Evaluating the impact of atrial dilatation on atrial calcium cycling

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This editorial refers to ‘Downregulation of the calcium current in human right atrial myocytes from patients in sinus rhythm but with a high risk of atrial fibrillation’ by S. Dinanian et al., on page 1190

With increased longevity, the prevalence of age-related diseases is increasing. Atrial fibrillation (AF) is one of the age-related conditions that is approaching epidemic proportions. AF is an important cause of cardioembolic stroke, and the primary cause of cardioembolic stroke in the elderly population. Thrombus formation is in part attributed to the greatly impaired atrial contractility during AF. As in the ventricle, atrial contractility is dependent on the excitation–contraction coupling process in which calcium influx promotes release of calcium from intracellular stores; it is the rise of intracellular calcium that initiates cross-bridge cycling and muscle contraction. Muscle relaxation during diastole occurs upon resequestration or extrusion of cytosolic calcium. Regulation of calcium cycling is a critical determinant of atrial contractility, and calcium influx via L-type calcium channels (ICa,L) during each heart beat is a critical determinant of calcium cycling. From a combination of electrophysiological studies in experimental animal models, it is now widely appreciated that calcium influx is dramatically (~70%) attenuated following the onset of AF. Comparisons of calcium current density in myocytes isolated from patients in either sinus rhythm or AF at the time of cardiac surgery have revealed a nearly identical downregulation that has been primarily attributed to the presence of AF.

Atrial enlargement (dilatation), especially of the left atrium, has long been identified as a predictor of increased risk of atrial fibrillation, stroke, and mortality. In 1994, Le Grand and colleagues were the first to characterize the cellular electrophysiology of patients with dilated atria. Their study documented a significant downregulation in ICa,L and the transient outward potassium current (IKO), suggesting that dilation is a sufficient stimulus to initiate the electrical remodelling process that is also characteristic of myocytes from patients with AF. It is probably not coincidental that AF is frequently characterized by atrial dilatation and myocyte hypertrophy, and that dilatation has a significant impact on the persistence of AF.

In an extension of the landmark studies of Le Grand et al., Dinanian et al. report on calcium current measurements made from right atrial myocytes isolated from an impressively large series of 86 cardiac surgery patients, with varying indications for cardiac surgery. Here the authors report that mitral valve disease and atrial dilatation independent of AF are accompanied by reductions in ICa,L that are as substantial as those changes associated with AF. Further, they report that a low ejection fraction (EF) has a similar effect on those patients presenting for surgery in sinus rhythm (with no reported history of AF). The lowest ICa,L values were recorded from myocytes that were most hypertrophied.

It is unclear (and was not studied) whether the reduction of ICa,L that is reported was the result of transcriptional regulation or post-translational modification(s) of channel activity. In an expression array study, it has been reported that there is substantial overlap in the profile of changes in mRNA expression in tissues from patients with valvular disease vs. those with AF and valvular disease. A comparison of calcium channel expression among patients in AF vs. matched patients in sinus rhythm using western blot and dihydropyridine binding assays suggests that transcriptional regulation of calcium channels was not prominent, and thus not a likely explanation for the observed current downregulation in AF.

Experiments using isoproterenol to stimulate β-adrenergic receptors revealed that, as is characteristic of myocytes from patients in AF, atrial myocytes with the lowest baseline ICa,L had the greatest response to stimulation by isoproterenol, suggesting that the channels are less active due, at least in part, to a relative state of dephosphorylation. Increased phosphodiesterase activity in response to increased atrial natriuretic peptide levels and activation of guanylate cyclase activity in the patients with dilated atria is one of the mechanisms proposed to underlie the observed reduction in ICa,L.

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Another interesting observation in this study is that of a lower mean density of $I_{Ca,L}$ in myocytes isolated from men. Recent studies in mice have shown that L-type calcium channels can be modified by S-nitrosylation, and that gender differences in the abundance of nitric oxide may contribute to gender-specific regulation of channel activity. We have recently shown that S-nitrosylation of the calcium channel occurs in human AF, and that nitrosylation is increased under conditions in which atrial glutathione levels are depleted (oxidant stress). Experimental glutathione depletion leads to impaired atrial contractility. It is interesting that increased wall stress increases oxidant production, in part due to increased NADPH oxidase activity. Thus, increased oxidant production might also contribute to the decrement in $I_{Ca,L}$ in the myocytes from patients with dilated atria.

NADPH oxidase activity is increased in human AF, and atrial NADPH oxidase activity at the time of surgery has recently been associated with the occurrence of AF following cardiac surgery. In this report, Dinanian et al. note in the Discussion that no relationship could be detected between the calcium current density in myocytes obtained at the time of surgery and the occurrence of AF during the post-operative period.

The observation of Dinanian et al., showing a downregulation of atrial calcium currents in myocytes isolated from patients with dilated atria and impaired cardiac function, is likely to be consistent with the increased risk of AF and stroke in these patients. However, the downregulation may protect the atria that are already haemodynamically challenged from the additional metabolic burden associated with increased contractile activity. Thus, efforts to improve the systemic haemodynamics (via control of heart rate, hypertension, cardiac perfusion, etc.) may have greater therapeutic benefit than efforts targeted at increasing atrial calcium influx directly.

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**References**