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Mechanisms of post-cardiac surgery atrial fibrillation: more pieces in a difficult puzzle

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Atrial fibrillation (AF) is common following cardiac surgery, affecting ~30% of patients. It is associated with increased morbidity and mortality. Various anti-arrhythmic drugs reduce the incidence of post-surgery AF,¹ but they also carry considerable potential for adverse effects. The development of safer and more effective treatments for this arrhythmia will require an improved understanding of its basic electrophysiological mechanisms. A variety of reentrant and non-reentrant arrhythmia mechanisms likely initiates and sustains AF.² Which of these predominate is unclear, and may depend on, e.g., underlying cardiac pathology, autonomic tone, and whether AF is paroxysmal or sustained. Atrial activation frequency characteristics have been studied during AF with spectral analysis using fast Fourier transformations. This technique provides clues as to the source of AF and its level of organisation. In patients with AF, the dominant frequency (DF) of activation was higher in the left atrium (LA) than right (RA), suggesting that the source of AF was located primarily in LA.³ Studies in sheep suggested that such LA sources could be reentrant. This is because acetylcholine, which shortens action potential terminal repolarisation, effective refractory period (ERP) and, therefore, reentry wavelength, increased atrial DF and accelerated reentrant rotors.⁴ The arrhythmia mechanisms involved in post-surgery AF are poorly understood, however, partly because of the considerable technical and ethical challenges of studying them in patients. A pressing question is whether the DF is higher in the LA than RA during post-surgery AF, and if so, what are the underlying electrophysiological and molecular mechanisms. Another important question is whether LA and RA electrophysiological or molecular characteristics which are present before surgery might predispose to the development of AF afterwards. Pre-surgery ECG P-wave characteristics independently predicted the development of post-surgery AF.⁵ Patch clamp studies of human atrial myocytes suggested that this was unlikely to involve membrane ion currents that influence terminal repolarisation or ERP.^{2,6,7} However, those studies were restricted to cells from RA, which is more readily available than LA during coronary artery bypass graft surgery. Furthermore, increased

atrial fibrosis, commonly associated with congestive heart failure (CHF) and ageing, affects LA DFs⁸ and could predispose to post-surgery AF, but again studies are often restricted to RA.⁹

In the present issue of *Heart Rhythm*, both of these questions have been tackled in an ambitious, technically challenging and well performed study by Swartz *et al.*¹⁰ A total of 44 patients consented to providing LA and RA appendage tissues during cardiac surgery, for subsequent analysis of ion channel expression and histology. 27 of these patients consented also to having their LA and RA epicardial electrograms recorded in the event that AF should occur after surgery. Of those, 9 developed such arrhythmia, and electrograms could be recorded simultaneously in LA and RA within 15 min of AF initiation in 7 patients. Spectral analysis of these electrograms revealed that the DF was 37% higher in LA than RA. This suggested that the source of early post-surgery AF resides in the LA. Swartz *et al* went on to investigate potential molecular causes of this interatrial difference in DF. They found that in the total cohort of 44, mRNA expression of the pore-forming α -subunits Kir 2.3 and Kir 3.4, which carry the inward rectifier K⁺ currents I_{K1} and I_{KACH}, respectively, was higher in LA than RA. Furthermore, expression of Kv1.5 and Cav1.2, which carry ultra-rapid delayed rectifier K⁺ (I_{Kur}) and L-type Ca²⁺ (I_{CaL}) currents, was lower in LA than RA. A statistical comparison between the atria was not made within separate post-surgery AF and sinus rhythm groups. However, the level of each transcript tended to differ between the atria by a similar degree in either patient group. Mathematical modelling studies have indicated that inward rectifier K⁺ currents substantially influence the ERP, and that an increase in atrial I_{K1} shortens terminal repolarisation and stabilises reentry.¹¹ If the higher LA Kir 2.3 and Kir 3.4 were to translate to increased LA current densities, then these molecular data would be consistent with a causative mechanism of the higher DF in LA. The lower LA Cav1.2 and Kv1.5 may not influence the interatrial difference in DF, because pharmacological or simulated block of I_{CaL}¹² or I_{Kur}¹¹ had no effect on human atrial ERP or terminal repolarisation, respectively. Swartz *et al* also report that there were no significant differences in either LA or RA expression of any transcripts between patients with and without post-surgery AF. This is in line with earlier studies of RA I_{K1} and I_{KACH},⁶ and of RA I_{K1}, I_{CaL}, I_{Kur} and I_{TO}.⁷ Moreover, it adds substantially to our knowledge, because it is the first such study in human LA, and supports the view that post-surgery AF is not predicted by pre-surgery atrial ion currents. Swartz *et al* also found that the degree of fibrosis was 2-fold greater in LA than RA in patients who had post-surgery AF. Moreover, LA fibrosis was almost 3-fold greater in patients who developed post-surgery AF than in those who did not, whilst RA fibrosis was similar between these patient groups. This finding suggests

that increased LA fibrosis may predispose to post-surgery AF, presumably by perturbing intermyocyte electrical coupling and conduction. It also highlights the importance of studying LA as well as RA where possible.⁹ Finally, Swartz *et al* discovered that in the 7 patients whose AF DFs were measured, there was a significant correlation between LA DF and either LA fibrosis or LA collagen expression, such that increasing fibrosis was associated with decreasing DF. Such an inverse correlation may seem paradoxical, because the marked increase in LA and not RA fibrosis in patients with post-surgery AF was associated with a higher DF in LA than RA. However, it is not anomalous, because increased LA fibrosis due to CHF in sheep was associated with a reduced DF in the LA whilst the interatrial difference in DF was maintained.⁸ Presumably, in the Swartz study,¹⁰ the influence of a higher LA I_{K1} and I_{KACH} to increase LA DF outweighed the influence of LA fibrosis to decrease it, but that would require further investigation.

The Swartz study¹⁰ answers some important questions about mechanisms of post-surgery AF. However, as with any good piece of scientific research, it also raises some useful questions. For example, why was fibrosis increased in LA but not RA in patients with post-surgery AF? This might relate to the higher incidence of valve surgery and severity of CHF. Left ventricular systolic dysfunction has been independently associated with human RA cellular electrophysiological changes,¹³ although LA cells or fibrosis were not studied. Would LA fibrosis independently predict post-surgery AF in a cohort sufficiently large to adjust for clinical confounders? Is there a positive correlation between inward rectifier K^+ channel expression and DF? That would support the idea that the influence of I_{K1} and I_{KACH} on DF outweighs that of fibrosis. Can we safely assume that the observed interatrial differences in ion channel α -subunit mRNA levels would translate to differences in ion current magnitudes sufficient to affect ERP and DF? Whilst ion channel expression and function do not always correlate, an earlier report of a higher LA than RA I_{KACH} and DF in sheep⁴ supports the validity of this assumption in the Swartz study¹⁰, at least for Kir3.4.

Post-cardiac surgery AF seems to be caused mainly by the surgical procedure, and promoted by the influence of age and atrial fibrosis on atrial electrophysiology. The Swartz study¹⁰ provides evidence to support the hypothesis that this arrhythmia has a source located in the LA, resulting from an interatrial difference in ion currents that affect ERP, and is facilitated by increased LA fibrosis. It therefore contributes substantially to our understanding of mechanisms of post-cardiac surgery AF, and thus improves our chances of finding better treatments to prevent this arrhythmia.

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