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**Duration of heart failure and the risk of atrial fibrillation:
different mechanisms at different times?**

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Chronic heart failure increases the risk of atrial fibrillation (AF), with the prevalence of AF paralleling the severity of heart failure.¹ Factors which underlie this increased susceptibility to AF may include electrical, structural and neurohumoral changes.² In AF it is recognised that atrial electrophysiological remodelling occurs and contributes to the perpetuation of the arrhythmia, most notably the decrease of effective refractory period (ERP) which predisposes to re-entry by shortening the wavelength. Does heart failure cause similar changes in atrial electrophysiology that predispose to the arrhythmia?

An extensively studied dog model, in which heart failure was induced by rapid ventricular pacing, has suggested not: atrial electrophysiological changes were either absent, or were in the opposite direction, with prolongation of the action potential duration (APD).^{3,4} Susceptibility to induced AF was increased, but this was more related to structural changes, in particular increased fibrosis,⁵ than electrophysiological properties. By contrast, our recent study of human right atrial isolated myocytes⁶ found that left ventricular (LV) systolic dysfunction was associated with electrophysiological changes – decreased APD and shortened refractoriness - which would predispose to AF, contrary to the findings in the dog model.

The study by Sridhar et al in this issue⁷ sheds some light on this discrepancy, indicating that the key factor may be the duration of heart failure. The main methodological difference in the dog model used in this study was the duration of ventricular tachypacing – at least 4 months, compared to a maximum of 6 weeks in previous studies. In contrast to the studies with short-term heart failure, this study of

chronic heart failure found that the LV dysfunction was not fully reversible, the induced AF was sustained rather than self-terminating, and there was atrial electrophysiological remodelling with shortening of left atrial myocyte APD (both at 50% and 90% repolarisation) and of right atrial ERP *in vivo*. They also found increased fibrosis similar to that described with shorter duration heart failure, suggesting that the progressive changes were electrophysiological rather than structural. This study provides a new insight into the association between chronic heart failure and AF but also raises a number of questions.

What are the ionic mechanisms underlying the shortening of APD and ERP with chronic heart failure? An increase in I_{to} was found,⁷ consistent with the observed shortening of early repolarisation, although it might be expected to have less influence on late repolarisation or ERP. However, a mathematical model of a canine atrial cell showed that such an increase in I_{to} would shorten both early and late repolarisation.⁸ Alternatively, the reported decreases in potassium currents (I_{Kur} , I_{Ks} , I_{K1}) would tend to oppose this effect. There was no change in I_{CaL} , although the shortened early APD due to the I_{to} increase might decrease the duration of I_{CaL} , and thus shorten late repolarisation.⁷ However, this would also affect other currents, such as the delayed rectifiers, which might be activated less strongly, opposing late APD-shortening.

Why did I_{to} increase, and not decrease as found in numerous models of atrial pathology, including short term heart failure in dogs³, and chronic AF⁹ or LV systolic dysfunction⁶ in humans? There was no change in Kv4.3 protein, the α -subunit which carries I_{to} , but the Kv channel interacting protein 2 (KChIP2), which affects Kv4 surface expression and functional properties, was increased.⁷ This would be consistent

with the observed I_{to} increase, as well as the I_{Ks} decrease, since I_{to} was decreased and I_{Ks} increased in mice in which the gene encoding KChIP2 was deleted.¹⁰ The role of increased oxidative stress was investigated, and an anti-oxidant prevented the I_{to} increase - but did not reverse the shortening of terminal repolarisation in chronic heart failure.⁷

What happens to atrial intracellular calcium handling with chronic heart failure? In the short-term heart failure model, after 2-weeks of ventricular tachypacing there was APD prolongation and cellular calcium overload with resultant triggered or spontaneous arrhythmic activity.¹¹ This is in contrast to the chronic heart failure model where the shortened action potential resulted in reduced I_{CaL} and thus less calcium entry.⁷ However, the changes in calcium handling and related regulatory proteins observed with short-term heart failure¹¹ have yet to be studied in chronic heart failure.

What are the mechanisms by which LV failure induces electrophysiological changes in the atria? For the left atrium, this could include direct mechanical effects, such as stretch, but right atrial changes induced by LV failure suggest a humoral mediator, in line with the finding of increased atrial angiotensin-1 receptor expression.⁷ Clinical studies have shown reduced AF in patients treated with ACE inhibitors or angiotensin receptor blockers, with or without heart failure.¹² In the short-term heart failure dog model, enalapril reduced the duration of induced AF, but by attenuating structural, rather than electrical, remodelling with reduction in atrial fibrosis.¹³

There are limitations to the study by Sridhar *et al*, and unanswered questions remain. It is not known whether the shortening in atrial ERP and APD in their model would be preceded by increases, since shorter periods of heart failure were not studied. It cannot be excluded that aspects of the model other than duration of pacing may differ between this and the earlier studies. The underlying changes in ionic currents (increased I_{to} ; decreased I_{Kur} , I_{Ks} , I_{K1} ; no change in I_{CaL})⁷ were different from those in human atrial myocytes (decreased I_{to} ; no change in I_{CaL} , I_{K1} , I_{sus}).⁶ Other findings in humans with LV dysfunction are not consistent (see review²) with reports of increased, or unchanged, APD₉₀ and a single study finding increased I_{to} . An *in vivo* study of atrial electrophysiology in patients with heart failure found a modest increase of ERP.¹⁴

Much work remains to be done, and the present study indicates the complexity underlying the association between heart failure and AF. Taken together with the previous studies of shorter duration heart failure, it suggests that there may be different electrophysiological mechanisms predisposing to AF depending on the duration of heart failure – altered substrate predisposing to re-entry with chronic heart failure in contrast to the increase in triggers due to calcium overload in acute heart failure.

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