Mounting Evidence That Fibrosis Generates a Major Mechanism for Atrial Fibrillation

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It is widely known that atrial fibrillation (AF) is the most common sustained cardiac arrhythmia, with the problem magnified by the clinical sequelae; e.g., thromboembolic events. It is pertinent that the incidence of AF is expected to increase in the future, especially in aging patients. Thus, finding preventive measures for this arrhythmia has become an increasingly important goal. In addition to considering clinical risk factors, focusing on prevention necessitates knowledge of the associated pathophysiology of AF, which involves the initiation of AF and the wavefront dynamics that sustain it.

In recent years considerable new information has appeared concerning AF mechanisms that occur in different regions of the atria in different cardiac states. This point is highlighted by the report of Tanaka et al in this issue of *Circulation Research*. These authors used high-resolution electrophysiological and microstructural techniques, along with computer model simulations, to study wavefront dynamics during acetylcholine (ACh)-induced AF in heart failure sheep hearts. The heart failure hearts had developed prominent fibrotic patches in the posterior left atrium near the pulmonary veins, whereas in the control (normal) hearts patches of fibrosis were smaller, diffusely distributed, and more centrally located with respect to the 4 pulmonary vein ostia. In the heart failure hearts, during AF variable wavefront breakthroughs to the endocardium occurred in the area of fibrotic patches adjacent to the pulmonary veins. The authors concluded that scroll waves within the posterior left atrial wall produced a microreentry source for the endocardial breakthroughs in the region of the larger collagen patches, thus providing the underlying mechanism of AF.

A myriad of reports provide varied information about substrates and mechanisms of AF as a background for the study of Tanaka et al. To simplify, a minimum degree of complexity of AF factors is considered here (Figure); i.e., ionic currents, atrial anatomy, fibrosis, and wavefront dynamics.

**Stepwise Increase in Information About AF Electrical Activity**

Wiggers comment in 1940 is worth noting because it provides a recurrent theme for fibrillation mechanisms since then: “As to the fundamental mechanism of fibrillation we have plenty of theories, but none is universally accepted. Space is lacking to review the different hypotheses, but we may note in passing that they all center around two ideas, viz., (a) that the impulses arise from centers, or pacemakers, or (b) that the condition is caused by the re-entry of impulses and formation of circles of excitation.”

Scherf’s aconitine experiments subsequently indicated that AF was attributable to “rapid impulse formation in a single center.” For different conditions, in 1964 Moe et al reported their widely known computer model results, which indicated that “multiple wavelets” produced AF. Over 2 decades later Allessie et al demonstrated in human and canine atria that multiple interactive wavelets of macro size supported Moe’s theory of AF. Schuessler et al then expanded reentrant mechanisms by demonstrating that a single rapid reentrant circuit can produce multiple wavelets in ACh-induced AF. Haïssaguerre et al subsequently reported in 1998 that in humans AF frequently is initiated by repetitive activity in the pulmonary veins, and ablation of these areas abolished AF. Since then, triggered activity within small areas has been considered important in both the initiation and maintenance of AF. With respect to repetitive activity in small atrial areas, however, Mandapati et al demonstrated in healthy sheep hearts that repetitive reentry in the posterior left atrium near or at pulmonary vein ostia can produce microreentrant sources for AF. Consequently, a challenge at present is to clarify whether the mechanism is triggered activity versus microreentry as the source of repetitive activity within small atrial areas.

In regard to repetitive activity, the results of Tanaka et al may be clinically relevant because their results in sheep hearts had similarities to those of Wu et al in humans with permanent AF. The patients with AF also demonstrated rapid repetitive activity in the posterior left atrium near or at the pulmonary veins. However, both Tanaka et al and Wu et al were unable to resolve whether microreentry versus focal discharges produced the rapid repetitive activities they found. Interestingly, associated computer simulations by Tanaka et al predicted that whether the AF was attributable to reentry or focal discharges, the larger fibrotic patches in heart failure had the major effect on AF wavefront dynamics. Thus, it is worth looking at some of the remodeling features of 2 common AF conditions, heart failure and aging, to answer questions about the origin of AF mechanisms.

**Atrial Ionic Remodeling With Heart Failure and Aging**

Li et al showed that atrial ionic remodeling during experimental heart failure decreases ICa,L and IK and increases the
Na⁺/Ca²⁺ exchanger current (NCX), while leaving other currents unchanged. There was no associated decrease in action potential duration (APD), which suggested other mechanisms of AF promotion. However, Li et al.14 noted that the increase in NCX with heart failure may be important in the initiation of AF because NCX currents are known to cause triggered activity. As to aging, ionic remodeling primarily affects repolarization currents with increased interregional dispersion of AP duration.15 In aged canine atria, Dun et al16 found decreased available Ca²⁺ currents whereas K⁺ currents were augmented. Baba et al.17 further showed slight enhancement of INa use dependence in the right atrium but not left atrium, and there was no remodeling of the Na⁺ current protein.

Remodeling Atrial Collagen (Fibrosis) With Heart Failure and Aging

As to a mechanism other than ionic remodeling for AF associated with heart failure, Lie et al.18 showed in canine hearts that the key change appeared to involve alteration in local atrial conduction properties caused by interstitial fibrosis. Thus, what are some of the known local conduction abnormalities associated with atrial fibrosis?

We found premature stimuli to initiate anisotropic conduction abnormalities that led to reentry within areas as small as 1.6 mm² in aging human atrial bundles.19,20 There were 2 major underlying conduction disturbances that produced the reentry in such a small area: one was a very low effective velocity with conduction across fibers (as low as in the AV node), and the other was decremental conduction to failure. Similar conduction disturbances and reentry did not occur in younger adult bundles. These conduction differences were related to the aging proliferation of connective tissue septa. In the younger adult bundles collagenous septa were short and scattered, whereas in bundles over 60 years of age there were extensive lengthy collagenous septa (microfibrosis). As to electrical mechanisms, collagenous septa mark areas in which there is an absence of side-to-side coupling between fibers.19 Interestingly, Miragoli et al21 recently demonstrated effects on conduction of high density myofibroblasts in cultured strands. The density of myofibroblasts and their effects provide an unexplored area in diseased hearts with collagenous septa.22

Electrophysiologically, we have considered fibrosis to be an abnormality of gap junctions with regard to their distribution because of the loss of cellular connectivity across areas of collagen deposition.19,20 When wavefronts propagate in a direction to cross collagenous septa, there is no cell-to-cell coupling between fibers on each side of the septa. Thus, these sites produce an obstacle by breaking the intracellular component of the circuit of currents necessary for the propagation of depolarization. A recent computer model of human aging atrial microstructure with collagenous septa20 reproduced the experimental results19 after premature stimuli, both the conduction disturbances and “microreentry”. The conduction events were related to INa-fibrosis interactions in which variations in the magnitude of INa were associated with decremental conduction (decreasing INa) that either failed (no INa turn-on) or led to incremental conduction (increasing INa).20 However, experimental techniques are not yet available to measure INa during propagating depolarization. Until such experimental measurements are achieved, use of computer microstructural models provides a promising alternative to gain insight to arrhythmogenic INa-microstructural interactions.

Although the precise signaling processes involved in the development of atrial fibrosis are unknown, the molecular pathways involved are beginning to emerge. The potentially important role of TGF-beta1 and the renin-angiotensin system in AF is presented in a recent article by Everett and Olgin.23 Thereby, the results of Tanaka et al 4 in this issue of Circulation Research provide an additional stimulus to resolve important unanswered questions about the origin of fibrosis and its electrical effects that enhance atrial fibrillation.

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None.

References


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