Reentry and atrial fibrillation

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The mechanisms of human atrial fibrillation (AF) are poorly understood. Experimental studies have demonstrated that cholinergic AF in the sheep heart is maintained by high-frequency reentrant sources (drivers) that result in a consistent left-to-right frequency gradient. More recently, clinical studies have confirmed the existence of a hierarchical organization in the rate of activation of different regions in the atria of patients with paroxysmal and chronic AF. Although maximal dominant-frequency sites were found to play a crucial role in the maintenance of AF in some patients, whether AF drivers in humans are focal or reentrant and whether changes in driver activity alter spatial frequency gradients are unclear. To test the hypothesis that localized functional reentry maintains AF in humans, we determined the effects of adenosine infusion on local dominant frequency at different sites of both atria. In patients with paroxysmal AF, adenosine infusion increases local dominant frequencies, particularly at the pulmonary vein–left atrial junction region, amplifying a left-to-right frequency gradient. In patients with chronic AF, dominant frequency is significantly higher than in patients with paroxysmal AF in all atrial regions surveyed, with the highest adenosine increase of frequencies outside the pulmonary vein region. Adenosine-induced driver acceleration is strongly suggestive of a reentrant mechanism in both groups of AF patients.

KEYWORDS Adenosine; Inward-rectifying potassium channels; Rotors; Wavebreak; Pulmonary veins-left atrial junction

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Atrial fibrillation (AF) is the most common arrhythmia seen in clinical practice.[1] It accounts for approximately one third of hospitalizations for cardiac rhythm disturbances and is associated with an increased long-term risk of stroke, heart failure, and all-cause mortality.[1] AF prevalence continues to increase due to a combination of factors, which include aging of the population, the rising prevalence of chronic heart disease, and the recent increase in survival rates from other cardiovascular diseases.[1,2] As a consequence, AF represents an extremely expensive public health problem, with an estimated overall cost of approximately $15.7 billion in the United States alone.[3] Unfortunately, medications aimed at suppressing AF and maintaining sinus rhythm (rhythm control) or at controlling ventricular rate (rate control) usually are not effective and may cause serious adverse effects.[4] The limitations of pharmacologic treatment have fueled the development of new interventional strategies, including radiofrequency (RF) ablation. Current techniques of RF ablation can achieve a 60%–80% improvement in highly selected patients with medically refractory AF. However, the procedure is not without risk; it is long-lasting, and recurrence rates still are high. Moreover, the results in patients with chronic AF are far from optimal, requiring the creation of extensive atrial lesions and use of repeated procedures to attain a success rate of 50%–60% without antiarrhythmic drugs.[1] Currently, the application of RF is primarily guided by the anatomy and is secondarily assisted by local electrical activity, although considerable variance exists among laboratories with regard to both the ablation procedure methodology and the results.

Arguably, the main explanation for our current disappointing ability to control AF is an incomplete understanding of the mechanism(s) underlying its maintenance, despite many years of research and speculation.[5] Over the past 50 years, the multiple wavelet hypothesis has been the dominant mechanistic model of AF.[6–8] The hypothesis, first postulated by Moe et al,[7] states that AF is the result of randomly propagating multiple electrical wavelets that interact in very complex ways, with local excitation limited by the heterogeneous distribution of refractory periods throughout the atria.[6,7] This concept was challenged by the observation in patients made by Haissaguerre et al[8] that a rapidly firing excitation source located inside or close to one of the pulmonary veins (PVs) could also be responsible for initiating, and in some cases maintaining the arrhythmia, particularly in patients presenting with paroxysmal AF.[8] However, whether the electrophysiologic mechanisms underlying such rapid discharges is enhanced automaticity, triggered activity, or even microreentry is unknown.[9] Optical mapping studies in isolated sheep hearts have suggested that at least some cases of AF can be maintained by high-frequency reentrant sources (rotors), usually located in the posterior left atrium (LA), which result in spatially distrib-

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uted frequency gradients.[9–13] According to the so-called *rotor hypothesis,* rapidly succeeding wavefronts emanating from an ectopic focus in a PV may break, when conditions of heterogeneity are appropriate, and initiate two counter-rotating vortices (i.e., rotors).[9] Eventually, only one of the rotors survives and becomes the high frequency engine that maintains AF through fibrillatory conduction to the remainder of the atria.[6,9] Thus, focal triggers at or near a PV may initiate rotors as a consequence of abnormal impulse conduction and wavebreak. A rotor that anchors anywhere in the atria, and generates spiraling waves at an exceedingly high frequency, may become the dominant source that maintains AF.[9–13]

Posterior LA–PV junction and the substrate for AF maintenance

Several studies performed in humans analyzed the electrophysiologic characteristics of the PVs and the LA junction and other atrial regions and demonstrated distinctive electrophysiologic properties in the PVs of patients with AF.[14–21] These studies showed the following. (1) Distal PVs have shorter refractory periods than do the proximal PVs, the atrial junction, and the LA appendage.[15,20,21] (2) The likelihood of AF induction is higher with distal PV extrastimulation.[21] (3) Directional conduction delay is present within the PV, with more frequent and greater likelihood of intermittent conduction block patterns to the LA,[20,21] most likely due to tissue expansion and source to sink mismatch. (4) The PVs possess both anisotropic conduction and repolarization heterogeneity, with evidence of reentry in response to extrastimulus testing.[17,21] Thus, the significant differences in the electrophysiologic properties in the PVs and PV–LA junction provide a fertile substrate for reentry within or around the PVs. However, these data do not provide direct evidence that reentry is the mechanism that maintains AF.

The thoracic veins and especially the PVs contain discrete myocytes fascicles that are electrically connected to the atria. In some cases, such fascicles spontaneously generate electrical impulses.[8,14,15] Several electrophysiologic mechanisms may explain the origin of such activity: abnormal impulse formation (automaticity), abnormal focal activity (afterdepolarizations), or abnormal impulse propagation (reentry). Experiments have demonstrated a high incidence of spontaneous rhythms, enhanced automaticity, and occurrence of early and delayed afterdepolarizations in the PVs, particularly in response to atrial distension, rapid atrial pacing, or congestive heart failure.[14] Moreover, the PVs and the posterior LA wall provide the electrophysiologic milieu capable of sustaining reentry.[15–17,21] The specific action potential configuration of the PV cells, with slower upstroke phase 0 and slower duration, leads to a shorter refractory period and a slower conduction velocity.[19] The architecture of the PVs and the LA junction provide preferential zones for reentry. The complex geometric arrangement of cardiac fibers around the veins with changing myocardial fiber orientation and the poorly coupled cardiac tissue overlying vascular smooth muscle seem to be an ideal substrate for unidirectional conduction block and for initiation of wavebreaks and sustained reentry.[16] Optical mapping studies in animal hearts have consistently demonstrated that AF is maintained by functional micro-reentry, in most cases localized to the posterior LA wall and the PV–LA junction.[9–13,18] Ionic differences in the channel distribution between the atria, responsible for the shorter action potential duration and effective refractory period in the LA, also favor reentry and may help to explain the preferential anchoring of rotors to the posterior wall and PV–LA junction.[19]

Role of the PVs and posterior wall in AF maintenance

The vast majority of atrial premature beats that initiate frequent paroxysms of AF originate in the PVs.[8] However, with the exception of some cases of rapid focal discharges with distal-to-proximal activation of the PV representing the true focally driven AF, the main role of these extrasystolic beats and rapid rhythms is triggering AF.[20] The results of PV isolation performed during ongoing AF have provided novel insights that underscore the important role of not only the PVs but also the LA junction. The focal ablation approach to eliminate AF triggers that initially was used is effective in less than 50% of patients because other nontargeted locations/veins may act as triggers.[22] This led to the development of the segmental ostial ablation technique, which aimed to electrically isolate the PVs.[23] After sequential PV isolation, progressive prolongation of the AF cycle length was obtained, culminating in AF termination in a significant proportion of patients with paroxysmal AF.[23] These results provided conclusive evidence for the direct participation of PV activity in the maintenance of AF. However, a randomized study showed that a more extensive ablation, which included the LA–PV junction area and the posterior wall, was more effective in preventing recurrences than was pure electrical PV isolation.[24] Several findings support the critical role of the posterior wall in AF maintenance. First, despite the high prevalence of dissociated spontaneous rhythms following PV electrical isolation, sustained PV tachycardias spontaneously occur or can be induced in only 2%–6% of patients. Thus, there seems to be a dynamic interplay between the LA and PVs during AF, with PV tachycardia depending on input from the LA.[25] Second, AF termination during PV isolation frequently occurs prior to complete electrical isolation of the vein is obtained. Elimination of the substrate needed for a reentrant circuit to be sustained is the most likely explanation for this finding. Finally, ablation of sites of short cycle length activity in the posterior LA leads to termination of the arrhythmia both in experiments and in humans.[26,27] Thus, these data point to reentry involving both the PVs and the LA junction as the most likely mechanism sustaining AF in some cases of paroxysmal AF, but more conclusive evidence is needed.