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AGING AND AF RESEARCH: WHERE WE ARE AND WHERE WE SHOULD GO

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Aging involves a relentless and systematic process of degeneration in living organisms leading to attenuation of most biochemical and physiological functions.¹ Further, aging is associated with a variety of diseases, including cardiovascular and neurodegenerative disorders, cancer and diabetes.^{1,2} It is now well known that aging also increases the propensity for occurrence of atrial arrhythmias, particularly atrial fibrillation (AF).³ However, the underlying mechanisms remain poorly understood. The atrial myocardium undergoes electrical and structural remodeling with age, both of which may play important roles in the initiation and/or perpetuation of atrial tachyarrhythmias.⁴

Age related electrical changes due to ionic current alterations include modifications in the cellular action potential shape and duration, as well as an enhanced dispersion of cardiac repolarization.^{4,5} Structurally the most important change in aged atrial bundles is an enhancement of the fibrous tissue interspersed between myocytes.⁶ In fact, fibrosis is ubiquitous in the atria of the aging heart. Cardiac fibrosis is characterized by excessive accumulation of fibrillar collagen in the extracellular space. It may result from cardiomyocyte loss (replacement fibrosis) or as an interstitial response to chronic diseases such as hypertension, myocarditis, and congestive heart failure (reactive fibrosis).^{7,8} For many years it has been known that interstitial fibrosis reduces the electrical coupling in the heart. In addition, it significantly increases the complexity of the myocardial architecture by electrically insulating cardiac cells and/or muscle bundles. A direct consequence is that the typical uniform anisotropic conduction in the atrial myocardium is now replaced by non-uniform anisotropic conduction.^{9,10} It has been shown that this fibrosis preferentially affects the lateral (or transverse), rather than longitudinal cell-cell connections, giving rise to a much slower and zig-zag transverse propagation, which manifests itself as fractionated extracellular electrograms.¹¹ Thus a premature response occurring in the aged atrial myocardium has a higher probability of undergoing unidirectional block due to an imbalance between source/sink currents, and initiating reentry because of the underlying arrhythmogenic substrate created as a result of the electrical and/or structural remodeling.

An inherent enhanced dispersion of repolarization is, however, not an absolute requirement for the initiation of arrhythmias, since such heterogeneities may also be created dynamically in the atrium, for instance, if it is being driven at very fast rates.¹² In this issue of *Heart Rhythm*, Spach and colleagues take this concept a step further,¹³ by showing that even in the absence of an intrinsic or dynamic electrical heterogeneity, increased microfibrosis can cause a

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propagation failure due to a source/sink mismatch, and under the appropriate conditions give rise to arrhythmogenic conduction responses. In experiments conducted on small pieces of old isolated human atrial tissue, the authors observed that an appropriately timed premature stimulus given at the same site where previous stimulation initiated a normal impulse propagation, gave rise to extracellular electrograms which were indicative of either (a) longitudinal propagation in the retrograde direction lateral to the site of stimulus, or (b) reentrant activation. To understand the underlying mechanisms, the authors first estimated in their preparation the amount of collagenous septa experimentally, and then utilized this information to construct a detailed two-dimensional (2D) mathematical model of the atrial syncytium, based on a strategy followed earlier for ventricular cells.¹⁴ The 2D model incorporated realistic cell geometry, transmembrane ionic currents found in the human atrium,¹⁵ and intercellular connections (or lack thereof due to interstitial fibrosis), but, the electrical properties were homogeneous throughout. By mimicking the experimental stimulus protocol at different sites within the 2D sheet, the authors were able to reproduce/simulate the arrhythmogenic conduction patterns as recorded in the isolated human atrial tissue. Further examination into the underlying mechanism suggested that the inward sodium (but not calcium) current was the major determinant of the pattern of propagation, and its interaction with the variable microstructural load (or sink) due to the fibrosis resulted in either microreentry or delayed retrograde conduction lateral to the site of stimulus. A key feature of either of these responses involved the so-called “conduction gating”, which has been defined earlier as the process of resumption of degraded conduction.¹⁶

These intriguing results provide further support to the hypothesis that structural remodeling is a key determinant, and by itself can initiate AF, without the need for preexisting repolarization gradients. Yet, many questions remain. One interesting observation by the authors was that the patients from whom the atrial bundles were isolated for experimental studies were devoid of any incidence of atrial arrhythmias. Does this reflect the possibility that ionic changes (remodeling) and subsequent heterogeneities even in such a small piece of tissue may indeed be important for the initiation of arrhythmias? Further, as acknowledged by the authors, since the so-called conduction gating is key to explaining the arrhythmogenic patterns, more detailed studies of subthreshold events and their underlying ionic mechanisms are necessary. These should include the potential role of ionic currents such as the inward rectifier K^+ current (I_{K1}), which has been found to be upregulated in chronic AF conditions,¹⁷ and is an important determinant of the threshold for excitability.¹⁸ The relationship of the slow microreentry generated via the mechanism postulated in this study to the fast rotors that are thought to underlie AF maintenance¹⁹ also remains unclear. Lastly, an important question that remains unaddressed is whether an electrical connection between fibroblasts and myocytes exists in the atrium *in vivo*. There is some evidence for the same in aggregates of neonatal cultured rat ventricular myocytes,²⁰ and in the sinoatrial node.²¹ This is important because even though fibroblasts may be electrically unexcitable, by means of their depolarized resting membrane potential,²² they may be able to provide considerable sink (electrical load) to viable atrial myocytes if found to be coupled. Ultimately, answers to these and related question may help in designing better antiarrhythmic strategies aimed at targeting and possibly reversing the structural and electrical remodeling, thereby preventing the initiation/maintenance of AF.

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