EDITORIAL COMMENT

Is Vagal Denervation a Good Alternative or Just Adjunctive to Pulmonary Vein Isolation in Catheter Ablation of Atrial Fibrillation?

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Since the first report of radiofrequency catheter ablation to cure atrial fibrillation (AF) by Haissaguerre et al. in 1994, many techniques have evolved (1–7). Currently, most ablation strategies for AF consist of pulmonary vein (PV) isolation with or without additional ablation lines in the left atrium and/or targeting the complex electrograms characterized by a short cycle length, fractionation, and/or continuous electric activity. The reported immediate success rate is higher than 90%. The long-term success rate ranges from 60% to 90% in patients with paroxysmal AF, but it is lower in patients with chronic AF (1–6). The effectiveness of catheter ablation is related to the precision of the atrial lesions created around the PV which aims to eradicate the triggers, isolate the PV, and modify the substrate for AF maintenance. However, these lesions create large areas of scarring in the atria that might become a substrate for the late onset of atrial tachyarrhythmias and depress the left atrial contractility (8), and they may involve more ablation than necessary in some patients. Furthermore, ablation along the posterior left atrial wall is associated with the risk of a lethal complication involving an atrioesophageal fistula (9). Therefore, new techniques for the ablation of AF are continually evolving.

Vagal tone is a trigger of AF in a subset of patients. In canine models, vagal stimulation shortens the atrial effective refractory period (ERP), increases its dispersion, and decreases the wavelength of re-entrant circuits that facilitate the initiation and maintenance of AF (10). In this issue of the Journal, Arora et al. (11) demonstrate that the PVs, left atrial appendage (LAA), and posterior left atrium (LA) had unique activation and repolarization characteristics in response to autonomic manipulation. They found that vagal stimulation and propranolol plus vagal stimulation caused more ERP shortening in the PV and posterior LA than in the LAA. The ERP difference between propranolol plus vagal stimulation and propranolol plus atropine was greatest in the LAA and corresponded with the expression of Kir3.1/3.4. The ERP change in response to the vagal manipulation was most heterogeneous in the posterior LA. This study provides a reasonable explanation of why, in addition to the PVs and superior vena cava, the posterior LA is an important source of foci or substrates of AF. Arora et al. also found a more pronounced ERP shortening in each region with propranolol plus vagal stimulation compared with vagal stimulation alone. They suggested that the ERP response to vagal stimulation appears to be modulated by the adrenergic manipulation. This important finding further complements the previous study by Sharifov et al. (12), who found that atropine prevented catecholamine-mediated AF. Propranolol did not prevent acetylcholine-induced AF, but it increased the threshold of the acetylcholine concentration needed for AF induction. Acetylcholine-mediated AF was facilitated by isoproterenol, which decreased the threshold of the acetylcholine concentration needed for AF induction.

In human AF, the Chen group (Tai et al. [13]) first demonstrated that vagal enhancement with sympathetic withdrawal by a phenylephrine infusion could suppress ectopic activity and bursts of AF originating from the PVs. These findings suggest the complex issues regarding the sympathetic and parasympathetic innervation and the initiation and maintenance of AF.

Can vagal denervation be a good alternative to the conventional PV isolation-based ablation strategy? In an animal study, Schauerte et al. (14) showed that radiofrequency catheter ablation of the parasympathetic pathways along the right pulmonary artery and/or parasympathetic fibers along the superior or inferior vena cava could abolish any cervical vagal nerve stimulation–induced AF in 10 out of 10 dogs. Chiou et al. (15) showed that total efferent vagal denervation of the atria and sinus and atrioventricular nodes is accomplished by radiofrequency catheter ablation of all 3 fat pads. Vagal denervation of the right atrium or both atria eliminates the induction of acute AF in dogs produced by atrial pacing and bilateral vagal stimulation (15). In the era of catheter ablation of AF, the Chen group (Taipei) (13) first demonstrated that RF catheter ablation of the PV tissue could evoke a variety of profound bradycardia–hypotension responses and transient autonomic dysfunction with alterations in the heart rate and heart rate variability. A Bezold–Jarisch–like reflex might be the underlying mechanism (16). Pappone et al. (17) reported that vagal reflexes could be...
elicited and abolished in 34.3% of patients. Vagal attenuation by PV denervation confers an additional benefit in patients undergoing circumferential PV ablation for paroxysmal AF. Nakagawa et al. (18) reported that patients, randomized to PV isolation plus atrial denervation guided by high-frequency stimulation, experienced a significant reduction in AF recurrence during the follow-up compared with those randomized to PV isolation alone. A recent study (19) used percutaneous epicardial and endocardial mapping to search for sites in which high-frequency transcatheter stimulation (20 Hz) induced vagal reflexes. It showed that selective vagal denervation alone could also prevent AF recurrences in selected patients with apparent vagal-induced paroxysmal AF. However, a high AF recurrence rate was observed during the follow-up (19). In that study, the patients who underwent radiofrequency ablation guided by the vagal reflexes induced by high-frequency stimulation who remained free of AF recurrence had a significant autonomic change during the noninvasive evaluation, whereas those patients with AF recurrence did not have the same level of an autonomic change.

Understanding the vagal innervation, anatomy, atrial electrophysiology, and autonomic modulation is important. In dogs, most efferent vagal fibers to the atria appear to travel through the third fat pad located between the medial superior vena cavae and aortic root (SVC-Ao fat pad), superior to the right pulmonary artery, and then project on to the IVC-LA (located at the junction of the inferior vena cava and left atrium) and right pulmonary vein (RPV) fat pads (located adjacent to the right pulmonary vein-left atrial junction) and to both atria. A few vagal fibers may bypass the SVC-Ao fat pad and go directly to the IVC-LA or RPV fat pads or atrial myocardium (15). Tan et al. (20) showed that the autonomic nerve density was highest in the anterosuperior segments of both superior PVs and inferior segments of both inferior PVs, highest in the LA within 5 mm of the PV-LA junction, and higher in the epicardium than in the endocardium. Makino et al. (21) demonstrated that the association between sympathetic nerve fibers and Marshall bundles was distinct at the PV-left atrium junction. At the CS juncture, a regression of the sympathetic nerve fibers and an increase in the parasympathetic ganglia were observed. All of these data showed that the parasympathetic innervation is very complex. Furthermore, adrenergic and cholinergic nerves were highly colocated, indicating that it is difficult to selectively target either vagal or sympathetic nerves during the catheter ablation procedures (21).

Therefore, the major issues in the catheter ablation of vagal ganglia include how to localize the ganglia precisely, how to eliminate the ganglia and fibers effectively, and the need for a randomized protocol with a larger population to prove the true role of vagal denervation in the catheter ablation of AF. Anatomic limitations are another concern. To avoid severe complications, it is not suitable to deliver radiofrequency applications to ganglia close to the esophagus, phrenic nerve, aorta, coronary arteries, or pulmonary arteries (22,23). An alternative energy source using cryotherapy or an epicardial approach could be one choice.

The ideal ablation technique should be safe, effective, and easy to perform. Current AF ablation techniques are remarkably effective but not yet perfect. Although there have been many improvements in this decade, it still carries about a 6% rate of major risks. Furthermore, it is not as safe, effective, or simple as the ablation of supraventricular tachycardias. Current data from humans seem to support that vagal denervation can be an adjunctive therapy for pulmonary vein isolation and might increase the ablation success rate (17,18). So far, however, the data from animal and human studies do not justify it as an alternative modality (19,24).

**REFERENCES**


