EDITORIAL COMMENT

Autonomic Modulation Preceding the Onset of Atrial Fibrillation*

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Autonomic influences on the heart have been recognized for many centuries. It was not until 1921, however, that a German physiologist named Otto Loewi stimulated a frog’s vagus nerve, collected the released substance, and applied it to a second, different frog heart to demonstrate its effects. For his discovery of this “vagusstuff” (subsequently shown to be acetylcholine), Loewi (1) shared the 1936 Nobel Prize in Physiology or Medicine. We now know that acetylcholine released by the vagus nerve is the predominant parasympathetic influence on the heart while epinephrine and norepinephrine mediate the principal cardiac sympathetic effects (2).

The measurement of autonomic tone in humans noninvasively presented new challenges. Subtle beat-to-beat variations in heart rate are influenced by autonomic tone, giving rise to the measure of heart rate variability (HRV). That changes in the RR-interval (heart rate) precede and predict clinically relevant events was first appreciated in the mid-1960s when beat-to-beat variations in heart rate were shown to portend fetal distress (2). Later, it was appreciated that reduced HRV was an independent predictor of ventricular arrhythmias, sudden cardiac death, and total mortality after myocardial infarction and predicted increased mortality in patients with organic heart disease and occurs more frequently in patients with normal hearts and occurs predominantly at night when vagal tone is relatively high, while adrenergically induced AF occurs more frequently in patients with organic heart disease and occurs more frequently during the day (11). However, not all studies support this simplified interpretation of the data. Indeed, there are many exceptions to this “rule.”

A number of important electrophysiologic changes occur in atrial myocardium in response to an increase in vagus nerve activity. Acetylcholine, acting via its effect on muscarinic receptors, reduces the slope of spontaneous depolarization of the sinoatrial node pacemaker cells and results in a slowing of the heart rate. Acetylcholine also shortens the atrial refractory period and increases the heterogeneity of atrial repolarization, effects that predispose to reentry (12,13). It appears that the relative sympathovagal balance is as important, or more important, than the absolute sympathetic or parasympathetic tone. Indeed, experimental regional cardiac denervation (e.g., withdrawal of sympathetic tone from a specific atrial site) can result in a relative increase in vagal tone without a change in the absolute vagal tone. This can result in regional shortening of the atrial refractory period, heterogeneity of atrial repolarization, and predisposition to induction of AF (14–16). This important interplay between sympathetic and parasympathetic tone is further underscored by the observation that AF induction in

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dogs occurs much more readily with infusion of isoproterenol and acetylcholine than with either isoproterenol or acetylcholine alone (17).

That increased vagal tone can predispose to the development of AF has been recognized since the initial description by Coumel et al. (18). Perhaps most exciting are the new therapeutic avenues that have been opened by our increased understanding of the autonomic influences that predispose to AF. Parasympathetic ganglia have been localized to discrete epicardial fat pads. Radiofrequency ablation of specific fat pads causes regional alterations of cardiac parasympathetic tone and, as a result, affects atrial refractory periods, atrioventricular nodal conduction properties, and heterogeneity of atrial conduction (15,19,20). In dogs, catheter ablation of parasympathetic nervous input to the atrium can abolish vagally mediated AF (21).

Loewi’s (1) initial description of “vagusstuff” opened the door to important advances in our understanding of cardiac autonomic regulation. Similarly, improved understanding of the autonomic influences that predispose to AF will be critical to the development of novel therapies. While there is much that remains to be learned, specific pharmacologic, catheter, or device-based therapies that alter or regulate autonomic tone may someday prove to be useful weapons in the battle against AF.

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