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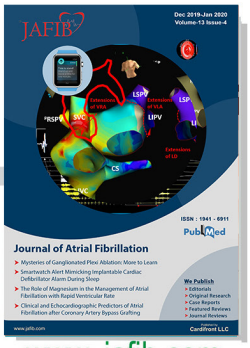

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Mysteries of Ganglionated Plexi Ablation: More to Learn

Tolga Aksu[1], *Rakesh Gopinathannair*[2]

[1]University of Health Sciences, KocaeliDerince Training and Research Hospital, Kocaeli, Turkey
[2]Kansas City Heart Rhythm Institute and Research Foundation, Kansas City, United States

Myocardial sleeves of the pulmonary veins (PVs) act as

Myocardial sleeves of the pulmonary veins (PVs) act as triggering foci for the great majority of patients with paroxysmal atrial fibrillation (AF)[1]. Although the exact mechanisms are not completely understood, studies have focused on electrophysiological properties of PVs and the adjacent left atrial myocardium. As a potential explanation, PV myocytes are more prone to autonomicnervous system (ANS) stimulation and associated shortening of action potential duration, early after depolarization formation and triggered firing compared to myocytes of the adjacent left atrium (LA)[2].

Autonomic control of the heart is regulated in a couple of feed back loops at different levels with a balance of sympathetic and parasympathetic signals between the heart and the central nervous systems [3]. While extrinsic part of ANS access the epicardial area as extensions of extracardiac nerves such as the left and right vagus nerves and both sympathetic trunks, the great majority of neurons of the intrinsic part of ANS reside inside epicardic ganglia that are interconnected by epicardial nerves on the human atria and ventricles [4, 5]. Based onhistologic studies, theseepicardiac ganglia are localized preferentially at certain epicardial sites adjacent to the left and right atriaand called as ganglionated plexi (GPs) [5]. Although earlier reports suggest that only the postsynaptic neuronal bodies of parasympathetic system exist in the ganglia, according to recently published reports, the nervous system in the mammalian heart contains populations of different neurons consisting of both efferent parasympathetic and sympathetic neurons, local circuit neurons/interneurons, and sensory neurons [6-9]. Although the density of sympathetic nerves was lowerthan that of parasympathetic ones in the cardiac tissue, the intracardiac nervous system of the heart possesses not only an extensive system of intrinsic parasympathetic postganglionic nerves but also a significant population of intracardiac ganglion cells possessing sympathetic activity. As an emerging technique, neuromodulation via ablation of GPs might be a potentially effective way at reducing afferent, efferent, or local circuit neuronal activity in epicardiac ganglia. Previous studies demonstrated that targeting the GPs endocardially with catheter ablation may alter cardiac autonomic activity and decrease the recurrence of atrial arrhythmias in patients with AF [11-14].

In this issue of the journal, Sohinki et al [15] present the results of GP ablation in addition to PV isolation in patients with AF and hypertension. The authors delivered high-frequency stimulation from endocardial locations corresponding to the epicardialLA GPs. Locations with a positive response (defined as > 3 seconds ofasystole noted on the arterial pressure waveform) were marked as GP on themap. A total 53 patients undergoing catheter ablation for AF were divided into 2 groups based on the LA size: normal LA size (n=16) and patients with LA enlargement (n=37).At the end of 12 months follow-up, systolic blood pressure (SBP) and number of used anti-hypertensive drugs were lowerin patients with normal LA size. While mean SBP did not change significantly in the LAenlargement group(increase of 3.72± 3.15 mmHg, CI-10.08 – 2.65 mmHg, p = 0.25), mean SBP decreased by 10.33 ± 5.1 mmHg, (CI 0.06 – 20.60 mmHg, p =0.04) in the normal LA size group. Authors concluded that in patients with AF and concomitant hypertension, normal LA size predictsimprovement in blood pressure control after PV isolation +GP ablation. We would like to congratulate Sohinki et al [15] for their contribution which allows a better understanding about additional effects of GP ablation in patients with AF. Previous studies proposed that ablation of GPs may decrease the parasympathetic control of the heart, and indirectly promote the sympathetic nerve sprouting. Considering the heterogeneous nature of GPs including both parasympathetic and sympathetic efferent neurons,similar and durable denervation on the sympathetic system as well as on the parasympathetic system might be possible after GP ablation.The concept of "cardiogenic" or "autonomically-mediated" hypertension which is driven by sympathetic tone was suggested by Dustan et al [16]. Thus, if sympathetic overactivity is playing a significant role in hypertension in a subset of patients, GP ablation would be expected to have a beneficial effect by modulating sympathetic output via GP ablation. As a supporting finding of this hypothesis, we found a significant and durable shortening of QTc after GP ablation

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Corresponding Author
Dr. Tolga Aksu
Mailing address: University of Health Sciences, KocaeliDerince Education and Research Hospital, Department of Cardiology, Kocaeli, Turkey, Zip code: 41500

in patients with normal corrected QT interval range and long QT syndrome [17, 18]. Shortening of QTc was attributed to the additional sympatholytic effect of GP ablation. In a recently published study, Pachon et al [19] studied whether the amount of parasympathetic and sympathetic denervation persists after one- and two-year after GP ablation. Isolation of PVs in addition to GP ablation was performed in 70% of cases. A significant and durable decrease was not only seen in the high-frequency band demonstrating parasympathetic tone but also seen in the low-frequency as an indicator of sympathetic tone after GP ablation. In the current study, blood pressure lowering effect was significantly higher in patients with normal LA size. This may be due to the fact thatlarger left atrial diameter might imply more extensive structural disease which may change electrophysiological response to ablation.

Several questions remain about the GP detection modality in the present study: were the GP sites located at only certain left atrial regions?; why were right atrial sites not tested?; and what about the autonomic effects of used general anesthesia on the reliability of GP identification? The mean heart rates and heart rate variability results of patients after the procedure were not provided by the authors. It might have demonstrated how effective ablation was in terms of neuromodulation. As another important limitation, AF free survival was not provided and compared between groups in the present study. Finally, classical lesion set of PV isolationmight be expected to partially ablate some of epicardial GPs, the relative importanceof PV isolation itself vs. the addition of HFS-based GP ablation remains unclear from the current study.

It is not yet clear which is the best way to modulate intrinsic cardiac ANS and what are the long-term consequences of these therapies. Based on experimental evidence, there might be a paradoxical interaction between neuromodulation and AF [19]. In a group ofdogs, ablation on the major GP swere compared with sham control group. In the ablated group, although the acute studiesshowed a significant prolongation of effective refractory period and a significant decrease in AF inducibility in the intervention group,eight weeksafter ablation, the effective refractory period was significantly shorter and AF inducibility was significantly greater than the sham control group. Further more, immunohistochemical staining demonstrated a higher parasympathetic and sympatheticnerve density in the ablation group but not in the sham group. Hopefully, larger randomized studies in the future would answer some of these questions.

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