Defining “Culprit Mechanisms” in Arrhythmogenic Cardiac Remodeling

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There has been increasing awareness of the importance of arrhythmogenic remodeling in the pathophysiology of cardiac arrhythmias. Arrhythmogenic remodeling, involving acquired changes in cardiac structure or function that promote the occurrence of cardiac arrhythmias, occurs in a wide variety of paradigms including congestive heart failure (CHF), atrial fibrillation (AF), hypertensive cardiac disease, acute myocardial infarction, and valvular heart disease. In many of these contexts, changes occur at many levels: ion-channel density, distribution, and function; ion-transporter (pumps and exchanges) function; connexin-protein density and distribution; tissue and cell structure; and cardiac-chamber dimension and shape. Progress in the identification of such changes has been impressive: in some cases, hundreds of alterations have been described in response to single well-defined experimental paradigms. A major resulting challenge is to determine which changes are particularly central to the pathophysiology of remodeling-related arrhythmias, and to establish therapeutic implications. In the present issue of Circulation Research, Verheule et al take advantage of a unique transgenic mouse model to address this issue.

Potential Role of Fibrosis in AF

Interstitial fibrosis has been associated with AF since at least the 1960s. Recent studies have demonstrated an association between atrial fibrous-tissue content, conduction abnormalities, and propensity to AF in animals with CHF, mitral regurgitation, and senescence. These observations point toward fibrosis-induced conduction abnormalities as promoters of local reentry and thereby AF. However, the evidence has been predominantly circumstantial. Other mechanisms, such as delayed afterdepolarization-related triggered activity, favored by the Na⁺-Ca²⁺ exchanger upregulation that occurs in CHF, could also play a prominent role.

Verheule et al studied mice engineered to overexpress a constitutively active mutant form of TGF-β1, causing atrial-specific interstitial fibrosis in the face of normal ventricular size and histology. The mice showed atrial conduction abnormalities and enhanced susceptibility to AF in the absence of abnormalities in atrial action potential properties or connexin protein distribution. These observations suggest that atrial fibrosis may itself create a substrate for AF, in agreement with recent studies showing that fibrosis and an AF substrate persist in atria of dogs that have recovered from CHF, despite the disappearance of CHF-induced ventricular dysfunction, hemodynamic alterations, atrial dilation, and ionic-current changes.

Potential Implications of Identifying “Culprit Mechanisms”

The prevention of arrhythmogenic remodeling is emerging as a potential new treatment strategy for cardiac arrhythmias. If individual components of the many remodeling-associated changes are shown to be particularly important in arrhythmogenesis, they may be worthy of specific targeting. Just as the “culprit lesion” in one coronary artery may be attacked in unstable angina syndromes, it may be possible to target the “culprit mechanism” in specific forms of AF. For example, the effectiveness of angiotensin-converting enzyme inhibition in attenuating fibrosis and AF promotion in experimental CHF led to the suggestion that angiotensin-antagonism might be useful in preventing clinical AF due to structural remodeling. Clinical trials have shown that converting-enzyme inhibition prevents AF in patients with left ventricular dysfunction, and further studies may lead to more effective and specific preventive approaches.

Potential Pitfalls

The idea of a single or limited number of primary mechanisms involved in arrhythmia generation is attractive in its simplicity and tractability; however, reality may prove much more complicated. When an experimental paradigm apparently isolates a single primary factor, like atrial fibrosis in the TGF-β1 mice or dogs recovered from CHF, it is tempting to identify that factor as established. However, more evidence is needed before fibrosis can be confirmed as causal in AF. It remains conceivable that fibrosis simply accompanies other as-yet unidentified causative factors. The efficacy of angiotensin antagonism in preventing AF associated with left ventricular dysfunction is consistent with the fibrosis hypothesis, but the observation that AF is also prevented by angiotensin-receptor antagonists and converting-enzyme inhibitors in patients without clear left ventricular dysfunction means either that angiotensin-related structural remodeling is a common feature in AF or that other mechanisms may be involved.
Determining the Significance of Specific Remodeling-Induced Changes

Paradigms that cause arrhythmogenic remodeling produce a wide range of alterations in cardiac structure and function. Many of these likely contribute little to the arrhythmia diathesis. Conversely, key arrhythmogenic factors may remain unidentified. Atrial-tachycardia remodeling provides illustrative examples. Atrial tachycardia alters a number of ionic currents, disrupts cellular ultrastructure, impairs atrial contractility, affects the function of many biochemical systems, and may alter intercellular communication via connexins.3,25–27 Which of these many changes plays a role in arrhythmogenesis? Although downregulation of L-type Ca2+ channels is likely involved in the refractoriness abbreviation that contributes to AF promotion, discrepancies in the time-course of refractoriness changes and AF development3,28 suggest the involvement of other factors that remain to be identified. What is the potential role of increases in inward-rectifier currents that are upregulated by atrial tachycardia,29,30 particularly in view of the potentially key role of inward-rectifier currents in ventricular fibrillation?31 What is the mechanism and importance of accelerated activity in the thoracic veins?32 These and other questions need to be answered to develop effective new mechanism-based therapies.

Conclusions

Over the past 5 to 10 years, we have been very successful in describing a host of changes that occur in arrhythmogenic remodeling. We have been less successful in determining which ones matter. We will have to do better in order to improve our understanding of underlying mechanisms and to develop more successful treatment approaches. The Verheule study published in this issue of Circulation Research is a step in that right direction.

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References


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