EDITORIAL COMMENT

Mapping Atrial Fibrillation

Uncertainty Despite Resolution*

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Atrial fibrillation (AF) affects more than six million people in the U.S. alone. It has been estimated to cause nearly 40% of all strokes in patients older than 70 years of age (1). Billions of health care dollars are spent each year on the care of patients with this arrhythmia and its sequelae. The incidence of AF increases with age and the coexistence of cardiomyopathy. With the aging of our population and improved longevity of patients with cardiomyopathy, the impact of AF on health care expenditures will continue to increase. Despite the human and economic importance of this clinical problem, many questions remain about the pathophysiology of AF and, as a consequence of this uncertainty, the most effective treatment. In this issue of the Journal, Okuyama et al. (2) attempt to address this void of knowledge with an investigation of the electroanatomical pattern of induced AF in a canine model of heart failure (HF). In particular, the investigators have tested the hypothesis that physiological and structural changes in the pulmonary veins and the vein of Marshall contribute to the increased stability of AF.

MECHANISM OF AF

A central question about the pathophysiology of AF that has reemerged is whether reentry of excitation wave fronts or focal excitation with “fibrillatory conduction” is responsible for its initiation and maintenance. Moe (3) was the first to advance the notion that multiple reentrant circuits are simultaneously present in the fibrillating atrium. This theoretical construct was well supported by animal and human mapping data of AF using multielectrode plaques on the endocardial or epicardial surface of the atria (4,5). In addition, the Maze procedure devised by Cox and co-workers cured AF in most patients with drug-resistant AF (6). The alternate hypothesis that a focal source of excitation sustained AF re-emerged with the landmark observations by Haissaguerre and co-workers that high-frequency discharges from the pulmonary veins maintain the arrhythmia in most patients with paroxysmal AF and in many patients with persistent AF (7). The observed waveform of AF recorded on the surface electrocardiogram represents the summation and collision of wave fronts emanating from the focal source in affected patients. The importance of these venous structures to the initiation and maintenance of AF is underscored by the high rate of cure achieved by catheter ablation protocols that electrically isolate the pulmonary veins (8).

Despite these observations, many uncertainties remain, including: 1) whether AF is a heterogeneous disorder with both focal and reentrant mechanisms operative in different patient groups, 2) whether the pulmonary veins participate in sustained AF in patients with important structural heart disease; and 3) whether both reentrant and focal mechanisms coexist and contribute to the sustenance of persistent AF.

ATRIAL ARRHYTHMIAS IN A CANINE MODEL OF HF

Okuyama et al. (2) studied AF using an established, experimental canine model for atrial arrhythmias produced by induction of congestive HF through long-term, rapid ventricular pacing. Earlier work with this preparation has demonstrated that the duration of electrically induced AF is prolonged though rarely sustained (9). In addition, important structural changes in the heart are induced, including fibrosis, that likely contribute to the increased stability of AF. After a period of recovery from rapid ventricular pacing, high-density recordings were employed to study activation of the atria, pulmonary veins, and vein of Marshall region during periods of electrically induced AF. Four recording plaques were employed, each of which recorded 420 bipolar signals. Only one pulmonary vein was studied with a high-density recording plaque at a time, so the investigators also recorded simultaneous bipolar electrograms from all pulmonary veins and the atria during induced AF. The histopathology of the heart was characterized after the recordings. Measurements were compared to a group of control animals.

A number of physiological and histological differences were observed between pulmonary veins from control animals and those of the HF animals. In control animals, induced AF was quite transient, lasting 6.1 s on average, with characteristic passive activation of the pulmonary veins from wave fronts originating in the left atrium (LA). Some degree of entrance block occurred so that the mean cycle length recorded in the pulmonary veins was prolonged relative to the adjacent LA. No evidence for fractionated or focal electrical activation of the pulmonary veins was seen.

In contrast, the animals with HF had more prolonged episodes of AF, lasting 80.7 s on average. Pulmonary vein activation in these animals was far more complex. In 50% of the AF episodes that were analyzed, pulmonary vein elec-

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trical activation was complex, with focal, fractionated, and mixed activation patterns. Although not quantified, the investigators describe the cycle length as either slower or faster than the corresponding LA cycle length during AF.

In the remaining episodes, pulmonary vein activation was similar to controls, with passive activation from LA wavefronts. Among pulmonary veins that exhibited complex activation, dynamic display of the pulmonary vein activation patterns demonstrated multiple activation wave fronts present simultaneously within the vein. The researchers could not definitively demonstrate reentry within the pulmonary vein, because of beat-to-beat changes in the activation pattern, although they comment that some wave fronts were compatible with reentry with slow conduction. The pulmonary vein morphology and wall thickness were unchanged in the HF preparation, and the pulmonary vein histology from the HF animals demonstrated an increase in interstitial fibrosis. In summary, the researchers demonstrated that the increased stability of induced AF in their canine HF model correlates with changes in the electrical and anatomical characteristics of the pulmonary veins.

Perhaps the most striking observation made by Okuyama and co-workers (2) is the complexity of electrical activation observed in the pulmonary veins. Pulmonary veins in 20-kg dogs are typically <1 cm in diameter with a myocardial sleeve extending about 1 cm out from the pulmonary vein LA junction. This geometry allows about 3 cm² for propagation of wave fronts within the pulmonary vein. Despite this constraint, multiple activation wave fronts were observed by investigators to occur simultaneously within single veins. Although the conduction velocity was not measured for activation wave fronts in the pulmonary veins, Okuyama and colleagues measured conduction velocity in the vein of Marshall at about 1 m/s. If the action potential duration is assumed to be about 100 ms, a single reentrant circuit would require a 10-cm circuit. However, if conduction velocity were slowed by 10 fold, the limited geometry of the pulmonary veins could support one or more reentrant circuits. Because of the observed complexity of the activation patterns in 50% of the analyzed episodes, the mechanism of the arrhythmia could not be defined. The observed activation patterns were therefore compatible with either multiple reentrant circuits or multiple focal discharges.

Have Okuyama et al. (2) provided a convincing case for a fundamental role of the pulmonary veins in sustaining AF in this preparation? Several observations that are not included in the study would be helpful to address this question. First, were the phenomena observed within the pulmonary vein recordings similar to phenomena recorded in the left atrial plaques? The investigators do note that the mean cycle length of LA activation was shorter than that recorded in the right atrium. This gradient of activation frequency, if continued into the pulmonary veins, would provide circumstantial evidence for the pulmonary veins functioning as drivers to sustain AF. In addition, whether a similar degree and character of complex activation was recorded in the LA would bear directly on whether the observed phenomena in the pulmonary veins was unique.

Second, the observed conduction velocity of activation wave fronts propagating across pulmonary vein recording plaques could be calculated from the researchers’ data. This value would provide some information about the feasibility of reentry within the pulmonary vein as noted above. Third, recordings near the ostium at the pulmonary vein to LA interface could provide a characterization of the manner in which the pulmonary veins interact with the LA during AF. If activation wave fronts predominantly exit the pulmonary vein, a “driver” role for the pulmonary vein could be inferred, particularly if the average cycle length recorded within the pulmonary veins was shorter than that recorded in the LA. Alternatively, if conduction predominantly blocked at the pulmonary vein LA interface or propagated from the LA to the pulmonary vein, the pulmonary vein would be implicated as a bystander to the maintenance of AF.

**AF IN CONGESTIVE HEART FAILURE**

The observations reported by Okuyama and co-workers (2) support a body of consistent observations that electrical and anatomical remodeling of the atria, as a consequence of congestive HF, prepares the substrate for AF. This is likely in addition to both the electrical and anatomical remodeling occurring as a direct result of sustained high-rate atrial pacing or AF, also reinforcing the stability of AF, and hence the epitaph “atrial fibrillation begets atrial fibrillation.” The precise genetic mechanisms underlying these changes are poorly understood, but they will likely provide the opportunity for therapeutic intervention when well delineated. In addition, the possibility that reversal of the electrical-anatomical changes in the atria can occur as a result of aggressive treatment of congestive HF is suggested by the data acquired from this experimental model.

**FUTURE OF AF MAPPING**

Can further insights from electroanatomical mapping of AF be gained? The complexity of activation patterns that are often recorded during AF in humans and in animal models of AF provide an implicit ambiguity with regard to the underlying mechanism of the arrhythmia. Multiple triggered sources can mimic many of the qualities of a reentrant mechanism. Nevertheless, further insights into the physiology of the pulmonary veins are required. The groundswell of effort around the world to treat patients with refractory AF by electrical isolation of the pulmonary veins either surgically or by a catheter approach has provided compelling evidence that these structures are critically involved in initiating and maintaining AF. This effort will be greatly aided by the development of a reliable animal model for AF in which further research can be performed. The present preparation (2) clearly had a limited capacity to sustain AF. Therefore, the relevance of observations made in this
preparation to the patient with persistent AF is probably also limited. A combination of rapid atrial and rapid ventricular pacing may provide a better preparation for sustained AF. A reliable animal model is clearly necessary for a more robust test of the hypothesis that the pulmonary veins are critically necessary to sustain AF.

**Pulmonary vein isolation.** Finally, the poor response of patients to antiarrhythmic medications both in terms of the medications’ side-effect profile and limited efficacy has continued to provide impetus for the development of a safe and efficacious non-pharmacologic approach to treat AF. The clinical success of a strategy to electrically isolate all the pulmonary veins has continued to drive the wider practice of this technique despite our limited understanding of the relevant physiology. Unfortunately, many features of this procedure prevent its recommendation as a first-line treatment for paroxysmal or persistent AF. Complications such as stroke or pulmonary vein stenosis remain an important problem. In addition, procedure times are lengthy and require considerable fluoroscopic exposure to both the patient and the operator. The long-term efficacy of the procedure is significantly less than that associated with catheter ablation of other arrhythmias. As a consequence, further developments in technology are clearly needed.

Precise catheter manipulation and targeting guided by three-dimensional imaging of the pulmonary vein ostial region have been incorporated into a magnetically guided catheter system that is remotely controlled (10). Whether the theoretical advantages of this system will facilitate the current catheter ablation strategy will be tested in a clinical trial. Alternatively, modifications to the Maze procedure to include a minimally invasive and “off-pump” strategy may also make this procedure more desirable and safer for less symptomatic patients or patients with more severe concomitant heart disease.

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**REFERENCES**