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

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Online publish-ahead-of-print 27 August 2009

This editorial refers to 'Chronic heart failure and the substrate for atrial fibrillation' by A. Sridhar et al., pp. 227–236, this issue.

Chronic heart failure increases the risk of atrial fibrillation (AF), with the prevalence of AF paralleling the severity of heart failure.1 Factors that underlie this increased susceptibility to AF may include electrical, structural, and neurohumoral changes.2 In AF, it is recognized 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. In 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.

Sridhar et al.7 shed 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 with 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% repolarization) 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 repolarization, although it might be expected to have less influence on late repolarization 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 repolarization.5 Alternatively, the reported decreases in potassium currents ($I_{K_{at}, I_{Ks}, I_{K1}}$) would tend to oppose this effect. There was no change in $I_{Ca,L}$, although the shortened early APD due to the $I_{to}$ increase might decrease the duration of $I_{Ca,L}$, and thus shorten the late repolarization.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 dogs5, and chronic AF7 or LV systolic dysfunction9 in humans? There was no change in Kv4.3 protein, the $\alpha$-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 $I_{K}$ decrease, since $I_{to}$ was decreased and $I_{K}$ 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 $I_{Ca,L}$ 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. Clinical studies have shown reduced AF in patients treated with ACE inhibitors or angiotensin-receptor blockers, with or without heart failure. 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.

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 would be preceded by increases in these parameters, since shorter periods of shortening in atrial ERP and APD would be preceded by increased atrial angiotensin-1 receptor expression. Clinical studies have shown reduced AF in patients treated with ACE inhibitors or angiotensin-receptor blockers, with or without heart failure. 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.

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.

Conflict of interest: none declared

References