Carotid sinus syndrome treated by cardioneuroablation: Is sinus node denervation enough? Insights from a syncope recurrence report

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Introduction

Cardioneuroablation (CNA) has been proposed as an alternative treatment for patients with refractory vasovagal syncope (VVS), functional atrioventricular block (AVB), or functional bradyarrhythmia instead of classical treatment or pacemaker.[1] Vagal denervation is achieved by endocardial catheter ablation targeting atrial fibrillation nests (AFN)[2] and ganglionic plexus (GP)-related areas. We describe a clinical case of cardioinhibitory carotid sinus syndrome (CSS) treated with CNA, where partial vagal denervation was achieved over sinus node. However, there was recurrence 6 months later. The correct denervation was achieved in a redo procedure additionally eliminating the atrioventricular node (AVN) innervation, making the patient totally asymptomatic.

KEY TEACHING POINTS

- Vasovagal syncope recurrence after cardioneuroablation (CNA) may be associated with incomplete vagal denervation. Patient selection includes clinical features, Head up Tilt Test (HUTT), heart rate variability analysis, response to atropine intravenous infusion, and response to extracardiac vagal stimulation (ECVS).
- Partial or low-level vagal denervation may be a predictor of syncope recurrences in CNA.
- Elimination of the ECVS-induced vagal response is a rational, easy, and clear endpoint that measures the level of denervation obtained by CNA.

Case report

History of presentation

A 45-year-old male patient presented with history of repetitive syncope, in standing and supine position, without prodromes and related to neck extension and rotation movements, compromising quality of life and refractory to conventional maneuvers and treatment. He was diagnosed with type 2B cardioinhibitory VVS and CSS and submitted to CNA procedure in August 2019. Syncope recurrence occurred 6 months after ablation.

KEYWORDS Cardioneuroablation; Carotid sinus syndrome; Cardiac pacemaker; Ganglionic plexuses; Recurrent syncope
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Past medical history

Reversible systemic, metabolic, and coronary artery disease etiologies were excluded. The initial CNA procedure was performed in August 2019 guided by AFN mapping and guided anatomical GP landmarks, performing endocardial biatrial ablation of the areas related to the superior right atrial GP at the vena cava and right atria junction (GP1), over the surfaces related to the interatrial septal GP described as P point (GP2), posteromedial left atrial GP, and posterior right atrial GP (GP3), confirming vagal denervation of the sinus node by extracardiac vagal stimulation (ECVS), Pachon's technique.[3] However, persistence of vagal effect over the AVN was observed as transient AVB. At the end of the procedure, increased sinus rate (pre-CNA: 46 beats/min; post-CNA: 90 beats/min) and negative response to the carotid sinus massage (CSM) and post-CNA atropine test were achieved; no significant changes were observed on the A-V or A-H intervals.

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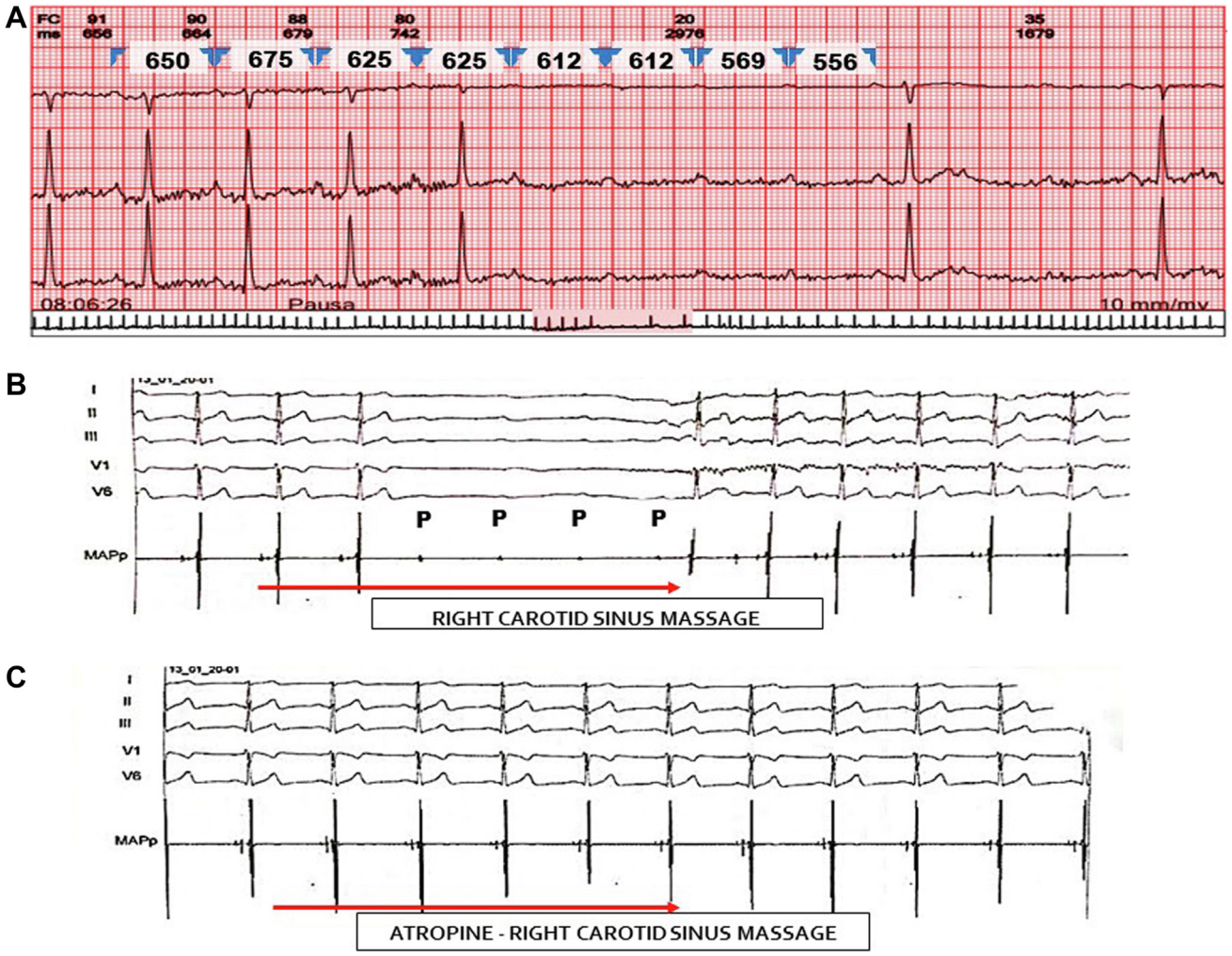

Figure 1 Six months after the first cardioneuroablation. **A:** Spontaneous atrioventricular block (AVB) during syncope. **B:** High-degree AVB during carotid sinus massage. **C:** Carotid sinus massage after atropine without AVB.

Investigation

After 6 months of follow-up syncope recurred, with 3 events. Fortunately, the second episode was registered on Holter recording, showing high-grade AVB during the syncope event. New clinical evaluation and CSM was performed, reproducing spontaneous findings: transient AVB and correlation with symptoms. This response was eliminated after 2 mg intravenous atropine infusion with no increase in sinus rate (Figure 1), and a redo CNA procedure was scheduled.

Management

Once reversible causes were excluded and refractoriness to conventional maneuvers was confirmed, and after informed consent of the patient, we considered the possibility of attempting a second CNA procedure. Electrophysiological evaluation confirmed absence of structural conduction system damage. ECVS was performed by using a deflectable quadripolar catheter that progressed up to the right and left jugular vein at the level of the upper wisdom tooth root apex (50 Hz / 50 µs / 70 volts / 5 s), showing no effect over sinus node rate. However, transient AVB was induced, reproducing the same finding obtained during CSM.

CNA was repeated under general anesthesia, with intravenous heparin aiming for activated clotting time from 300 to 400 seconds. Biatrial radiofrequency (RF) ablation of the neuro-endomyocardial interface guided by filtered endocardial electrograms (300–500 Hz), anatomical landmarks, and fractionation mapping (EnSite Velocity; Abbott, Chicago, IL) tracking AFN areas related GP4 location on the posterior surface of left superior and left inferior pulmonary veins antrum, and the GP3 location, the posterior medial GP in left and right atrium posterior septal space and coronary sinus roof,[4] using a FlexAbility (Abbott) irrigated catheter (30 W / 43°C / 30–60 s) guided by impedance drop of 10%–15% (Figure 2); nonsignificant changes were observed in electrophysiological parameters (Table 1). Total ablation time was 18 minutes.

New ECVS were performed at the left jugular foramen, the same location as preablation, and the following was observed: complete abolition of vagal-induced AVB without sinus bradycardia, maintaining 1:1 AV conduction even

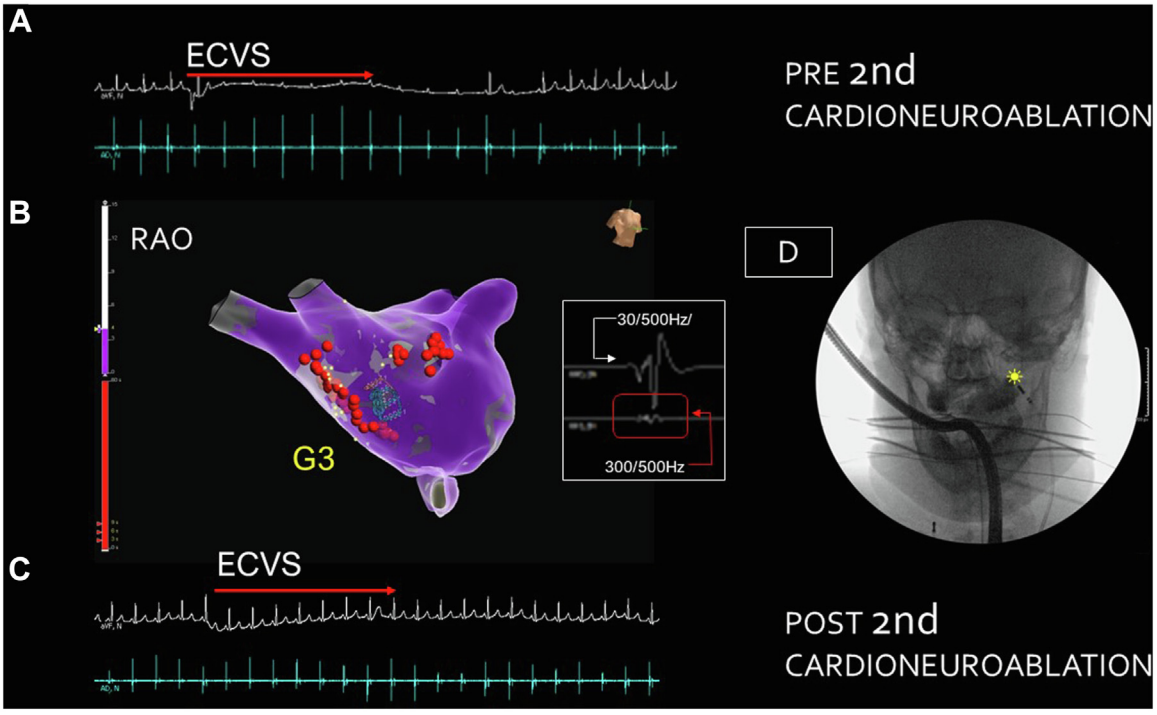

Figure 2 Before and after second cardioneuroablation (CNA): extracardiac vagal stimulation (ECVS) evaluation, atrial fibrillation (AF) nest, anatomical- and fractionation map–guided CNA. **A:** Initial ECVS response showing transient atrioventricular block (AVB) and absence of sinus rate changes. **B:** Electroanatomic mapping right anterior oblique (RAO) view of fractionation map location G3 (area related to posterior medial ganglionated plexus) and radiofrequency (RF) lesion set. Red circle = filtered ablation catheter electrogram (300–500 Hz) for atrial fibrillation nest mapping at the G3 location; red dots = RF lesion set. **C:** ECVS response after biatrial second CNA showing absence of vagally induced asystole or AVB. **D:** Left vagus ECVS catheter position.

under right atrial pacing at 400 ms, achieving complete elimination of the vagal AVN response. At the end of the second CNA, CSM was repeated with no effect on the sinus node and the AVN conduction (Figure 2). Additionally, at this point, atropine test was performed with 2 mg intravenous infusion, reconfirming absence of heart rate increase. The patient was discharged without complications 2 days postprocedure, and oral anticoagulation was prescribed for 1 month.

Follow-up

Clinic evaluation was done at 1, 3, 6, 12, and 20 months, with 12-lead electrocardiogram and CSM at the third and fourth visits, with no vagal response or complications. Heart rate variability 24-hour Holter recording analysis showed sympathetic predominance, no signs of significant reinnervation (Figure 3), and no symptoms or syncope recurrence.

Table1 Pre- and post-cardioneuroablation electrophysiological parameters of the second cardioneuroablation

	PRE CNA	Post CNA
HR (beats/min)	85	85
P-R (ms)	154	144
A-H (ms)	68	66
WC (ms)	154	171
EARP (ms)	320	300

EARP = effective atrial refractory period; HR = heart rate; WC = Wenckebach cycle.

Completing 20 months after the second CNA, the patient remains free of dizziness and syncope episodes, with normal quality of life and self-confidence.

Discussion

Since the first CNA studies it has been shown that elimination of the vagal reflex may be useful in patients with cardioinhibitory VVS, providing a possible indication of the CNA technique described by Pachon in 2005[1] as an alternative to pacemaker implantation.[5–7] However, the denervation must be targeted to the sinus node and also to the AVN.

We report a case of a patient suffering from repetitive syncope, refractory to conventional treatment. CSS was confirmed by clinical features and CSM. Pacemaker implantation was considered following the guideline recommendations. It is well known that pacemakers including closed-loop pacing therapy have a sufficient evidence level of recommendation.[8] However, the patient refused the pacemaker implantation, so the CNA was proposed as an alternative treatment.

To perform an efficient CNA, extensive denervation must be achieved in the index procedure. It is important because there is significant natural reinnervation, mainly in the first year post-CNA.[9] For this purpose, it is recommended to have a solid way to confirm the denervation degree during the procedure. In the early studies, changes in the electrophysiological parameters showing parasympathicolysis and

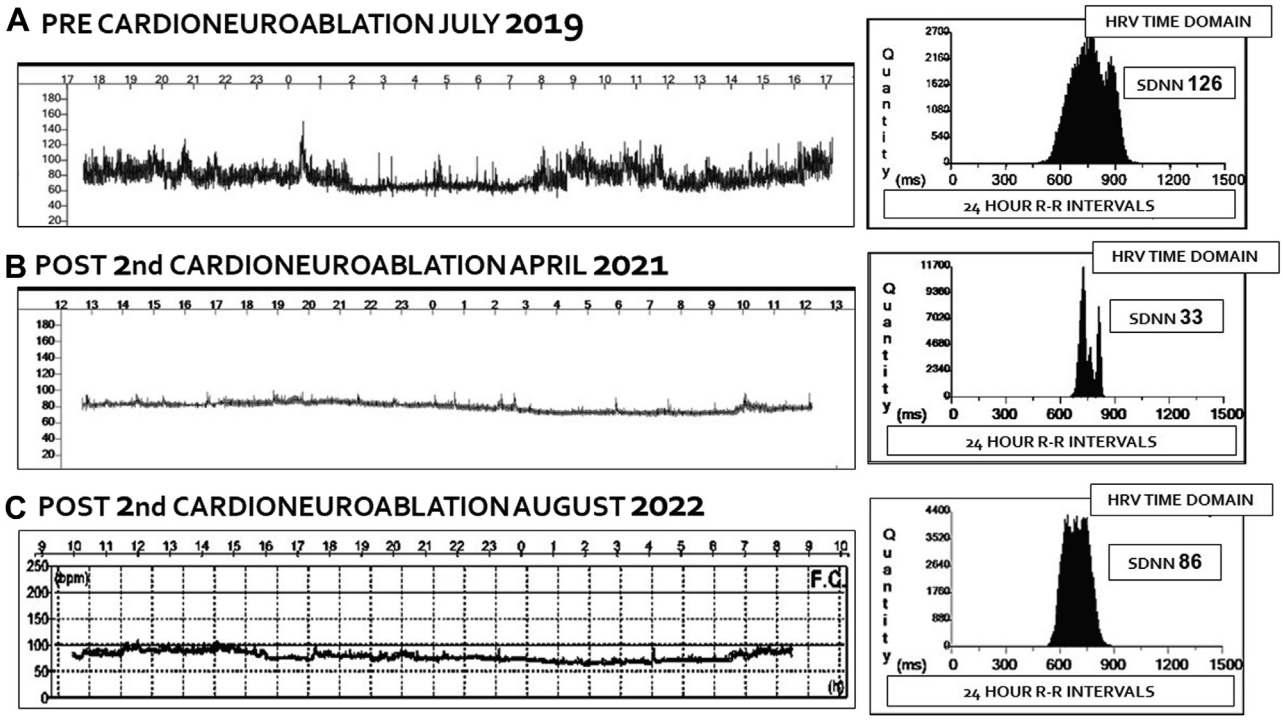

Figure 3 The 24-hour ventricular heart rate pattern and heart rate variability (HRV) in time domain. **A:** Before cardioneuroablation. **B:** Six months post second cardioneuroablation. **C:** Twenty months post second cardioneuroablation.

the absence of the atropine response at the end of the procedure were the gold-standard parameters to confirm vagal denervation.[7,10]

Since 2015, there has been a significant improvement in the technique with the development of the ECVS, which makes it possible to have a gradual assessment of the vagal denervation as the CNA progresses. This tool assumes that the CNA should be resumed until the complete elimination of the vagal response by the ECVS. In this patient the first CNA was performed obtaining sinus node denervation only, assuming that it was sufficient for symptom release because no spontaneous AVB was observed and CSM cardioinhibition was eliminated. However, after the first CNA the physiopathology changed, and the syncope recurred because of high-grade AVB. At first the main problem was sinus node arrest and then, the sinus node vagal denervation having been eliminated, the problem returned by cardioinhibitory effect over the AVN. If there is a sinus arrest the AVB is not observed by the absence of atrioventricular (AV) conduction. This is very illustrative, as it shows that in the reflex syncope both innervation of the sinus node and the AVN must be treated in the index ablation procedure. The sinus node vagal denervation after the first CNA was clear, considering that there was no more CSM-induced bradycardia by CSM and no increase in sinus rate by atropine. The AV node innervation persistence after the first CNA was demonstrated by the spontaneous high degree of AVB during syncope recurrence and by the new CSM. This new CSM had no effect on the sinus node, confirming the persistence of sinus node denervation.

There are few reports in the literature describing CNA as a treatment for carotid sinus syndrome,[11] or addressing recurrence situations,[12] or describing applicability as a redo procedure, and no information about recurrence predictors. We consider that partial or low-level parasympathetic denervation, reinnervation process, variations in GP locations, and low predictive value of increased heart rate and atropine response as endpoints were decisive predictors of recurrence in this case.

The results in this patient also suggest that identification and ablation of the neuro-endomyocardium interface on the right and left atria, obtaining transmural lesions for ablation of body cell and fibers of parasympathetic neurons, is essential for long-term denervation, being necessary to achieve a consistent level of denervation and reduce reinnervation processes. Tracking of AFN and defining the location of the GP was achieved by filtered electrograms, anatomical landmarks, and fractionation mapping in sinus rhythm, as described in the first study and reproduced by several authors.[10,13,14]

With this clinical case of syncope and vagal etiology, we demonstrate that CNA represents an alternative for the treatment of refractory CSS reflex syncope. The response to ECVS, CSM, and atropine infusion was completely abolished through parasympathetic denervation evaluated sequentially until full elimination of the vagal response, allowing observation of the effect of RF ablation on each GP region and measuring the effect of radiofrequency ablation on every single GP area applying ECVS as a guide, defining a high level of vagal denervation.

The maximum level of denervation achieved was sufficient to avoid new syncope and presyncope episodes after a follow-up of more than 20 months. This case describes the

feasibility, efficacy, and safety of the CNA in CSS, with satisfactory results in a long-term follow-up.

Conclusion

In cases of cardioinhibitory reflex syncope, the treatment of the sinus node innervation as well as of the AVN is mandatory to prevent recurrences.

After treating the sinus node innervation alone, the syncope may recur owing to changes in the physiopathology of sinus arrest to high-grade AVB.

Elimination of the sinus node and AVN vagal response by ECVS is critical to achieve the best outcome for CNA in the cardioinhibitory reflex syncope.

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