

Vasovagal syncope with isolated atrioventricular block following cardioneuroablation demonstrating distinct innervation of the sinus and atrioventricular nodes



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Introduction

Vasovagal syncope (VVS) is a common and typically benign cause of transient loss of consciousness. Nevertheless, it can cause reduced quality of life and disability, prompting consideration of a pacemaker implant. In younger patients, pacemaker implantation creates a risk-to-benefit dilemma due to the risk of long-term exposure to potential device-related complications.^{1,2} First described by Pachon and colleagues in 2004, endocardial radiofrequency (RF) catheter ablation of the myocardial tissue adjacent to and containing the autonomic nerve fibers related to the intrinsic cardiac parasympathetic ganglionated plexi (GPs), termed cardioneuroablation (CNA), has been shown in observational cohorts to successfully reduce the burden of VVS in selected patients.^{3–6} The primary GPs providing vagal innervation to the sinus node include the aortic–superior vena cava ganglionated plexus (Ao-SVC GP), right superior ganglionated plexus (RSGP), right inferior ganglionated plexus (RIGP), left superior ganglionated plexus (LSGP), left inferior ganglionated plexus (LIGP), and Marshall tract ganglionated plexus (MTGP).^{7,8} Atrioventricular (AV) nodal function is mostly controlled by the posteromedial ganglionated plexus (PMGP), located near the coronary sinus in the fat pad at the inferior vena cava–left atrial junction. There is significant overlap and interconnections between GPs, and the AV node receives additional parasympathetic fibers from the Ao-SVC GP, RSGP, and MTGP.^{7,9,10}

We present a case of CNA in a young patient with VVS and documented cardioinhibitory response with dramatic si-

KEY TEACHING POINTS

- The sinus node and atrioventricular (AV) node have partially distinct parasympathetic innervation from atrial epicardial ganglionated plexi. Cardioneuroablation of only the sinus node–innervating sites can unmask vagally mediated AV block because AV conduction cannot be assumed during sinus arrest. Targeting the AV node innervation requires further ablation of the posteromedial ganglionated plexus area.
- Implantable loop recorders in patients with refractory vasovagal syncope can help determine a cardioinhibitory vs vasodepressor response, as well as the vagal effect on the sinus and AV nodes. The presence of nonconducted p waves during a vagal event necessitates a full cardioneuroablation.
- Cardioneuroablation endpoints when targeting the AV node can include reductions in PR interval, AV nodal effective refractory period, and AH interval. The reduction in AH interval is best demonstrated at faster atrial paced cycle lengths. An external vagal denervation control with extracardiac vagal stimulation is the optimal method for assessing procedural endpoints.

KEYWORDS Autonomic nervous system; Cardioneuroablation; Ganglionated plexi; Implantable loop recorder; Radiofrequency ablation; Syncope (Heart Rhythm Case Reports 2022;8:765–770)

Funding Sources: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. **Disclosures:** Jordan Zinner is an employee of Biosense Webster Inc. All other authors report no conflicts of interest. **Address reprint requests and correspondence:** Dr Timothy Maher, Beth Israel Deaconess Medical Center, Harvard Medical School, 185 Pilgrim Avenue, Baker 4, Boston, MA 02215. E-mail address: tmaher@bidmc.harvard.edu.

nus arrests and nonconducted p waves. The initial ablation targeted the sinus node–specific GPs; however, the patient experienced recurrent syncope with exclusively AV nodal block. A second CNA targeting the PMGP was performed, which eliminated further syncope. The case highlights the distinct sinus and AV node GP influence and the need for a complete set of CNA lesions in patients with documented sinus and AV node involvement.

Case report

The patient was a 36-year-old man with 12 episodes of syncope that started 4 months before his presentation to the electrophysiology (EP) laboratory. He reported lightheadedness, déjà vu, and a warm flushing sensation over his head before losing consciousness. His cardiac and neurological workup, including 1-week event monitor, transthoracic echocardiogram, and electroencephalogram, was unremarkable. Baseline 12-lead electrocardiogram showed sinus bradycardia at 58 bpm, with a PR interval of 207 ms (Figure 1A). An intravenous injection of atropine 1 mg resulted in an increase in sinus rate from 53 to 85 bpm, with PR shortening from 236 to 176 ms. An implantable loop recorder (ILR) was inserted, which captured sinus rate acceleration followed by gradual slowing and sinus arrest with occasional nonconducted P waves (Figures 1B and 1C) at the time of syncope. A diagnosis of VVS with predominant cardioinhibitory response was made. Given the patient's young age, recurrent disabling episodes, and desire to avoid permanent pacemaker implantation, he was referred to the EP laboratory for CNA.

The patient's medical history included anxiety, migraine headaches, and gastroesophageal reflux disease. He was taking escitalopram 10 mg by mouth daily and ibuprofen 800 mg by mouth as needed for pain.

Baseline electrophysiological study (EPS) showed AH of 137 ms and HV of 50 ms at a sinus cycle length of 1290 ms. A biatrial map was created using the CARTO® 3 Version 7 electroanatomic mapping system (Biosense Webster Inc.) with a Biosense Webster PentaRay multielectrode mapping catheter and Thermocool Smarttouch Surroundflow (STSF) ablation catheter to manually annotate areas of highly fractionated (>4 deflections) atrial electrograms (EGMs) as potential areas of GPs as described by Aksu et al.⁵ Ablations lesions were delivered at the anatomic sites of the LSGP, MTGP, LIGP, RSGP, and Ao-SVC GP. A vagal response with sinus slowing was seen during LSGP ablation, and a sinus rate increase from 60 to 78 bpm was seen during RSGP and Ao-SVC GP ablation (Figure 2A). Extracardiac vagal stimulation (ECVS) was not performed because of difficulty in advancing the catheter to the jugular veins. After ablation, atropine 2 mg was administered intravenously, with no change in sinus rate. The patient tolerated the procedure well and was discharged the same day with 1-month therapy of apixaban 5 mg by mouth twice a day and aspirin 81 mg by mouth daily. His immediate postprocedure electrocardiogram showed a sinus rate of 77 bpm with PR interval of 210 ms.

For the next 5 months, the patient reported 2 prodromal episodes without syncope and no corresponding bradycardia, suggestive of an isolated vasodepressor response. ILR interrogations registered a sustained marked reduction in heart rate variability. Five months after his index CNA, the patient had recurrent syncope corresponding to an 11-second episode of complete AV block with ventricular asystole (Figure 3A) and minimal change in sinus rates. The patient

was taken back to the EP laboratory for a repeat CNA procedure with specific targeting of the PMGP from the left and right atrium and the floor of the coronary sinus os. Transient AV block and PR prolongation was noted at 2 sites near the PMGP during RF application (Figure 2B). After the ablation, there was a decrease in PR interval from 213 to 176 ms, AV nodal Wenckebach cycle length from 500 to 450 ms, AV nodal effective refractory period from 600/450 to 600/370 ms, and progressive decrease in AH interval with decreasing pacing cycle length (700 ms: from 101 to 93 ms; 600 ms: from 142 to 120 ms; 550 ms: from 163 to 129 ms; 500 ms: from 193 to 142 ms) (Supplemental Figure 1), with no change after atropine challenge. No further syncopal events or bradycardic events were noted on ILR tracings during 9 months of follow-up. Two severe presyncopal episodes occurred following exercise, with ILR showing sinus tachycardia at 100–110 bpm with normal AV conduction (Figure 3B). The patient has experienced a sustained increase in sinus rate and a sustained reduction in heart rate variability (Figure 3C).

Discussion

Although observational research has demonstrated that CNA in young patients with VVS can reduce the burden of syncope with the goal of avoiding permanent pacemaker implantation,¹¹ its practical techniques are still evolving. Our case demonstrates the selective impact of excessive vagal tone on the sinus and AV nodes during a cardioinhibitory response leading to both sinus arrest and AV block. Our initial strategy of sinus node–directed ablations resulted from a desire to avoid higher-risk PMGP ablations, as well as an initial underrecognition of signs of vagal effect on the AV node (such as prolonged baseline PR interval and the presence of nonconducted P waves during some initial syncopal events) (Figure 1C). However, the effect was a shift of the syncopal mechanism from primarily sinus node arrest to isolated AV block and a failure to achieve a complete clinical effect.

Therefore, it is advisable to perform a full CNA on patients with VVS because many individuals may have episodes with varying combinations of sinus arrest and AV block, which can be masked by the absence of P waves during sinus arrest. To avoid the time and procedural risk required for ablation of all the accessible GPs during CNA (which requires transeptal access, intravenous anticoagulation, and ablation near the AV node), some groups favor a limited CNA targeting the Ao-SVC GP and RSGP from the right atrium.¹² However, successful PMGP ablation can require left atrial ablation.¹¹ In addition, during RF application near the PMGP, transient AV block and PR prolongation were observed, highlighting the risk of ablation in this area. It can be difficult to determine whether the transient AV block is due to parasympathetic GP stimulation, coronary artery spasm, or AV node damage, thus putting the patient at risk for requiring a permanent pacemaker.

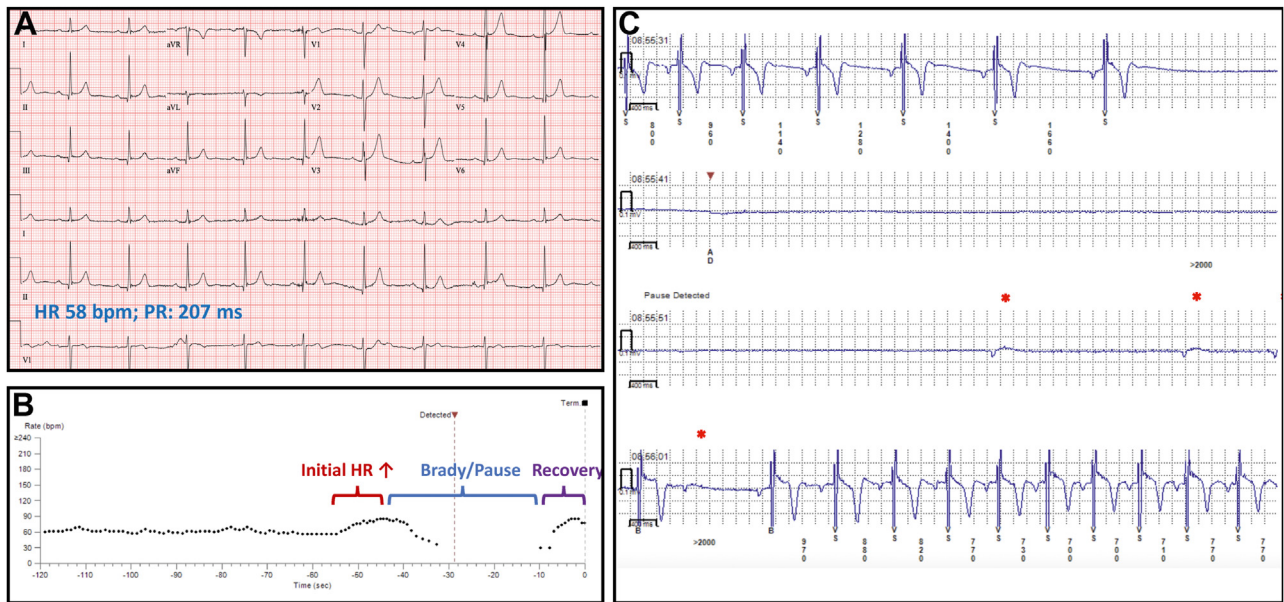


Figure 1 Baseline electrocardiogram (ECG) and syncope episode. **A:** ECG with sinus rate 58 bpm and PR interval of 207 ms. **B:** Heart rate (HR) plot from implantable loop recorder during a syncopal episode. **C:** Implantable loop recorder ECG tracing during syncope, with sinus slowing, sinus arrest, and few non-conducted P waves (red asterisks) showing vagal effects on both the sinus and atrioventricular nodes.

Targeting the PMGP and related nerve fibers can be performed safely to treat functional AV block as demonstrated by Pachon et al⁴ in 2006 using spectral mapping techniques and has been reproduced by other groups using fractionated atrial EGMs or anatomic landmarks to guide the ablation.¹⁰ Assessment of AV node denervation can be difficult in the setting of a normal baseline PR (AH) interval because changes in the PR interval after CNA may be subtle. In reported cohorts of CNA for VVS, endpoints include lack of increase in the P-P interval after high-dose intravenous atropine injection, reduction in AH and AV Wenckebach cycle length (AVWB), absent vagal responses on high-frequency stimulation at GP sites, elimination of fractionated EGMs at presumed GP sites, and absent vagal responses on ECVS.^{5,13–15}

To confirm that PMGP ablation provided vagal denervation of the AV node, we performed programmed stimulation documenting shortening of the AH intervals across the wide range of paced cycle lengths, AVWB, and AV nodal effective refractory period. However, in our case the AH reduction was only modest during longer atrial cycle lengths. With atrial pacing at faster cycle lengths, the postablation reduction in AH was more marked, which helped unmask the AV nodal autonomic modulation post-CNA. The lack of significant change in AV nodal EPS parameters after vagolysis with atropine injection provided further evidence of vagal denervation.

Finally, this case demonstrates the value of ILRs in patients with refractory VVS. The ILR was able to (1) diagnose a cardioinhibitory mechanism of VVS, an important criterion for CNA candidacy; (2) demonstrate the mechanism of VVS,

as even with the first recorded episode there was evidence of both sinus arrest and AV block during the episode, predicting the need for a full CNA targeting the innervation of both the sinus and AV nodes; and (3) monitor for sustained response to CNA with longitudinal assessment of heart rate and heart rate variability.

Study limitations

Several limitations to the CNA approach performed in this patient reflect our early experience with this ablation approach. No comprehensive EPS was performed during the first CNA procedure, so whether the original CNA had an effect on AV nodal innervation or reinnervation occurred during follow-up is not clear. ECVS was not performed because of difficulty in advancing the catheter to the jugular foramen, which prevented the ability to test for full denervation during both procedures. ECVS is important and may have a learning curve; its use is recommended, and techniques such as ultrasound guidance and guidewires can increase the rates of success. It is possible that ECVS or higher-dose atropine could have revealed incomplete denervation from the CNA, so these maneuvers should be attempted. Although a post-atropine AVWB test was not performed, the PR and AH intervals and AV nodal effective refractory period all showed evidence of vagolysis. Appropriate dosing of atropine is critical, as up to 0.04 mg/kg may be required to assess for complete vagolysis.¹³ Finally, interpretation of the procedural endpoint can be partially confounded due to concomitant sympathetic fiber destruction.

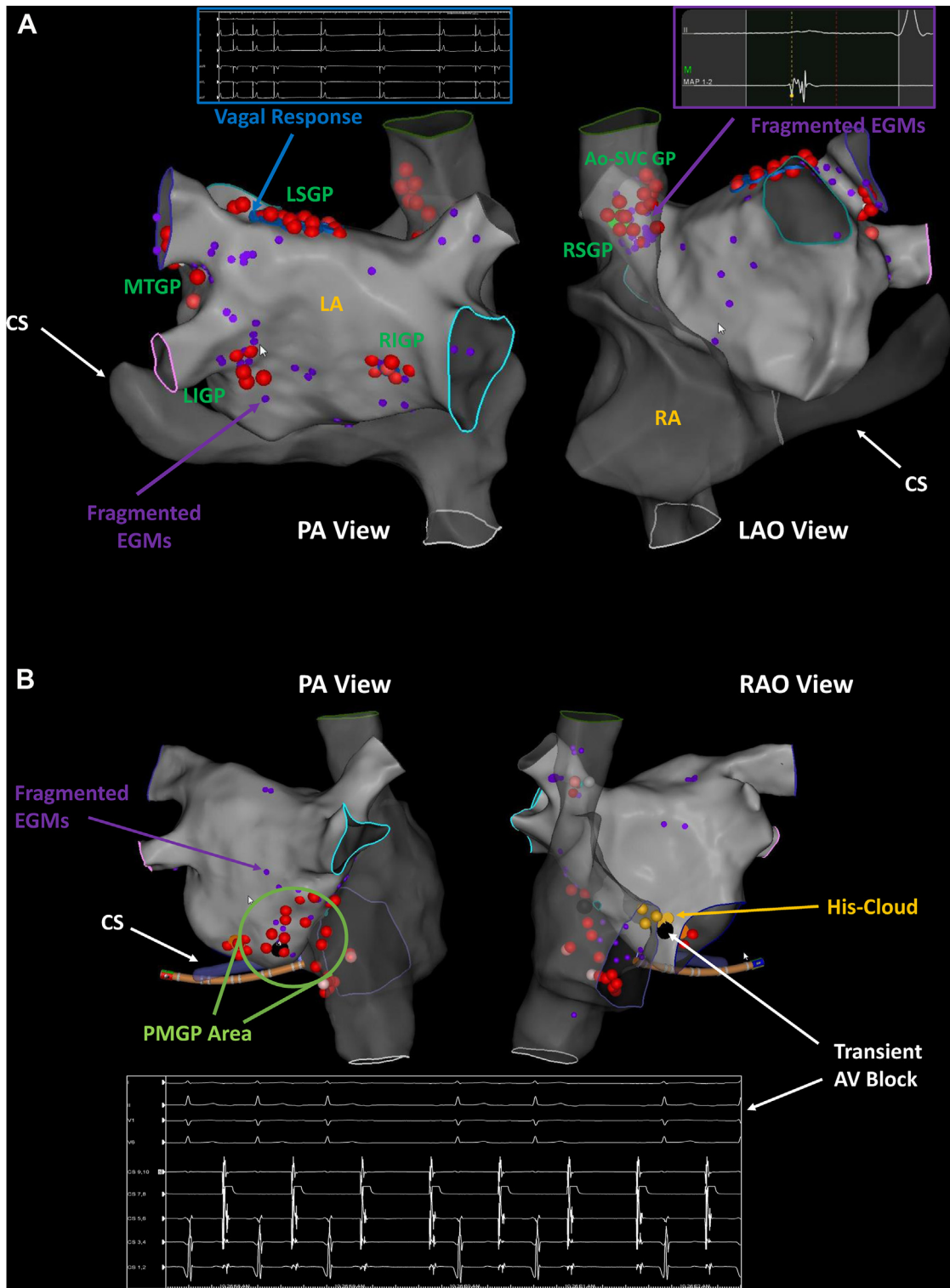


Figure 2 Cardioneuroablation procedure. **A:** Biatrial map from the index cardioneuroablation showing the ablation lesion tags (red tags), fragmented atrial bipolar electrograms (EGMs) (purple tags; inset: with atrial EGM), and sites with vagal response during radiofrequency (RF) ablation (blue tags; inset: ECG of vagal episode). **B:** Biatrial map from the redo ablation targeting the posteromedial ganglionated plexus (PMGP) and showing the ablation lesions (red tags), fragmented atrial bipolar EGMs (purple tags), His-bundle EGM locations (yellow tags), and areas with PR prolongation or transient atrioventricular (AV) block with RF application (black tags; inset of with AV block). Ao-SVC GP = aortic–superior vena cava ganglionated plexus; CS = coronary sinus; LA = left atrium; LAO = left anterior oblique; LIGP = left inferior ganglionated plexus; LSGP = left superior ganglionated plexus; MTGP = Marshall tract ganglionated plexus; PA = posteroanterior; RA = right atrium; RAO = right anterior oblique; RIGP = right inferior ganglionated plexus; RSGP = right superior ganglionated plexus.

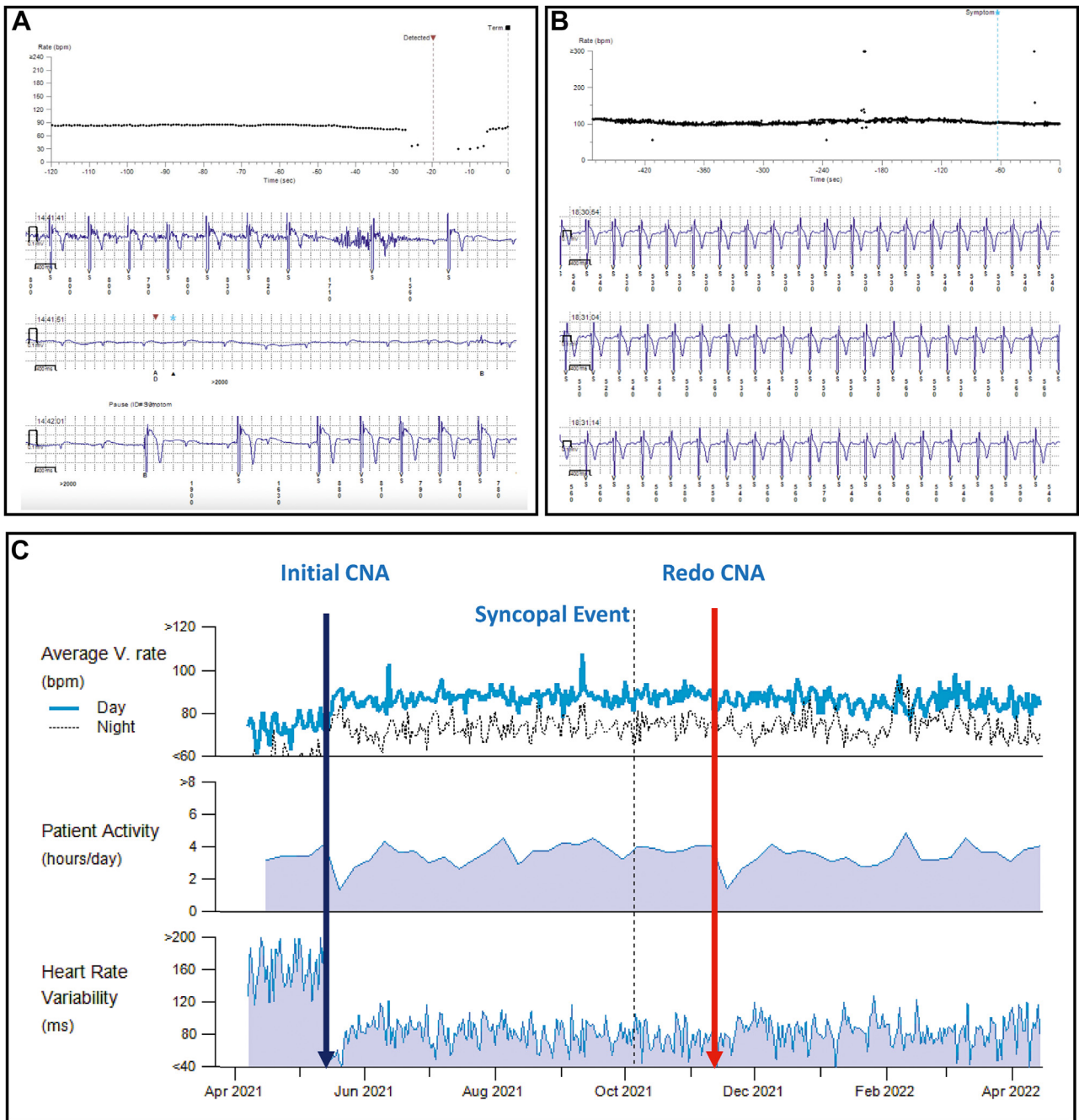


Figure 3 Implantable loop recorder episodes. **A:** Implantable loop recorder heart rate plot and electrocardiographic tracing showing 11 seconds of atrioventricular (AV) block. **B:** Postablation prodromal episode without bradycardia. **C:** Time plots of average heart rate, patient activity, and heart rate variability with markers showing the time of the initial cardioneuroablation (CNA), recurrent syncope with isolated AV block, and redo cardioneuroablation targeting the posteromedial ganglionated plexus. Note the sustained increase in heart rate and sustained drop in heart rate variability after the initial ablation.

Conclusion

CNA can reduce the burden of VVS. Isolated ablation of the GPs providing innervation of the sinus node may only partially treat the cardioinhibitory response due to shifting of the syncopal mechanism from sinus arrest to vasovagal AV. Therefore, patients with VVS undergoing CNA may require ablation of the PMGP to best reduce recurrent syncope.

Appendix

Supplementary data

Supplementary data associated with this article can be found in the online version at <https://doi.org/10.1016/j.hrcr.2022.08.007>.

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