In search of an arrhythmic cause of coronary artery disease: the electrophysiologist’s next frontier?

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This editorial refers to ‘Cavotricuspid isthmus dependent flutter is associated with an increased incidence of occult coronary artery disease’ by J.P. de Bono et al., on page 1774

de Bono et al. report the coronary angiogram results on 138 patients undergoing ablation for typical atrial flutter (AFL, \( n = 37 \)) or atrial fibrillation (AF, \( n = 61 \)), in comparison to a control group of patients undergoing ablation for supraventricular tachycardia (SVT) or idiopathic right ventricular outflow tract tachycardia (RVOT-VT) (\( n = 40 \)). The demographic data for these groups were statistically similar, and the groups were evenly matched for age and coronary disease risk factors. The authors observed that patients undergoing ablation for typical AFL had a significantly higher incidence of occult (i.e. asymptomatic) coronary artery disease (CAD, \( P = 0.005 \)) compared with those undergoing ablation for AF, SVT, or RVOT-VT. Specifically, 54% of the AFL patients had coronary atheroma, compared with 26% of the patients with AF and 21% of the patients with SVT or RVOT-VT. No difference was noted in the incidence of coronary atheroma in patients with AF compared with those with SVT or RVOT-VT (\( P = 0.68 \)). However, the majority of the CAD detected was mild non-obstructive plaque, 75% in AFL patients, 44% in AF patients, and 67% in patients with SVT or RVOT-VT.

The authors conclude that there may be a mechanistic link between the right atrial substrate underlying typical AFL and that it may be responsible for a higher incidence of CAD in these patients, when compared with similar age- and CAD risk factor-matched patients with AF, SVT, or RVOT-VT. What specific mechanistic link this might be, however, is not determined by this strictly observational report. The authors note that there is a close relationship between AF and AFL, with pulmonary vein ectopy commonly triggering both AF and AFL. However, although not all patients with AFL have AF, most patients with AF have AFL at one time or another. Thus, the authors note that patients with typical AFL probably have a substrate that ‘specifically allows initiation and maintenance of AF’. This has been previously shown to be true, with slower conduction velocity noted in the right atrium in the medial cavo-tricuspid isthmus (CTI) and inferior septum compared with other areas in the atrium, and slower conduction in the CTI in patients with AFL compared with those with SVT. The mechanism responsible for this slower conduction velocity is not known and has never been specifically studied. Thus, the findings of this study are intriguing, suggesting that underlying CAD could be a possible causative factor, leading to ischaemia and fibrosis of the right atrium. Unfortunately, it appears that the CAD in most patients with AFL in this study was very mild, and not likely to cause ischaemia. Therefore, an alternative explanation must be sought if this phenomenon is true, and not just a chance observation due to the small number of patients included in this study.

The authors propose alternative links between the occurrence of AFL and increased incidence of CAD, specifically abnormal redox signalling or inflammation. They do not discuss the possibility of abnormal redox signalling, but do focus on the possible role of inflammation. Prior studies have shown that C-reactive protein levels fall after AFL ablation, suggesting that it is the arrhythmia itself that causes the inflammation, rather than inflammation causing the arrhythmia. Since inflammation may be secondary to or a possible cause of CAD, it would have been useful to know what percentage of patients in this study with AFL actually presented in AFL vs. sinus rhythm. If a greater percentage of patients undergoing AFL ablation actually presented in AFL compared with those undergoing AF ablation presenting in AF, it is possible that the arrhythmia itself could have caused a greater incidence of mild CAD, rather than the CAD creating a substrate for AFL. Frankly, it would not make physiological sense that the presence of underlying CAD would be more likely to create a substrate...
for AFL than it would for AF, since the structural and electrophysiological milieu is similar for both AF and AFL. Whatever the mechanism between AFL and CAD, the authors suggest that patients undergoing AFL ablation should be treated with statins, since these drugs are known to stabilize atheromatous plaque. This recommendation is probably not warranted based on this small observational study, since there is no data proving a direct link between AFL and CAD. Nonetheless, since many patients with AFL also have or will develop AF (and it was not clear from this study whether the patients undergoing only AFL ablation had prolonged outpatient telemetry monitoring to determine whether they also had AF at any time), the use of statins in such patients is already commonplace, especially since many in this age group will also have hyperlipidaemia.

The authors of this study also propose that another reason for performing coronary angiography in all patients undergoing AFL ablation, who may be expected to have a higher incidence of CAD according to their findings, is that they may be candidates for class 1c antiarrhythmic drugs, which would be contraindicated in patients with CAD. To a degree this recommendation is illogical however. First, the use of class 1c antiarrhythmic drugs is not contraindicated in patients with asymptomatic mild CAD and only relatively contraindicated in those with more severe CAD but normal left ventricular function. Secondly, although class 1c antiarrhythmic drugs may be proarrhythmic for ventricular arrhythmias, they may also be proarrhythmic for AFL, with a nearly 10% risk of converting AF into AFL, often with a 1:1 ventricular response due to slowing of atrial conduction. This AFL may be atypical or non-isthmus-dependent, in some cases as well. It is for this reason, rather than the risk of ventricular proarrhythmia, that class 1c drugs are prescribed with caution in AF patients who are prone to AFL, unless prescribed with an atroventricular nodal blocking drug as well. However, in those patients undergoing CTI ablation for typical AFL, the success rate is so high (i.e. in excess of 90%) that there is usually little concern of typical AFL recurrence when prescribing class 1c drugs to prevent recurrent AF.

In summary, the findings of this study are interesting. However, as the authors themselves note, additional larger studies will be required to confirm a correlation between AFL and CAD. In addition, significant additional data, including presenting arrhythmia, arrhythmia burden, levels of inflammatory markers before and after ablation, and outcomes data, would be required to prove causality and to justify the recommendations of the authors for statin treatment and coronary angiography in all AFL patients undergoing ablation.

**Conflict of interest:** none declared.

**References**