Cavotricuspid isthmus dependent flutter is associated with an increased incidence of occult coronary artery disease

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Aims
Atrial flutter (AFl) and atrial fibrillation (AFib) share many clinical risk factors and potential mechanisms with atherosclerosis. Despite this, an association between stable coronary artery disease (CAD) and atrial arrhythmias has not previously been documented. To investigate this hypothesis we measured the incidence of occult coronary atheroma on coronary angiography in patients undergoing radiofrequency ablation procedures.

Methods and results
Consecutive coronary angiograms performed on patients with no history or symptoms of CAD undergoing elective ablation of arrhythmias were analysed. Patients were divided into three groups according to their arrhythmia: Typical right AFl, AFib, and a matched control group undergoing ablation for either atrioventricular node-dependent supraventricular tachycardia (SVT) or idiopathic right ventricular outflow tract tachycardia (RVOT). Atherosclerosis on angiography was graded according to the most severe stenosis. A total of 138 patients were included. Groups were evenly matched for age ($P = 0.4$), risk factors for coronary disease including hypertension ($P = 0.38$) and diabetes ($P = 0.2$). The incidence of asymptomatic, occult coronary atheroma was significantly greater in patients with AFl (AFl 54%, AFib 26%, SVT/RVOT 21%, $P = 0.005$). In contrast there was no higher incidence of occult atheroma in patients with AFib than those with SVT/RVOT ($P = 0.68$). The majority of atherosclerosis observed was mild, non-obstructive plaque disease (AFl 75%, AFib 44%, SVT/RVOT 67%).

Conclusion
There was a significantly greater incidence of occult coronary atheroma in asymptomatic patients undergoing ablation for AFl, suggesting that the mechanism underlying the development of atherosclerosis may also be important in creating the substrate that allows typical right AFl to develop.

Keywords
Atrial fibrillation • Atrial flutter • Atherosclerosis

Introduction
Atrial fibrillation (AFib) in the context of acute myocardial ischaemia is well recognized.\(^1\) In the Global Registry of Acute Coronary Events, AFib was present in 8.6% of patients.\(^3\) The association between occult, asymptomatic coronary artery disease (CAD) and atrial arrhythmias is less well characterized. There is histological evidence that sub-clinical ischaemia from occult CAD may be an important substrate for the development of atrial arrhythmias through damage to the atrial myocytes.\(^3\) In both animal and human subjects, AFib is associated with histological changes which alter atrial tissue structure, composition, and function.\(^3\) Fibrosis involves deposition of collagen and fibronectin between the individual cells, creating a substrate for re-entry.\(^4,5\)

Evidence from the longitudinal Rotterdam study demonstrated that in patients without clinically significant CAD, AFib was associated with an increase in carotid intimal thickness, a marker of atherosclerosis on ultrasound.\(^6\) Studies have demonstrated that carotid intimal thickness is a good non-invasive surrogate measure of atherosclerosis.\(^7\) However, no studies have examined the angiographic presence of occult coronary atheroma in patients with no symptoms or signs of CAD presenting with AFib or atrial flutter (AFl).
This study compared the coronary angiographic results of patients undergoing AFib or AFI ablative procedures to those undergoing supraventricular tachycardia (SVT) ablative procedures to see whether there was a difference in the incidence of occult CAD.

**Methods**

This study was based at a UK tertiary referral centre. This retrospective analysis examined the angiograms of patients aged 35–75 referred for elective radiofrequency ablation of their arrhythmia between 2002 and 2007. Patients were excluded from this study if they had a previous history of myocardial infarction or angina or evidence of myocardial or valvar heart disease. It has been the Department’s standard practise to perform coronary angiography on all patients undergoing ablation for AFib or AFI to identify patients where subsequent use of Class 1 antiarrhythmic medication might be contraindicated. A control group of angiograms was also analysed from patients who had coronary angiography as part of their ablation procedure for either SVT (accessory pathway-mediated or atrioventricular nodal re-entrant tachycardia) or RVOT.

Patients were divided into groups according to their arrhythmia: AFib, typical right AFI, and a matched control group undergoing ablation for either SVT (accessory pathway-mediated or atrioventricular nodal re-entrant tachycardia) or RVOT.

The presence of risk factors for CAD, namely diabetes, hypertension, a family history of premature coronary disease, hypercholesterolaemia, and current or previous smoking history were documented on all patients. Any patients with an alternative indication for coronary angiography such as exertional chest pain or heart failure were excluded, as were those patients who had more than one arrhythmia mechanism.

The number of coronary vessels affected and the severity of the atherosclerosis was recorded. Atherosclerosis was graded according to the most severe stenosis seen [occluded, severe (>75%), moderate (50–75%), or mild (<50%)] (Figure 1). This grade was assessed by two operators independent of each other.

Data were analysed using SPSS, continuous variables were assessed using ANOVA, while the $\chi^2$ test was used to compare frequencies between groups. Data are expressed as mean ± standard deviation.

**Results**

The study population consisted of 138 patients (mean age 58 ± 10 years, 70% males). Sixty-one had ablations for AFib, 37 for AFI, and 40 had ablations for either SVT or RVOT.
The groups were all evenly matched for age and risk factors for CAD (Table 1).

Angiographically visible atherosclerosis was present in 33% of all the patients included in this study. The incidence of asymptomatic, occult coronary atheroma was significantly greater in the AFl group compared with either the AFib or SVT/RVOT groups (P = 0.005). In the AFl group, 54% of patients had atheroma present on their angiogram compared with 26% of the patients undergoing ablation for AFib and 21% of the control SVT/RVOT group (Figure 2). There was, however, no difference between the incidence of coronary artery atheroma in patients with AFib when compared with those patients with SVT or RVOT as their underlying arrhythmia (P = 0.68).

The majority of the atherosclerosis detected was mild non-obstructive plaque disease (Figure 3). In the AFl group 75% of the CAD was mild, in the AFib group 44% was mild and in the control group 67% of the atherosclerosis was mild.

Table 1  Group characteristics and risk factors for coronary artery disease

<table>
<thead>
<tr>
<th></th>
<th>Atrial fibrillation</th>
<th>Typical right atrial flutter</th>
<th>SVT/RVOT</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>61</td>
<td>37</td>
<td>40</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>58 ± 9</td>
<td>59 ± 9</td>
<td>56 ± 11</td>
<td>0.41</td>
</tr>
<tr>
<td>Male</td>
<td>74%</td>
<td>78%</td>
<td>55%</td>
<td>0.053</td>
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<tr>
<td>Diabetes</td>
<td>3%</td>
<td>11%</td>
<td>6%</td>
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<tr>
<td>Hypertension</td>
<td>37%</td>
<td>33%</td>
<td>25%</td>
<td>0.48</td>
</tr>
<tr>
<td>Smoking history</td>
<td>13%</td>
<td>19%</td>
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<tr>
<td>Statin treatment</td>
<td>23%</td>
<td>35%</td>
<td>23%</td>
<td>0.34</td>
</tr>
</tbody>
</table>

SVT/RVOT, supraventricular tachycardia/right ventricular outflow tract tachycardia.

Discussion

This study has demonstrated an increased incidence of occult coronary artery atheroma in unselected, asymptomatic patients with typical right AFl compared with other arrhythmia mechanisms. In contrast, despite the association of AFib with acute coronary ischaemia there was no increased incidence of occult CAD in patients presenting for ablation of AFib compared with patients with SVT or RVOT. This suggests that the mechanism underlying the development of coronary atheroma may also be fundamental in creating the substrate for typical right AFl.

Both AFib and AFl are initiated by rapidly firing triggers commonly originating within the pulmonary veins. Indeed, the majority of patients with AFl will subsequently develop AFib following cavo-tricuspid isthmus ablation. In contrast only a small minority of AFib patients have pre-existing AFl. This suggests that patients with AFib have a particular right atrial substrate that specifically allows the initiation and maintenance of AFl. The present study suggests that such a right atrial substrate is associated with the presence of coronary atheroma. It is unlikely to represent a direct ischaemic effect as the majority of the atheroma detected in this study was mild, non-obstructive disease. Possible linking mechanisms include abnormal redox signalling or inflammation.

C-reactive protein levels are raised in patients with AFl compared with those with paroxysmal SVTs. They are also raised in patients with AFib. The role of inflammation in the development of CAD is well-documented and partly demonstrated by the ability of statins to stabilize plaques. There is also evidence that statins may help prevent the development and continuation of AFib, giving further weight to the involvement of inflammation in the pathogenesis of atrial arrhythmias, but at present these data are inconclusive.

In addition, following ablation for AFl, C-reactive protein levels fall, suggesting that inflammation is secondary to the arrhythmia rather than being causative.

Many studies have demonstrated the association of AFib with some of the risks factors for CAD, such as hypertension. However, we did not show an increased incidence of occult CAD in patients presenting for ablation of AFib despite these
previously documented associations. Our findings correlate with the earlier Cardiovascular Health study that showed no significant difference in surrogate markers of atherosclerosis; carotid intima-media thickness and the ankle-arm index, in subjects with AFib compared with those without.16 This is in contrast to the Rotterdam study.6 There are a number of potential explanations for this discrepancy: it may reflect the small study size of this population, alternatively carotid intimal thickening may correlate less well with coronary atheroma in patients with AFib than those with sinus rhythm. Most importantly, the Rotterdam Study did not distinguish between patients with AF and AFib, classifying them identically, hence their results may be skewed by a higher incidence of coronary disease in patients with lone AF or a combination of AF and AFib. Finally, our study only included patients undergoing ablation treatment for AFib. Such patients represent only a small proportion of the overall population of patients with AFib and are typically younger, active and highly symptomatic.17 Further prospective studies are needed to confirm the potential link between AFib and occult coronary atheromatous disease. There are important clinical implications following the discovery of occult coronary atheroma. Many patients with atrial arrhythmias may be candidates for drug therapy with Class Ic antiarrhythmic drugs such as flecainide. These drugs can be proarrhythmic, particularly in the setting of acute myocardial ischaemia.9 Acute coronary syndromes may result from rupture of atheromatous plaques that are frequently non-obstructive and have previously been asymptomatic.18 The presence of CAD has thus been regarded as a relative contraindication to the use of Class Ic antiarrhythmic drugs.8,19 Although there are no long-term prospective studies looking at the safety of Class Ic agents in patients with either AF or occult CAD, the relatively high incidence of atheromatous plaque disease seen on angiography in AF patients may encourage clinicians to investigate these patients for the presence of atheroma and consider the use of plaque-stabilising medications (e.g. statins), particularly if they are considering the long-term use of Class Ic antiarrhythmics in these patients.

Limitations
This study is retrospective and performed on a relatively small group of patients selected for ablation therapy and thus may not be representative of the wider populations. Further prospective studies on a larger patient population are indicated to see whether these observations are also valid in other patient populations with a significant association between the incidence of occult CAD and typical right AF.

Conclusions
This study has demonstrated a higher incidence of occult CAD in patients presenting for ablation of typical right AF than patients presenting for ablation of either AFib or SVTs. This suggests a possible aetiological link between the development of coronary atheroma and the substrate which allows right AF to initiate and be maintained. This has potential clinical implications for the prescribing of Class Ic antiarrhythmic drugs and statin therapy.

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References