EDITORIAL COMMENT

Pulmonary Veins in the Substrate for Atrial Fibrillation

The “Venous Wave” Hypothesis*

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Atrial fibrillation (AF) is classically proposed to result from multiple wandering atrial wavelets (1,2). However, recent experiments by Jalife et al. (3) have implicated an additional role for single micro-re-entrant circuits within the left atrium in AF.

The pulmonary veins (PVs) are an important source of spontaneous electrical activity that initiates AF (4–6). Such activity may also manifest in isolated extrasystoles or slow/rapid atrial rhythms (4–6). In addition, rapid focal discharges (sustained sometimes for hours, days, or even longer) have been observed to drive sustained AF in some patients, representing the true “focal or focally driven” AF (7). High-density mapping at the time of surgery in patients with chronic AF has identified rapid activity emanating from the PV region (corners of the mapping plaque) continuously, intermittently, or alternately (8). Other studies have observed episodic bursts of paroxysmal short-cycle-length activity with a distal-to-proximal activation of the PV, suggesting that these bursts may have a role in AF maintenance (9–12).

The mechanisms (automaticity or re-entry) by which these structures are arrhythmogenic are the source of intense investigation, with recent studies expanding our understanding of the electrophysiologic properties of the PV.

Electrophysiologic mechanisms of PV arrhythmogenicity. Evidence exists to suggest that the PVs are capable of sustaining automaticity. Blom et al. (13), studying the human embryo using monoclonal antibodies to stain conducting tissue, demonstrated the presence of cardiac conduction tissue within the PV during embryonic development. However, although node-like cells have been observed in the PVs of rats, a detailed histology of the atrial myocardial sleeves in human hearts has thus far failed to reveal any node-like structures. Cheung (14) found spontaneous activity from the PV with digitalis in the guinea pig. Other experiments have demonstrated early and delayed after-depolarization and automatic high-frequency irregular rhythms related to calcium-sensitive inward currents following infusion of ryanodine, atrial distension, rapid atrial pacing, or congestive heart failure, but most groups have not observed these in normal PV cardiomyocytes (15–19).

A possible role for re-entry has been implicated in the genesis of spontaneous activity from the PV in connection to complex muscular architecture and short cellular refractoriness. Conduction delay and block have been associated with changing myocardial fiber orientation, producing non-uniform anisotropy and fractionated electrograms in PVs and at the PV-left atrial (LA) junction (19,20). Arora et al. (21), performing optical mapping studies of normal canine PVs, demonstrated that these structures possess both anisotropic conduction and repolarization heterogeneity. With extrastimulus testing Arora et al. (21) observed regions of unidirectional conduction block and slowed conduction that initiated leading-circle re-entry and became sustained with isoproterenol. Focal sources of activity were observed to occur more proximally.

Clinically, ectopy-initiating episodes of AF have been largely localized to the distal PV musculature from multiple PVs or from multiple sites within a given PV (22), which after isolation could occur proximal to the ablated site (23). Chen et al. (5) demonstrated that the distal PV had significantly shorter refractory periods than the adjacent LA. Jaïs et al. (24) demonstrated distinctive electrophysiologic properties in the PVs of patients with AF (compared with controls), with shorter PV refractory periods, more frequent and greater decremental conduction to the LA, and a propensity for PV extrastimuli to initiate AF. At shorter coupling intervals there was an increased complexity of the circumferential activation sequence, with fractionation, double potentials, and a change in the LA breakthrough (24).

Expanding ablation strategies have improved our knowledge, demonstrating that the PVs are electrically connected to the atria by discrete or wide fascicles, allowing complete electrical isolation of the PV by ostial ablation. Following electrical isolation, dissociated spontaneous rhythm within the PV has been observed in up to 33.6% of the PVs, whereas sustained PV tachycardia occurred spontaneously or could be induced in 2.6% to 6% of patients with features suggestive of either automaticity or re-entry (the latter suggested by the induction and termination with stimulation, a large proportion of the tachycardia cycle length being mapped within the PV, and progressive fusion during entrainment maneuvers) (25). The low incidence of PV tachycardias after disconnection suggests an important role for the PV-LA interface or atrial inputs in the development of sustained arrhythmia.

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In a study reported in this issue of the *Journal*, Kumagai et al. (26) provide further evidence supporting a re-entrant mechanism for arrhythmia originating from the PVs. The authors confirm several of the electrophysiologic properties previously reported in experimental and clinical studies. In addition, they used a 64-pole basket catheter to identify the mechanisms resulting in PV arrhythmogenicity in humans: 1) a gradient of refractoriness that increased from the distal to proximal PV; 2) directional conduction delay within the PV; 3) preferential conduction within the PV with both programmed extrastimuli and spontaneous ectopy from the PV; 4) exit and entry of the activation front at the PV-LA junction; and 5) short-lived circuits (up to two rotations). Although this finding expands our understanding that the PVs in humans with AF possess the substrate for re-entry, the authors acknowledge that it does not provide direct evidence for re-entry having a critical role in the mechanisms of AF. This study has other limitations inherent to clinical electrophysiology studies: 1) limited mapping density; 2) short duration of activation analysis; and 3) absence of data correlating the findings with individual or paired PV. Nevertheless, the authors demonstrate the existence of preferential and re-entrant activation fronts within the PV and at the PV-LA junction.

**PVs in the maintenance of AF.** Pulmonary vein isolation performed during ongoing AF has revealed novel insights. We performed PV ablation in patients with long-duration spontaneous or induced AF while monitoring the atrial fibrillation cycle length (AFCL) at a site remote to ablation (coronary sinus) (27). Pulmonary vein isolation produced a progressive prolongation of the AFCL, varying in extent from vein to vein and between individuals, culminating in AF termination in most patients after a significant cumulative increase in the AFCL. This decline in AF frequency was less in patients without AF termination. There was a significant relationship between the number of PVs requiring isolation to achieve termination and the initial duration of AF, but no correlation with the amount of radiofrequency energy delivery. Strikingly, AF could not be re-induced after PV isolation in 57% of patients despite repetitive and aggressive burst pacing from up to three atrial sites; patients without inducible arrhythmia demonstrated significantly greater prolongation of AFCL during ablation.

The progressive decline of fibrillatory activity with PV ablation provides conclusive evidence for the direct participation of PV activity in the maintenance of AF. Pulmonary vein isolation not only prolonged AFCL but terminated AF as previously observed during pharmacologic cardioversion (thought to represent fusion or reduction of wandering atrial wavelets). Accumulating evidence, as in the study by Kumagai et al. (26), demonstrates that the PV and the PV-LA junction provide the electrophysiologic milieu capable of sustaining re-entry. Our results extend these observations by providing direct evidence that the activity perpetuating AF emanates from the PV region in some patients with paroxysmal AF. We posit an alternative hypothesis to the classical multiple wavelet mechanism proposed by Moe (1): that in at least some patients with AF the PV is the source of fibrillatory activity that maintains the atria in fibrillation—the “venous wave hypothesis” (Fig. 1).

**Conclusions.** An accumulating body of evidence demonstrates that the PV-LA region has heterogeneous electrophysiologic properties that are capable of sustaining re-entry. These structures are implicated not only as a trigger of AF in patients with the appropriate substrate, but also as a source of “venous waves/drivers” that are capable of maintaining the atria in fibrillation.

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REFERENCES