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EDITORIAL COMMENT

Cardioneuroablation: A game-changer for vasovagal syncope

Cardioneuroablação: mudança de paradigma no tratamento da síncope vasovagal

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Vasovagal syncope (VVS) is the most common cause of transient loss of consciousness. Although generally considered a benign condition, treatment of VVS remains challenging in some aggressive forms with frequent syncope events, mainly in those with short or no prodromes. These episodes can result in traumatic injuries and seriously jeopardize quality of life. Non-invasive therapies include both non-pharmacological measures such as compression socks, fluids and salt intake, physical counterpressure maneuvers, tilt training, and pharmacological agents such as fludrocortisone or midodrine.[1] Permanent pacemaker therapy may be effective if asystole is a dominant feature of reflex syncope. Recent 2021 European Society of Cardiology guidelines on cardiac pacing recommend pacemaker implantation for asystolic reflex syncope in patients aged >40 years with severe, unpredictable, recurrent events. No such recommendation has been established for younger patients.[2] In fact, pacing has been used as a last choice in malignant forms of cardioinhibitory VVS, but the decision to implant a permanent pacemaker is uncomfortable in the more dominant younger population (<40 years-old) with non-diseased hearts.

In 2005, Pachon et al. proposed cardioneuroablation (CNA) as a new strategy for treating conditions associated with hypervagotonia.[3] The rationale for CNA is based on the anatomy and physiology of the cardiac autonomic nervous system (ANS), which consists of components from parasympathetic and sympathetic pathways. While parasympathetic activity causes negative chronotropic and dromotropic effects, the sympathetic system primarily affects cardiac contractility and regulates peripheral vasoconstriction. Excessive parasympathetic tone is an important cause of several clinical bradyarrhythmias such as functional atrioventricular block, some forms of sinus node dysfunction, and cardioinhibitory type reflex syncope.

Structurally, the ANS of the heart is represented by a complex neural network formed by extrinsic and intrinsic parts. The extrinsic part consists of the nuclei in the brain stem and along the thoracic segments of the spinal cord, as well as their axons en route to the heart. A ganglion is a cluster of neuronal cell bodies outside the brain. In the ANS, efferent axons from the central nervous system to the ganglion are known as preganglionic nerve fibers, and efferent axons from the ganglion to the effector organ are called postganglionic nerve fibers. While ganglia of the sympathetic division are located within the sympathetic chain

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or paravertebral ganglia, ganglia of the parasympathetic division are distributed mainly in fat pads within the epicardial surface of the heart, forming clusters known as the ganglionated plexuses (GPs).[4]

A catheter-based autonomic neuromodulation can be performed by endocardial ablation at the atrial wall, targeting the main GP locations. Since 2005 publication by Pachon et al.,[3] other investigators have reported positive results from small- to moderate-sized nonrandomized patient cohorts but currently, only one small, randomized study has been published reporting efficacy with the use of CNA in cardioinhibitory VVS.[5] In this prospective, open, randomized, controlled study, Piotrowski et al. compared a CNA procedure with optimal nonpharmacologic therapy in 48 patients (mean age 38±10 years). After a 24-month follow-up period they reported 8% syncope recurrence in the ablation group versus 54% in the control group (p=0.0004).[5] Acknowledging the lack of larger, randomized, multicenter, controlled trials, CNA has emerged as a promising therapy for patients with refractory VVS with a predominant cardioinhibitory response.

In this issue of Portuguese Journal of Cardiology, Silva et al.[6] report positive results from extracardiac vagal stimulation-assisted CNA. In this prospective, single-arm study, 19 patients (mean age 37.8±12.9 years; 68% male), who had recurrent syncope with a predominant cardioinhibitory component and refractory to conventional measures were included. Through a left atrial approach, the investigators targeted mainly 4 GP using a purely anatomic criterion. A stepwise strategy was performed, starting ablation at the ganglia most likely responsible, according to the clinical and extracardiac vagal stimulation (ECVS) response (sinus arrest versus AV block), with the right anterior ganglionated plexus (RAGP) being the main targeted GP, as expected. After the first GP ablation, if positive vagal response to ECVS persisted, ablation sequentially continued to other GPs. The procedure was acutely successful in all patients and 17 remain free of syncope after a mean follow-up of 21.0±13.2 months. There were no complications directly related to the procedure.

The investigators are to be congratulated on their work. However, limitations should be kept in mind, such as the nonrandomized nature and absence of a control group. In this scenario, some degree of placebo effect due to the procedure cannot be ruled out. Nevertheless, these results add useful information to the scientific community about the efficacy and safety of CNA. The more data we have about its benefits, the closer we are to considering CNA as a validated treatment for severe forms of cardioinhibitory VVS and perhaps to recommend it in future guidelines. But many issues concerning CNA are currently unanswered, and still matter of debate.[7]

First, the optimal catheter-ablation methodology to effectively modulate the intrinsic cardiac autonomic nervous system, and the number of GPs to be targeted remain unclear. Most investigators consider a multisite ablation from both right and left atria to be necessary to achieve a complete denervation, but one should acknowledge that an extensive biatrial approach may increase procedure risks and complication rate.

There are published heterogeneous ablation targets and concordant favorable clinical outcomes. For instance, Debruyne et al. demonstrated durable physiological changes and decreased syncope after unifocal right-sided ablation, targeting the RAGP from the right atria solely, in a population of 50 patients (mean age 42.4±17 years).[8] The procedure was associated with a lower burden of syncope (−95%) at 12 months versus baseline (p<0.001), without safety concerns. Thirty-seven patients remained entirely free of syncope at 12 months, and the syncope-free survival curve remained stable between the 12- and 30-month follow-up. Their protocol did not include ECVS response to guide ablation endpoints. Another empirical right atrial anatomical approach was also performed by Calo et al. in a cohort of 18 patients (mean age 36.9±11.2 years).[9] At a mean follow-up of 34.1±6.1 months, 16.6% subjects experienced syncope and 27.7% experienced only prodromal episodes. On the other hand, Piotrowski et al., who recently published the first randomized controlled study, demonstrated CNA efficacy using combined left and right atria ablation.[5]

So, which is the best CNA technique: one target, two targets, multiple targets? Bilateral, right- or left-sided ablation? A ''one-size-fits-all'' strategy or a tailored approach? Should ECVS always be employed to assist in a sequential GP ablation strategy? One should bear in mind that the ideal treatment should be a thoughtful balance between efficacy and safety, ensuring the lowest procedure risks and, at the same time, the least amount of denervation that can predict a good, sustained, clinical response. Head-to-head studies are needed to compare the success rate of the different techniques.

Second, although several investigators have shown favorable medium and long-term follow-up results, outcomes of GP ablation over a five year horizon or longer are yet to be reported. Clinical observations suggest that some degree of reinnervation is systematic, whatever the technique or ablation sites, although the proportions may vary. The extent and depth of the lesions caused by radiofrequency ablation may be crucial for this issue. The general concept is that if the cell body of the neuron is damaged, the cell will not regenerate, but if only the postganglionic fibers are damaged, axonal regeneration will occur and reinnervation will evolve. Some studies suggest that the effect of reinnervation is non-significant at two years.[5,10] Even if there is some degree of reinnervation,[9] it might be partial and there is not sufficient data indicating that the magnitude of recovery is associated with the risk of syncope recurrence.

Increased heart rate occurring after CNA could affect functionality, symptoms, and perhaps long-term prognosis. Besides, the natural history of reflex syncope in young patients is characterized by a high rate of spontaneous remission of syncope episodes with advancing age. So, one can hypothesize that complete and permanent atrial denervation might not be needed, and that the reinnervation process may not be a bad thing after all. Only very long-term follow-up studies will provide an answer to this issue.

Finally, there is consensus within the scientific community on the need for well-designed multicenter randomized efficacy trials, although real double blindness with the introduction of a sham procedure for the placebo control group might be a controversial issue (currently ongoing trial, NCT04755101). Future randomized trials should also compare CNA efficacy against current standard of care for cardioinhibitory VVS, validated by published guidelines, including general measures, drugs and, importantly, pacemaker implantation.

Answering these questions would be desirable before a widespread application of this promising catheter-ablation treatment.

Conflicts of interest

The author has no conflicts of interest to declare.

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