular pulses should undergo an ECG to confirm the diagnosis and although routine screening is not currently recommended, pilot screening programmes (through pulse palpation of elderly patients in primary care) have shown potential cost-benefit. Once the diagnosis of AF is confirmed a stroke risk assessment should be undertaken. Utility of the CHADS₂ and CHA₂DS₂-VASC scores are encouraged to identify patients at higher risk of stroke, which can be performed by physicians or general practitioners. Once a bleeding risk assessment (with the use of the HAS-BLED tool) has been made and the decision for OAC made, this should be initiated promptly and referral to an anticoagulation service can be made. Patients should be educated about the importance of OAC and (in the case of warfarin) the need for regular dose-monitoring or adjustment. Patients will need to be monitored to ensure they remain within the therapeutic range (INR range 2-3) and need a service provided to respond to out-of-range INR levels. Interruption of OAC therapy, for example prior to surgical procedures, should be kept to a minimum and treatment re-instated as soon as possible (usually the evening of or morning after the procedure).

Physicians and general practitioners should be educated in the benefits of OAC, particularly in the elderly age group, where the greatest benefit lies. The risk of intracranial haemorrhage in elderly patients has been shown to be less in patients receiving warfarin as compared to aspirin, whilst the benefit of stroke prevention is far greater with warfarin. Further work is clearly required to increase the use of OAC in patients with AF. Novel therapies such as the oral thrombin inhibitors (eg dabigatran and rivaroxaban) will hopefully increase usage. They negate the need for dose monitoring or adjustment and are expected to replace warfarin in the near future.

References


