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Epicardial Adipose Tissue and Neural Mechanisms of Atrial Fibrillation

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In this issue of the *Circulation: Arrhythmia and Electrophysiology*, Nagashima et al[1] reported that there is higher epicardial adipose tissue (EAT) volume and greater serum inflammatory biomarker levels in patients with persistent atrial fibrillation (PerAF) than in patients with paroxysmal atrial fibrillation (PAF). Furthermore, they noted that high dominant frequency (DF) sites are located adjacent to EAT sites. The authors proposed two possible explanations for these findings. One is that EAT secrets proinflammatory cytokines that alter local atrial and pulmonary vein (PV) electrophysiology and facilitates the development of atrial fibrillation (AF). Two is that EAT contains abundant ganglionated plexi (GP). Activation of the autonomic nerves in the GP facilitates the maintenance of AF. The results of the present study extended their previous observation on EAT[2] by providing new data on the correlation between high DF sites and EAT sites. These novel observations provide new insights into the anatomical and physiological differences between PAF and PerAF.

After the initial diagnosis of PAF, there is a slow (5–10% per year) but steady progression to chronic (permanent or persistent) AF.[3] Baseline echocardiographic variables, age, cardiomyopathy and heart rate are independently associated with progression to chronic AF. On the other hand, PerAF is also frequently the initial diagnosis without preceding PAF episodes. How often PerAF and permanent forms of AF are preceded by recurrent PAF remains unclear. Improving the understanding of PAF to PerAF progression may help secondary prevention efforts to reduce the complications associated with AF.

Wijffels et al[4] performed intermittent rapid atrial pacing in goats to study the progression of PAF to PerAF. They found that when AF is maintained artificially, the duration of the paroxysms progressively increases, until after 1 to 3 weeks AF becomes sustained. The transition from PAF to PerAF is associated with a marked shortening of atrial effective refractory period and wavelength, which the authors propose as major factors responsible for

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the development of PerAF. This "AF begets AF" hypothesis suggests that reducing PAF episodes might be an effective measure in secondary prevention of AF. However, the authors also noted that the time course of changes in atrial refractoriness does not parallel with the time course of development of PerAF. These findings suggested to the authors that, besides the shortening of refractoriness, other factors may play a role in the development of PerAF. One of these factors in animal studies is the site of pacing. Right atrial pacing in dogs takes over 100 days to induce PerAF.[5] In contrast, it usually takes half as long to induce PerAF if the dogs are paced from the left atrium. A possible explanation for this finding is that electrical current induces cardiac nerve sprouting and heterogeneous sympathetic hyperinnervation near the pacing site.[6] Because of the unique cellular electrophysiology of the PVs,[7] pacing near the PVs may facilitate the development of PerAF. However, even using the same pacing sites and the pacing protocol, there is still a large variation of the durations needed for intermittent high rate pacing to induce Per AF. We retrospectively analyzed the nerve discharge patterns of 12 dogs that underwent chronic intermittent ambulatory nerve recording and rapid left atrial pacing with the same pacing protocol.[8] We found that baseline nerve discharge pattern is a major factor that determines the inducibility of PerAF. The stellate ganglion (sympathetic) activation and vagal activation do not occur randomly in ambulatory dogs. Rather, their discharges are highly coordinated. In about 25% of the dogs, the sympathetic and vagal nerves fire together. In these dogs AF can be induced in only 13–20 paced days. However, if the sympathetic and vagal activation occur separately, then 23–72 days of pacing are needed to induce PerAF. These findings indicate that the autonomic nerve activities play important roles in the development of PerAF.

Immunohistochemical studies showed high density of autonomic nerves in the human left atrium within 5 mm of the PV-left atrial junction.[9] Adrenergic and cholinergic nerves are highly co-located at tissue and cellular levels. A significant proportion (30%) of ganglion cells expressed dual adrenocholinergic phenotypes. Activation of GP in the EAT precedes all episodes of spontaneous PAF in ambulatory dogs, suggesting that these intrinsic nerve structures are essential for the initiation of AF.[10]

Putting these findings together, the EAT contains both adrenergic and cholinergic nerves. These intrinsic cardiac ganglia interact with extrinsic sympathetic and parasympathetic nervous system to modulate cardiac electrophysiology.[11] Adrenergic activation increases calcium entry while cholinergic activation shortens the action potential duration (APD). The large calcium transient persists during the late phase 3 of the action potential, leading to late phase 3 early afterdepolarization and triggered activities in the PVs and/or atrial myocardium.[7, 12] Patients with large amount of EAT may have increased intrinsic adrenergic and cholinergic nerves. Simultaneous activation of these nerve structures in response to extrinsic cardiac nerve activations may enhance triggered activity and facilitate the development of PerAF.

In addition to finding an increased amount of EAT in patients with PerAF, the authors also found that there are high DF sites near the EAT. While high DF suggests rapid atrial activation due to either reentry or triggered activity, it can also represent contamination of atrial electrograms by intrinsic nerve discharges.[10] The association between EAT and high DF sites is therefore consistent with a neural mechanism of AF. This mechanism is further supported by a recent genome wide association study (GWAS) that linked KCNN3 to AF.[13] The KCNN3 encodes subtype 3 of the small conductance calcium activated K (SK) channels. All 3 subtypes of SK channels are widely distributed in the brain but are also found elsewhere in the body.[14] The primary function of SK channels in the nervous system is to produce afterhyperpolarization following a neural action potential and to protect the cell from the deleterious effects of continuous tetanic activity.[15] SK channel inhibition or

downregulation can lead to increased and erratic neuronal discharges. The increased nerve activities can increase the contamination of atrial electrograms, which increases DF.

In addition to its effects in regulating neuronal discharges, seminal studies from Chiamvimonvat's laboratory documented the presence of SK channels in the atria and that these channels play important roles in atrial repolarization and arrhythmogenesis.[16] A unique property of SK channel is that it is activated by intracellular calcium and not by voltage. It is thus highly active in conditions associated with calcium accumulation, such as AF. Therefore, another possible mechanism for the association between increased EAT and high DF is that the cholinergic nerve structures within the EAT causes APD shortening near the PV and LA junction, where EATs are located. The shortened APD facilitates the development of reentry or triggered activity at the PV-LA junction. Rapid rate of activation induced by reentry and triggered activity further increases intracellular calcium, which in turn increases the activation of SK current and further shortens the APD. This positive feedback mechanism maintains high DF near PV-LA, and may facilitate the transition from PAF to PerAF.

The association between KCNN3 and AF also suggests that SK channels may be a new antiarrhythmic target for AF. Consistent with this hypothesis, recent studies showed that inhibition of SK channel may suppress pacing-induced AF in animal models.[17] In addition, preliminary results from Turker et al[18] showed that amiodarone inhibits SK currents in cultured cells. SK channel suppression may partially explain the antiarrhythmic efficacy of amiodarone in AF. On the other hand, because SK channels are important in the function of neural progenitor cells,[19] SK channel suppression may play a role in the amiodarone neurotoxicity.

Nagashima et al[1] also suggest that EAT may release inflammatory cytokines such as hs-CRP and IL-6, which may change the electrophysiologic characteristics of atrial and PV cardiomyocytes, leading to the progression of AF. However, these cytokines also have potent effects in regulating nerve growth.[20] Nerve growth factor, which is released by EAT,[21] is a major factor that promotes nerve growth. IL-6 is also important in regulating nerve growth by inducing cholinergic transdifferentiation of the cardiac sympathetic system via a gp130 signaling pathway.[20] A relatively higher level of these cytokines in PerAF than in PAF is consistent with the neural mechanisms of AF. However, the authors measured the levels of these cytokines in serum, and not near the EAT sites. Therefore, it is unclear if sufficient cytokines have been released locally to change the nerve densities at those locations. Moreover, the hs-CRP and IL-6 levels reported in both group of patients are within the range reported in healthy adults.[22, 23] Further studies will be needed to establish a direct relationship between the cytokines and the DF in PerAF.

In summary, Nagashima et al[1] presented novel and intriguing data on the relationship between EAT, DF, inflammatory cytokines and PerAF. These findings help to fill the gap of knowledge on the development of this arrhythmia, and may contribute to the secondary prevention efforts in the management of AF.

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