Editorial

Fibrosis, Myofibroblasts, and Atrial Fibrillation

Bruce H. Smaill, PhD

There can be little doubt about the association between interstitial fibrosis and heart rhythm disturbance. In patients with cardiomyopathy, the extent of myocardial fibrosis has been linked with arrhythmic burden and risk of sudden cardiac death. In atrial fibrillation (AF), the relationship between fibrosis and electric dysfunction seems, if anything, to be even stronger. This is driving ongoing attempts to stratify the risk of sudden cardiac death and stroke from estimates of the extent of interstitial fibrosis derived from magnetic resonance images of the heart. What remain unclear are the mechanisms responsible for the association between fibrosis and propensity for re-entrant arrhythmia.

Features of the electric dysfunction that contributes to increased risk of sudden cardiac death or sustained AF have been widely reported in the clinical literature. These include slow activation, dispersed refractoriness, fractionated electrograms, and low frequency repolarization alternans. Laboratory studies on hearts explanted from patients in end-stage heart failure undergoing heart transplantation or from animal heart disease models replicate the observations above but also provide more detailed information about impulse propagation in the presence of ventricular fibrosis. Conduction velocity is preserved in the myofiber direction, but propagation transverse to this is both slower and more rate-dependent. Comparable studies in the atria are less easy to interpret because regional variation in myofiber architecture is much greater than in the ventricles. However, electric anisotropy increases with age-related fibrosis in human pectinate muscle bundles and interstitial fibrosis may also cause electric dissociation between the epicardial layer and endocardial muscle bundles in the atria, increasing the complexity of AF.

These alterations in electric behavior have been viewed as a consequence of the increased electric anisotropy and nonuniform electric properties that accompany fibrosis. In this paradigm, slow activation and fractionated extracellular potentials are the result of tortuous electric propagation and focal activation delay. This is caused by physical barriers to propagation, as well as rate-dependent conduction slowing and block because of electric source–load mismatch. Biophysically based computer models indicate that these mechanisms are sufficient to account qualitatively for many aspects of the electric dysfunction associated with fibrosis. Non-uniform discontinuities which resemble patchy fibrosis seen in many forms of heart disease give rise to activation- and repolarization-time dispersion, spatially discordant alternans rhythm and wavebreak.

A possible mechanism, which has attracted considerable attention of late, is the modulation of impulse transmission by electrotonic coupling between cardiac myocytes and fibroblasts. Fibroblasts form a network of interconnected cells within the cardiac extracellular matrix and can also convert to activated fibroblasts or myofibroblasts. Both are electrically passive, with a membrane potential that is less negative than resting cardiac myocytes and more negative than the cardiac action potential throughout most of its duration. There is also evidence for bidirectional electric coupling via gap junctions among cardiac fibroblasts, myofibroblasts, and myocytes. Depending on the level of this coupling, the fibroblast/myofibroblast network could act as an electric source for cardiomyocytes during diastole and as a sink during activation. On this basis, it has been argued that fibrosis probably causes conduction velocity slowing, because of partial membrane depolarization of resting myocytes and inactivation of sodium channels, and also accelerates repolarization. These predictions have been confirmed in cardiac myocyte fibroblast coculture experiments. Furthermore, sophisticated image-based computer models suggest that coupling between myocytes and fibroblasts could account for complex fractionated electrograms, repolarization alternans, and the maintenance of AF in fibrotic atria. However, a qualification should be made here. The coculture experiments were performed in preparations with high myofibroblast densities, where gap junction coupling was greater than between fibroblasts and myocytes. Also, related computer models assume electric coupling consistent with myofibroblasts rather than fibroblasts. Although cardiac myofibroblasts are formed during myocardial injury, the extent to which they are expressed in chronic fibrosis is not established.

The article by Krul et al in this edition of Circulation: Arrhythmia & Electrophysiology is the first, as far as I am aware, to address the relationship between atrial fibrosis, fibroblast activation, and impulse propagation using atrial tissue. Activation mapping has been performed in left atrial appendages, excised from patients with AF. Collagen organization was quantified, together with fibroblast and myofibroblast distributions. The authors show that activation delays were more prolonged in left atrial appendages with thick layers of interstitial collagen between myocyte bundles than in preparations with a more diffuse distribution of fibrosis. The former were acquired from patients with persistent AF in almost all cases and were
associated with increased fibroblast densities. However, in these preparations, longitudinal conduction velocity was increased rather than reduced, whereas myofibroblasts were not detected in any left atrial appendage specimens.

Aspects of this study are certainly open to criticism. For instance, its power is reduced by inherent limitations in experimental design. The research was performed in the left atrial appendage only, numbers are relatively small with no controls, and patients have varying ages, disease characteristics, and medication histories. Finally, the authors have not demonstrated that there is no electric interaction between fibroblasts and myocytes. The important feature of this work is that the authors have sought to test a widely held premise based on studies with model systems (both cell culture and computational physiology) by comparing predictions with observations in fibrotic atrial tissue. An integrated approach incorporating such information is necessary, if we are going to develop a robust understanding of the mechanisms that link fibrosis, fibroblasts, and atrial arrhythmia. I look forward to further, more systematic, experimental, and translational studies along these lines.

Disclosures

None.

References


KEY WORDS: Editorials • atrial fibrillation • fibroblasts • fibrosis
Fibrosis, Myofibroblasts, and Atrial Fibrillation
Bruce H. Smaill

Circ Arrhythm Electrophysiol. 2015;8:256-257
doi: 10.1161/CIRCEP.115.002881

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circep.ahajournals.org/content/8/2/256