

## Invited Editorial / Davetli Editöryal Yorum

### Cardioneuroablation: Present status as a tenable therapy for vasovagal syncope

#### Kardiyonöroablasyon: Vazovagal senkop için uygulanabilir bir tedavi olarak mevcut durum

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Aksu et al.<sup>[1]</sup> ask a legitimate question: What place does cardioneuroablation have today in the treatment of vasovagal syncope (VVS)? They point out that adequate and effective therapy for more symptomatic VVS patients is lacking, and it is reasonably used to support their argument in favor of this relatively new treatment. Since one of the present authors (RS) was a member of the task force that wrote the European Society of Cardiology (ESC) Syncope Guidelines 2018,<sup>[2]</sup> it is not possible to discuss some criticisms in this review.<sup>[1]</sup> However, it is possible to underline that all of the references that they quote and many more were available to us before writing the ESC guidelines. The committee discussed cardioneuroablation and elected not to include it in the recommendations, as we agreed that there was too little evidence on the therapy at the time. In guidelines, emphasis must be placed on therapies that have a sufficient base of evidence. In syncope, this is all too often not the case, and we are forced to rely on expert consensus or the combined clinical experience of a chosen task force. Looking to the future, it will be mandatory for us to do better. For this commentary, however, we will focus solely on cardioneuroablation.

#### Cardioneuroablation

In general, what is meant by cardioneuroablation is understood as using endocardial ablation techniques

to modify the behavior of the cardiac autonomic nervous system to prevent some/all of the autonomic processes occurring in VVS. Beyond this, there is little understanding of the mechanisms of ablation success, or whether ablation results in the destruction of vagal, sympathetic, interconnecting, or all neurons, what impact there is on the afferent and efferent neuronal pathways, and how permanent these effects may be. Moreover, there is little agreement on how to perform ablation. The early protagonists, Pachon in 2005<sup>[3,4]</sup> and Yao in 2012,<sup>[5]</sup> employed quite different approaches. Aksu et al.<sup>[6]</sup> reviewed the subject in detail.

Pachon used radiofrequency (RF) energy to treat both left and right atrial sites, considered to represent ganglionated plexi, identified by spectral analysis using fast Fourier transforms of local endocardial electrograms identifying potential ganglionated plexi sites demonstrating right-shifted and fractionated spectra. The authors then ablated ganglionated plexi based on anatomical localization. The aim of the ablation was to eliminate areas displaying fractionated spectra and to create changes in the resting autonomic state to achieve, as far as possible, vagal denervation.

#### Abbreviation:

EPS	Electrophysiological study
ESC	European Society of Cardiology
RF	Radiofrequency
VVS	Vasovagal syncope

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Yao targeted ganglionated plexi in the left atrium, particularly at the ostia of the pulmonary veins. The plexi were identified with high frequency stimulation causing a vasovagal response, notably with asystole, intense sinus bradycardia, or atrioventricular block. RF energy was used, and the proximity of the RF delivery to the ganglionated plexi was confirmed with a repetition of the vasovagal response within a few seconds of the energy application. Ablation was confirmed by abolition of the vasovagal response. The sites of ablation were carefully marked on the endocardial map. Thus, it can be said that 3 techniques were employed by these 2 groups:

- ablating sites with fractionated endocardial signals, identified using spectral analysis,
- identifying sites by high frequency stimulation, and
- anatomical site selection.

One group ablated sites in both atria while the other focused only on the left atrium.

In their first report, Pachon et al.<sup>[3]</sup> had 21 patients, but only 6 had reflex syncope (VVS). In Yao's report<sup>[5]</sup> there were 10 well-documented patients with VVS followed for a mean (m) of 30 months post-ablation compared with m-9 months for Pachon's patients. Other research followed, with another Brazilian group reporting on 1 case in 2009 using high frequency stimulation in the left atrium. Later, the group published a series<sup>[7]</sup> with another variation on the technique focusing the ablation sites on each side of the inter-atrial septum and addressing anatomical sites of ganglionated plexi from previous work. They had only 4 patients with VVS, who apparently sustained no recurrence of syncope in 22 months of follow-up. Subsequently, both pioneering groups published larger series: Pachon et al.<sup>[4]</sup> in 2011 and Sun et al.<sup>[8]</sup> in 2016.

Pachon et al.<sup>[4]</sup> described the results of 43 VVS patients who were treated with their published technique and there were only 3 recurrences of syncope in m-45 months follow-up. Yao's<sup>[8]</sup> series of 57 patients saw recurrent syncope in only 5 patients over m-36 months. They used high-frequency stimulation in 10 and anatomical ablation site identification in 47 patients. The left atrium only was the target in all cases. There was no statistically significant difference in outcome between the 2 techniques.

The results of all 3 of these approaches<sup>[4,7,8]</sup> were good and without serious complications, despite the substantial differences in techniques employed, but all of the studies suffer from non-randomized, non-blinded design. However, it will be readily appreciated that there was some degree of overlap in technique as far as left atrial ablation is concerned. Electrophysiologists interested in the treatment of VVS need to establish a definable and reproducible technique for wider use that is relatively easily performed and accompanied by good results.

One potentially attractive method to qualify results was proposed by Pachon,<sup>[9]</sup> who was able to stimulate the vagus at the level of the neck through the jugular vein upstream to the heart, causing asystole, an effect that could be abolished following ablation, thereby providing a clear endpoint for endocardial cardioneuroablation. This technique requires testing in other centers for reproducibility.

The results of cardioneuroablation appear superior to the latest available in studies of pacing for VVS,<sup>[10-12]</sup> although the volume of experience remains small. It must be born in mind that 2 of these 3 pacing results stemmed from randomized, controlled trials.

There is a huge need for more data on ablation in VVS. There was clearly too little for the ESC Task Force to consider at the time for the 2018 Guidelines.<sup>[2]</sup> Most of all, a randomized, blinded, sham-controlled trial is required. Given the small number of patients who qualify for this invasive treatment on the basis of refractory symptoms, such a trial is likely to be multi-center in design. The protocol of such a trial presents considerable difficulties in what constitutes a control group. Perhaps the best solution is to offer an electrophysiological study (EPS) to all trial patients and some, randomly selected, are ablated while the remainder are not. If an EPS is considered too aggressive for controls, they would still have to go to the EP laboratory and undergo a femoral venous approach. Acceptance by ethics committees is likely to present problems.

## Conclusions

The evidence for cardioneuroablation is attractive, but was insufficient to be included in the 2018 guidelines. Interested electrophysiologists are encouraged to expand their experience and to coordinate and refine their techniques. Asking questions that demand answers is to be supported, and when new guidelines

are considered in approximately 5 years, perhaps we will have some hard data on which to base recommendations regarding cardioneuroablation.

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