Reduced myocardial perfusion in atrial fibrillation: when the egg comes before the chicken

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This editorial refers to ‘Impaired myocardial perfusion and perfusion reserve associated with increased coronary resistance in persistent idiopathic atrial fibrillation’ by F.T. Range et al., on page 2223

Atrial fibrillation (AF) is the most common arrhythmia requiring clinical intervention, and yet critical gaps persist in our understanding of AF mechanisms as well as the implications of this condition for afflicted individuals. AF appears to be associated with a significantly worse prognosis, yet it has remained problematic whether the shortened life expectancy is due to the AF or due to the condition causing the AF. The most recent guidelines from the European Society of Cardiology list 13 categories of conditions associated with an increased risk for AF, one of which is the familiar but uninformative ‘idiopathic’.1 Many of the maladies associated with an increased risk of AF, i.e. hypertension or hyperthyroidism, are systemic disorders with serious negative prognostic implications independent of AF. It has therefore been difficult to determine how much of the morbidity (beyond that associated with stroke) experienced by AF patients is due to their AF per se, and how much is due to the underlying conditions driving their AF. Clinicians may well regard this as an unsolvable or nonsensical issue akin to worrying whether the chicken preceded the egg, or vice versa. The need to understand which element is cause and which effect, though, has become more acute now that electrophysiologists and cardiothoracic surgeons can greatly reduce or even eliminate the arrhythmia by ablation.

Although discrepant studies exist, the preponderance of evidence points to a significant independent contribution of AF to cardiac mortality.2 AF was associated with a significantly increased risk of cardiac death in a registry of 16 048 consecutive subjects undergoing myocardial perfusion imaging at Cedars-Sinai Medical Center.3 Of these, 384 (2.4%) had AF, and in this group mortality was significantly higher for all strata of myocardial perfusion and was an independent predictor of cardiac death in a Cox multivariate analysis including age, diabetes, shortness of breath, use of vasodilator stress, resting heart rate, and nuclear variables; indeed, the presence or absence of AF was a more powerful predictor of mortality than ejection fraction. Of particular significance, the subgroup with a perfusion scan evaluated as ‘normal’ in those in sinus rhythm had a 0.4% per year mortality rate, while those with a ‘normal’ perfusion scan and AF had a 4-fold increased rate of 1.6% per year ($P < 0.001$). This failure of myocardial perfusion imaging to identify a low-risk cohort in this study is particularly alarming and difficult to comprehend. An intriguing study by Range et al.4 may provide an important clue to one source of increased morbidity associated with AF, as well as good evidence that the source of the problem is the AF itself.

Using $^{15}$H$_2$O-positron emission tomography (PET) scanning, 25 individuals with persistent idiopathic AF were compared with 13 age- and risk factor-matched controls in sinus rhythm as well as with nine young healthy controls, the points for comparison being resting myocardial blood flow (MBF), maximal vasodilated MBF after adenosine, and MBF during a cold pressor test. In addition, these measures were repeated in 10 individuals who were able to maintain sinus rhythm 4 months after cardioversion. In summary, the investigators found that resting, hyperaemic, and post-cold pressor test MBF was significantly reduced in the AF subjects compared with both control groups, and that cardioversion completely normalized resting MBF along with response to cold pressor challenge while improving the hyperaemic response to adenosine.

Although the exact importance of reduced resting and hyperaemic MBF still needs to be elucidated, comparison of these absolute values with those of other similar studies is sobering. The mean value for resting MBF in the AF group was $0.95 \pm 0.19$ mL/min/mL. After adenosine, it was $2.07 \pm 0.80$ mL/min/mL. These values are comparable with those found using $^{15}$H$_2$O-PET in subjects with left bundle branch block and NYHA class III–IV heart failure prior to biventricular pacing ($0.82 \pm 0.25$ mL/min/mL at rest; $1.91 \pm 1.03$ mL/min/mL after a similar dose of adenosine).5 One could speculate that such impaired resting and hyperaemic MBF in AF would put the patient at increased risk for episodes of myocardial ischaemia and stunning over time, and significantly contribute to a poorer prognosis.
in a manner demonstrated in subjects with non-ischaemic cardiomyopathy. It is worth noting that conventional perfusion imaging, such as that used by the Cedars-Sinai group, would not have detected a reduction in MBF in AF subjects in the present study, as no regional heterogeneities in blood flow were present.

The limitations of the present study are significant. Principally, the presence of coronary artery disease by angiography was excluded in only 16 of the 25 subjects, although all subjects underwent conventional stress testing, as well as a PET scan, and had no evidence of inducible ischaemia. The study only included males, and the mean age of 58 ± 13 years is a reflection of the average age of neither subjects with persistent AF (who tend to be older) nor those undergoing AF ablation (who tend to be younger). Nevertheless, the present study suggests that AF per se exposes the patient to significantly reduced MBF at rest, and that conversion to sinus rhythm is associated with a return to normal. So in this instance, the egg (AF) appears to have preceded the chicken (reduced resting MBF).

One hopes that these data will be replicated in subjects undergoing ablation for AF. Ultimately, ablation should be compared with medical therapy for AF in a large, AFFIRM-style randomized trial with mortality as the primary end-point. Until that day, referring physicians need to consider such collateral evidence as presented by Range et al., and decide whether the restoration of sinus rhythm justifies the risks associated with the procedure(s). If restoration of sinus rhythm by ablation results in normalization of myocardial blood flow, one would anticipate an improvement in prognosis.

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References