In this issue of the Circulation: Arrhythmia and Electrophysiology, Kurotobi et al determined the number of arrhythmogenic foci in atria provokable with isoproterenol infusion in patients with paroxysmal, persistent, and permanent atrial fibrillation (AF). The results show that persistent AF has more foci than paroxysmal AF. However, when AF persists for >12 months, the number of foci were reduced. The authors suggest that the increased number of foci probably is involved in the development of persistent AF. However, because this association is not observed for AF that persists for >12 months, the importance of these foci in AF maintenance remains unclear.

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**Sympathetic Stimulation and the Development of Arrhythmogenic Foci**

In ambulatory canine models, simultaneous sympathovagal discharges (rather than isolated sympathetic activation) are typical triggers of paroxysmal atrial tachycardia (AT) and AF. These observations are explained by the late phase-3 early afterdepolarization (EAD), which depends on the coexistence of increased amplitude and duration of intracellular calcium (Cai) transient and the shortened action potential duration (APD). Vagal stimulation shortens APD and therefore is needed to promote the late phase-3 EAD. In the Kurotobi study, however, arrhythmogenic foci were induced by isoproterenol alone, without the need of vagal stimulation or the use of parasympathomimetic agents. These results are different from that obtained in canine studies.

**Short APD in Pulmonary Veins**

The first possible explanation is that the pulmonary veins (PVs) naturally have shorter APDs with elevated (less negative) membrane potentials. Rapid activation may further shorten the APD in the PVs. These changes are independent of the vagal tone. Jais et al. reported the effective refractory periods of the PVs were shorter than that of the left atrium (LA) in AF patients (185±71 ms versus 253±21 ms, P<0.001) but longer than LA in control patients, suggesting an association between short APD in the PVs and the development of AF. Sympathetic stimulation not only increases the Cai transient but also increases heart rate. The rapid rate can promote both Cai accumulation and APD shortening in the PVs, leading to late phase-3 EAD. Kurotobi et al. reported that the coupling interval of the PV foci was shorter than that of the non-PV foci (196±68 ms versus 255±90 ms, P<0.001). These values are consistent with the coupling interval expected for late phase-3 EADs.

**Vagal Responses Triggered by Isoproterenol**

A second possible explanation is that isoproterenol infusion might have provoked vagal responses, resulting in a condition similar to sympathovagal coactivation. In the Discussion, Kurotobi et al. stated that “High dose isoproterenol often invokes vagally mediated nerve reflex bradycardia, which seems to cause an increased arrhythmogenicity due to autonomic nerve competition.” Similar observations have also been made during the tilt-table studies in which high-dose isoproterenol infusion helps to induce bradycardiac responses. When stellate ganglion nerve activity and vagal nerve activity were simultaneously monitored in ambulatory dogs, most vagal nerve activity occurred during or after the stellate ganglion nerve activity. These findings suggest that these 2 arms of the autonomic nervous system may interact with each other and that it is possible for heightened sympathetic activity to trigger vagal discharges. It is therefore possible that isoproterenol infusion provokes the vagal responses, which helps shorten the APD and facilitate late phase-3 EAD and triggered activity, causing both PV and non-PV foci.

**Delayed Afterdepolarization and the Diastolic Cai-Membrane Voltage Coupling Gain**

A third mechanism by which isoproterenol alone can induce arrhythmogenic foci is through delayed afterdepolarizations (DADs). Because of Cai accumulation in AF, the overloaded sarcoplasmic reticulum (SR) may spontaneously release Ca, which then activates Ca-sensitive membrane ionic currents such as the f<sub>Ncx</sub>, forming DADs and triggered activity. Therefore, DAD-mediated triggered activity may also facilitate the development of arrhythmogenic foci without the need of vagal stimulation. The process of Ca<sub>d</sub>-dependent changes in membrane potential (V<sub>m</sub>) is also called reverse excitation-contraction coupling. There are 2 important promoting factors that determine whether the reverse excitation-contraction coupling can induce triggered activities: large SR Ca release and high diastolic Cai-membrane voltage coupling gain (CVCG). The CVCG is defined by the magnitude of membrane potential responses to elevated Cai during diastole. AF is known to increase SR Ca releases from the SR Ca
release channels. Therefore, AF may promote spontaneous SR Ca release, which favors the developing DADs and triggered activity. However, even with the same amount of SR Ca releases, the membrane voltage response may vary due to differences in CVCG. For example, the Purkinje fibers but not epicardial ventricular myocytes develop DAD-mediated triggered activity after rapid pacing or successful defibrillation in rabbit ventricles. These findings suggest that the Purkinje fibers have a higher diastolic CVCG than the epicardial ventricular myocytes. The higher CVCG can be attributed to the reduced $I_{K_{1}}$ density in Purkinje cells as compared with ventricular myocytes. Similar to the relation between Purkinje and ventricular cells, $I_{K_{1}}$ density in the PV myocytes is smaller than in the LA. The lower $I_{K_{1}}$ may explain the less negative resting membrane potential in the PV than in the LA and imply a higher CVCG in the PV and a greater propensity for generating triggered activities than in the non-PV sites.

Reentry and Maintenance of AF

The reduced $I_{K_{1}}$, however, does not apply to atrial myocytes in AF because their $I_{K_{1}}$ levels are upregulated. Upregulation of $I_{K_{1}}$ hyperpolarizes the cell membrane, reduces CVCG, and may prevent DADs and triggered activity. However, upregulation of $I_{K_{1}}$ may shorten APD and promote late phase 3 EADs. Furthermore, $I_{K_{1}}$ activity is important in the rotor stability and frequency. A larger $I_{K_{1}}$ in the left ventricle than in the right ventricle may explain the development of stationary rotors in the left ventricle that sustains ventricular fibrillation. Adenosine, which activates an inward rectifier potassium current, can increase the dominant frequency in AF. These findings are consistent with acceleration and stabilization of the reentrant circuit. Upregulation of $I_{K_{1}}$ in the atrial cells during AF may stabilize the rotor and help reentrant activity to sustain itself. In addition, PVS have smaller $I_{NS}$ and maximum phase 0 upstream velocity than the LA. Conduction velocity may be slower, and reentry is more likely to be sustained in the PVS. Increased fibrosis, larger LA size, and the reduced conduction velocity may jointly promote reentry and persistence of AF. It is possible that because AF persisted for more than 1 year, these net remodeling changes favor the development of sustained reentry at the expense of triggered activity. Because more than half of the patients with persistent AF have right atrial foci whereas only about a quarter of patients with paroxysmal AF have right atrial foci, these findings also suggest that the progression of disease and remodeling increased the importance of non-PV foci in the generation of arrhythmogenic foci and in the maintenance of AF.

In summary, the study by Kurotobi et al raises many important questions about the mechanisms that sustain AF. Although both triggered activity and reentry are important in the generation and maintenance of AF, their relative importance may evolve over time. One of the reasons is the ion channel remodeling that promotes reentry (such as increased $I_{K_{1}}$) may reduce the CVCG and prevent DADs. In addition, the remodeling processes may be heterogeneous, resulting in increased importance of non-PV foci in persistent and permanent AF as compared with paroxysmal AF. Therefore, an increased number of foci in persistent AF and a reduced number of foci when AF persists >12 months imply that the mechanisms of AF change over time. Better understanding of the differential remodeling processes in different parts of atria during long-duration AF is needed to fully understand the implications of these studies.

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Disclosures

None.

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