In this issue of Circulation: Arrhythmia and Electrophysiology, Nagashima et al report 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 2 possible explanations for these findings. One is that EAT secretes proinflammatory cytokines that alter local atrial and pulmonary vein (PV) electrophysiology and facilitates the development of atrial fibrillation (AF). The second is that EAT contains abundant ganglionated plexi. Activation of the autonomic nerves in the ganglionated plexi facilitates the maintenance of AF. The results of the present study extended their previous observation on EAT by providing new data on the correlation between high DF sites and EAT sites. These novel observations provide new insights into the anatomic 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. 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 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, becoming sustained after 1 to 3 weeks of AF. 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 the development of PerAF. This AF begets AF hypothesis suggests that reducing PAF episodes might be an effective measure in the 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 >100 days to induce PerAF. 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 electric current induces cardiac nerve sprouting and heterogeneous sympathetic hyperinnervation near the pacing site. Because of the unique cellular electrophysiology of the PVs, pacing near the PVs may facilitate the development of PerAF. However, even using the same pacing sites and pacing protocol, there is still a large variation of the durations needed for intermittent high-rate pacing to induce PerAF. 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. 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 ≈25% of the dogs, the sympathetic and vagal nerves fire together. In these dogs, AF can be induced in only 13 to 20 paced days. However, if the sympathetic and vagal activations occur separately, then 23 to 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. Adrenergic and cholinergic nerves are highly colocated at tissue and cellular levels. A significant proportion (30%) of ganglion cells expressed dual adrenergic and cholinergic phenotypes. Activation of ganglionated plexi 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. Putting these findings together, the EAT contains both adrenergic and cholinergic nerves. These intrinsic cardiac ganglia interact with the extrinsic sympathetic and parasympathetic nervous system to modulate cardiac electrophysiology. Adrenergic activation increases calcium entry, whereas cholinergic activation shortens the action potential duration. 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 atrial myocardium.\textsuperscript{7,12} Patients with a 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. Although high DF suggests rapid atrial activation because of either reentry or triggered activity, it can also represent contamination of atrial electrograms by intrinsic nerve discharges.\textsuperscript{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 that linked \textit{KCNN3} to AF.\textsuperscript{13} The \textit{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.\textsuperscript{14} The primary function of SK channels in the nervous system is to produce afterhyperpolarization after a neural action potential and to protect the cell from the deleterious effects of continuous tetric activity.\textsuperscript{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 laboratory documented the presence of SK channels in the atria and that these channels play important roles in atrial repolarization and arrhythmogenesis.\textsuperscript{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 cause action potential duration shortening near the PV and left atrial junction, where EATs are located. The shortened action potential duration facilitates the development of reentry or triggered activity at the PV-left atrial 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 action potential duration. This positive feedback mechanism maintains high DF near PV-left atrium and may facilitate the transition from PAF to PerAF.

The association between \textit{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 channels may suppress pacing-induced AF in animal models.\textsuperscript{17} In addition, preliminary results from Turker et \textit{al}\textsuperscript{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,\textsuperscript{19} SK channel suppression may play a role in the amiodarone neurotoxicity.

Nagashima \textit{et al}\textsuperscript{11} also suggest that EAT may release inflammatory cytokines, such as high-sensitivity C-reactive protein and interleukin-6, which may change the electrophysiological characteristics of atrial and PV cardiomycocytes, leading to the progression of AF. However, these cytokines also have potent effects in regulating nerve growth.\textsuperscript{20} Nerve growth factor, which is released by EAT,\textsuperscript{21} is a major factor that promotes nerve growth. Interleukin-6 is also important in regulating nerve growth by inducing cholinergic transdifferentiation of the cardiac sympathetic system via a gp130 signaling pathway.\textsuperscript{22} 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 whether sufficient cytokines have been released locally to change the nerve densities at those locations. Furthermore, the high-sensitivity C-reactive protein and interleukin-6 levels reported in both groups of patients are within the range reported in healthy adults.\textsuperscript{22,23} Further studies will be needed to establish a direct relationship between the cytokines and the DF in PerAF.

In summary, Nagashima \textit{et al}\textsuperscript{11} presented novel and intriguing data on the relationship among 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.

### Sources of Funding

This study was supported, in part, by National Institutes of Health Grants P01HL78931, R01HL78932, R01HL71140, a Medtronic-Zipes Endowment, and the Indiana University Health-Indiana University School of Medicine Strategic Research Initiative.

### Disclosures

Dr Chen’s research laboratory receives equipment donations from Medtronic Inc, St Jude Inc, Cryocath Inc, and Cyberonics Inc. Dr Chen is a consultant to Cyberonics Inc.

### References


**Key Words:** Editorials • atrial fibrillation • inflammation • nervous system • autonomic