Editorial

Structural correlates of electrical remodeling in ventricular hypertrophy


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See article by Peschar et al. [2] (pages 510–517) in this issue.

Ventricular remodeling is an adaptive change in cardiac chamber structure and function in response to volume and/or pressure overload. In the last few years, it became clear that this process also involves the electrical system of the ventricular chambers. Electrical remodeling associated with left ventricular hypertrophy and heart failure causes an increased frequency of ventricular ectopy and a high risk of cardiac arrest. The degree of electrical remodeling and arrhythmic risk is not directly proportional to the severity of left ventricular (LV) dysfunction. For example, in the VHeFT study (Veterans Administration Heart Failure Trial), the risk of sudden cardiac death was greater in patients with modest LV dysfunction [1]. It has been shown that there is a temporal relationship between the progression of structural and electrical remodeling of the left ventricle in response to various pressure and volume overload states. Concurrent regression of structural and electrical remodeling in pressure overload hypertrophy is seen, but there seems to be a dissociation in these processes in certain types of volume overload hypertrophy (Fig. 1). Such an interesting dissociation is shown in this issue of Cardiovascular Research by Peschar et al. [2]. The findings of this paper underscore the independent nature of electrical remodeling in volume overload hypertrophy in contrast to pressure overload hypertrophy. Furthermore, the adverse and irreversible nature of electrophysiological changes in volume overload hypertrophy become abundantly clear.

Electrical remodeling is characterized by delayed repolarization, prolonged action potential duration (APD), increased dispersion of refractoriness, and increased electrophysiological heterogeneity within the ventricular myocardium [3–6]. These changes, which are primarily due to an alteration in the function of ion channels, termed ionic remodeling, predispose to arrhythmias.

Various cellular and electrophysiological changes seen in hypertrophied heart constitute a favorable substrate for atrial and ventricular arrhythmias [7,8]. These changes manifest as action potential duration prolongation resulting in early and late afterdepolarizations and re-entry secondary to enhanced dispersion of APD and refractoriness [9]. Anisotropic conduction, increased intracellular calcium levels, and redistribution of gap junctions further predispose to re-entry [10–13].

1. Correlation of electrical remodeling with structural remodeling

Regression of hypertrophy is associated with reversal of the electrical remodeling in pressure overload states [14,15]. This is seen following treatment with ACE inhibitors and AT1 receptor blockers via a reversal of increased Na\(^+\)–Ca\(^{2+}\) exchanger (NCX) activity and an enhanced \(I_N\) (inward potassium current) [16]. In Lim’s transgenic disease model, calcineurin inhibition with cyclosporin prevented an increase in ventricular mass and myocyte size associated with pressure overload hypertrophy [6,17,18]. It also attenuated the APD prolongation in both subepicardial and subendocardial myocytes, although the APD did not normalize completely [6]. The calcineurin inhibition may have a direct effect on hypertrophy through inhibition of L-type calcium channels resulting in diminished intracellular Ca\(^{2+}\), which acts as a central point in hypertrophic signaling pathways [19]. Apparently, as shown by Peschar et al. [2] in this issue of the journal, the electrical remodeling that occurs in a bradycardia–volume overload state may be more persistent or permanent even after the volume overload is corrected.

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This raises the question of whether processes of electrical remodeling and myocardial hypertrophy are independent phenomena and are dissociated. It has been shown that an agent like cyclosporin A that reverses hypertrophy does not decrease the incidence of sudden death [19]. If it is not hypertrophy, then myocardial fibrosis and resultant electrical anisotropy, electrophysiological intramyocardial heterogeneity, and changes in intracellular calcium handling may be the underlying reasons for this electrophysiological remodeling and arrhythmogenesis. The changes in the collagen content, phenotype and cross-linking associated with myocardial fibrosis and remodeling [20] can be an important contributor to these electrophysiological changes.

The difference in the regression of electrical remodeling in pressure versus volume overload states is enigmatic. Upregulation of the NCX gene, NCX transcript, and proteins is essential in myocardial hypertrophy, but the NCX exchanger current (activity) is downregulated in hypertrophied myocardium [5]. In bradycardia-induced volume overload hypertrophy, studies have documented small increases in NCX exchanger activity [21]. There are also differences in structural remodeling associated with volume overload hypertrophy compared to pressure overload hypertrophy. The degree of eccentricity of hypertrophy, arrangement of the myocytes in relation to one another, and the spatial orientation of the myofibrils may play an important role in the heterogeneity of the electrical remodeling process seen in volume overload states. Moreover, the extent of collagen remodeling and its cross-linking nature may have an impact on the electrical remodeling process by an increase in the dispersion of refractoriness.

2. Unanswered questions and future goals

Further research is required to address several unanswered questions in the area of electrical remodeling. Do the extent and type of electrophysiological remodeling differ in the various types of volume overload states? Is the extent of APD-prolongation greater in volume overload states than in pressure overload states? The electrical remodeling in age-related myocardial hypertrophy is more persistent and this may be due to a greater prolongation of APD [22]. Does the aberration due to chronic pacing itself contribute to electrophysiological remodeling? The electrical remodeling seen in volume overload secondary to
complete heart block with a ventricular escape rhythm can result from the altered and aberrant conduction. We do not know whether remodeling changes in this model can be extrapolated to the changes in other volume overload states.

Current evidence suggests that electrical remodeling as well as reverse electrical remodeling depend upon the patterns of myocardial hypertrophy. In addition, electrical and structural remodeling and their reversal may be independent or interdependent based on certain circumstances. It is likely that both structural and electrical remodeling in hypertrophy should be considered clinically as independent processes, each playing an important role in the regression of hypertrophy and future occurrence of heart failure and fatal arrhythmias.

Studying the role of ionic remodeling in initiation and propagation of cardiac arrhythmias has significant relevance to antiarrhythmic therapy. Understanding the signal transduction mechanisms of channel downregulation could help in developing newer and more effective antiarrhythmic drugs. Further work is needed to understand the specific effects of individual ion channel remodeling, signal transduction mechanisms, and positive and negative consequences of ionic remodeling and to evaluate their therapeutic implications in the management of various cardiac diseases. For instance, increased NCX expression appears to improve diastolic function in patients with CHF [23]. Immune modulation may be an attractive option in the prevention and reversal of structural and electrical remodeling [24]. Elucidating the gene-specific novel targets for drug intervention would be another area to be explored [25]. In spite of extensive, ongoing research in this field, only a small proportion of the actual mechanism has been revealed. It would require a lot of effort and dedication to explore the intricacies of these remodeling patterns and to develop effective strategies to prevent or reverse potentially fatal arrhythmic complications.

References