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CASE REPORT

CLINICAL CASE

Cardioneuroablation for Drug Refractory Vasovagal Syncope After COVID-19 Infection

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ABSTRACT

Cardioneuroablation is a novel approach to treat patients with recurrent vasovagal syncope (VVS), targeting the ganglionated plexi around the atria and thus reducing the vagal input to the heart. This study reports a case of drug-refractory VVS after COVID-19 infection, successfully managed with cardioneuroablation. (J Am Coll Cardiol Case Rep 2024;29:102373) © 2024 Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

HISTORY OF PRESENTATION

A 30-year-old previously healthy woman presented for an evaluation regarding pacemaker implantation after three episodes of severe presyncope, and one brief syncopal episode without injury, first starting 2 months after COVID-19 infection documented by a polymerase chain reaction test. She also reported decreased exercise capacity and fatigue during the same period, but no dyspnea or chest discomfort. Her symptoms prevented her from working as an active-duty police officer and interfered with her daily activities. She denied any personal history of vasovagal syncope (VVS), presyncope, orthostatic intolerance, alcohol or drug use, and she was never pregnant, had no chronic diseases, and had no family history of VVS, atrioventricular (AV) blocks, or need for pacemaker implantation. Prior to COVD-19 infection, she was previously able to vigorously exercise and work as an active-duty police officer without limitations. Physical examination including orthostatic vital signs was unremarkable. Specifically, blood pressure in the supine and post-standing for 3 minutes was in the range of 110 to 120/60 to 70 mm Hg and heart rate was 70 to 80 beats/min, whereas in the standing position blood pressure and heart rate were in the range of 110 to 120/60 to 70 mm Hg and 75 to 85 beats/min, respectively. A previous ambulatory patch cardiac monitor revealed a 5.2-second pause due to intermittent heart block (**Figure 1**), associated with near syncope,

LEARNING OBJECTIVES

- To evaluate treatment options for patients with cardioinhibitory VVS to improve symptoms.
- To recognize eligible patients with cardioinhibitory VVS for CNA.
- To summarize the evidence for using CNA for the treatment of cardioinhibitory VVS.

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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ABBREVIATIONS AND ACRONYMS

AV = atrioventricular

CNA = cardioneuroablation

GP = ganglionated plexi

HCF = human chorionic gonadotropin

ILR = implantable loop recorder

TSH = thyroid stimulating hormone

VVS = vasovagal syncope

but other symptoms of mild dizziness and fatigue occurred during sinus rhythm at 85 to 90 beats/min.

PAST MEDICAL HISTORY

The patient was fit and healthy prior to COVID-19 infection. She had been vaccinated with two doses of the Pfizer-BioNTech messenger RNA vaccine several months prior to COVID-19 infection. COVID-19 infection was manifest with symptoms of cough and fever that spontaneously resolved within 7 days without need for hospitalization or adjuvant therapy.

DIFFERENTIAL DIAGNOSIS

Differential diagnosis included VVS associated with long COVID, Lyme disease, primary genetically mediated conduction system disease, or infiltrative cardiomyopathy.

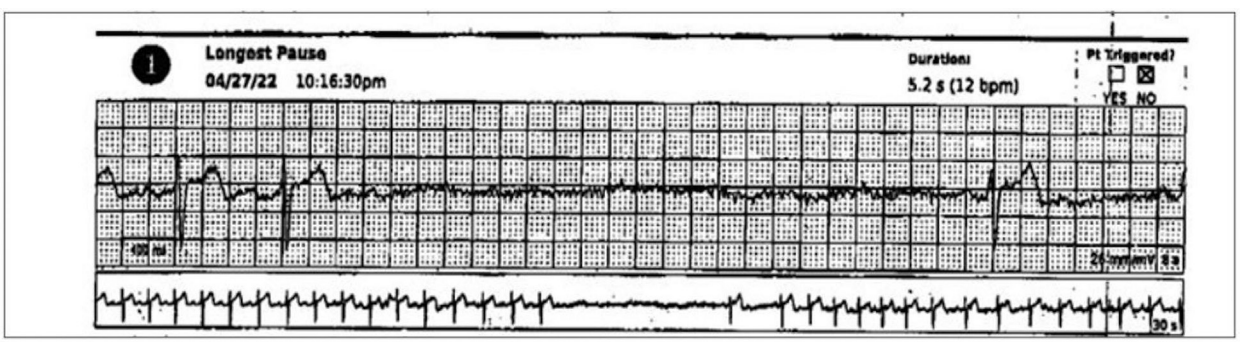
INVESTIGATIONS

Baseline electrocardiogram was normal (Figure 2). Laboratory results, including TSH, cortisol, beta-HCG, and Lyme titers, were normal. Echocardiogram and cardiac magnetic resonance were also normal.

MANAGEMENT

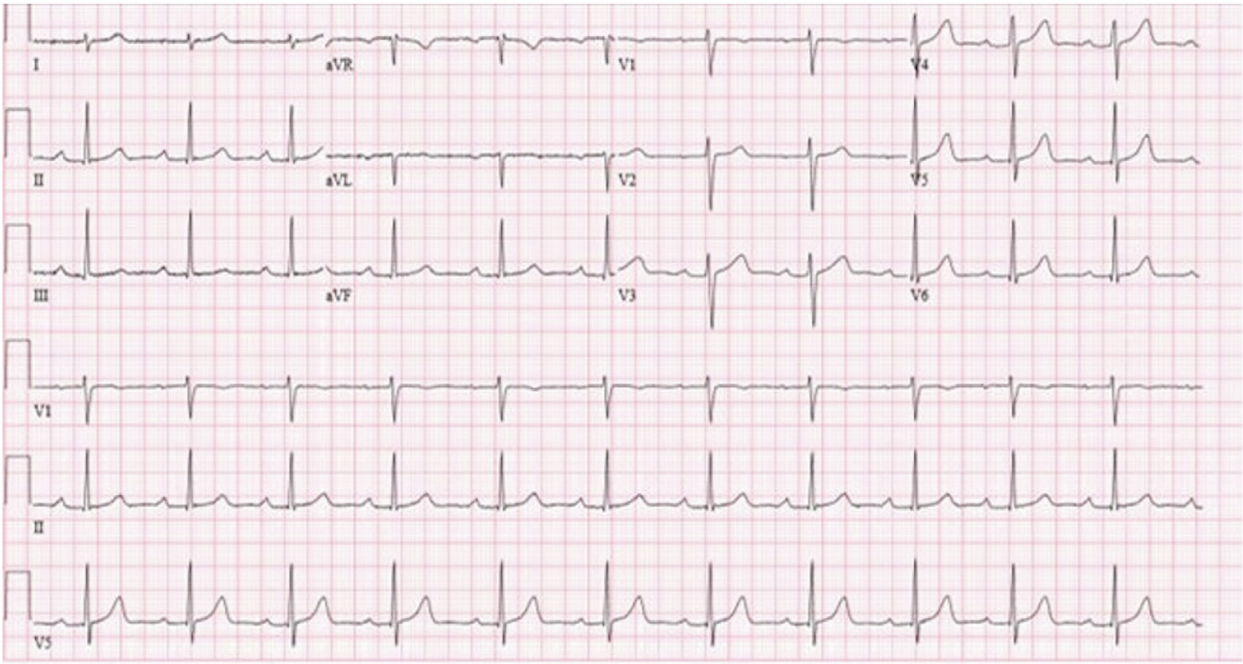
Due to the patient's young age, and high likelihood of dysautonomia provoked by COVID-19, a pacemaker was not recommended. She was managed conservatively with 4 weeks of increased salt and water intake; despite that, she continued to have dizziness, but not syncope. Midodrine was initiated but discontinued due to lack of clinical improvement and suboptimal compliance. She was not interested in fludrocortisone or selective serotonin reuptake inhibitor therapy. Although theophylline was considered, the patient avoided caffeine due to feeling jittery; therefore, we did not try theophylline for this patient. Despite unclear benefits in clinical studies, she was treated with disopyramide 150 mg twice a day for its anticholinergic effects, which resulted in reducing symptoms to 2 mild episodes monthly. After a repeat 2-week ambulatory patch cardiac monitor, she experienced a single episode of dizziness associated with intermittent AV block, preceded by P-to-P prolongation, suggesting a vagal component (Figure 3). After detailed discussion, including consideration of a leadless pacemaker, and her desire to eventually return to full duty as a policewoman, she opted for cardioneuroablation (CNA) and agreed to an implantable loop monitor (ILR) prior to proceeding. A contact force-sensing catheter (TactiCath Contact Force Ablation Catheter, Sensor Enabled, Abbott) was used to create a three-dimensional electroanatomical voltage map of the right atrium. The left atrium was mapped using the fractionation mapping software with a multielectrode grid catheter (Advisor HD Grid Mapping Catheter, Sensor Enabled, Abbott) and a contact force-sensing catheter. Areas with sinus electrograms with more than 3 deflections crossing the baseline were identified as potential ganglionated plexi (GP) sites. Although we attempted to confirm these sites with high frequency stimulation, we did not elicit any bradycardia. We did use intracardiac echocardiography as well to confirm the electroanatomical sites because the procedure was done without any fluoroscopy. Radiofrequency ablation was performed anterior to the right and left

FIGURE 1 Initial Outpatient Rhythm Monitor



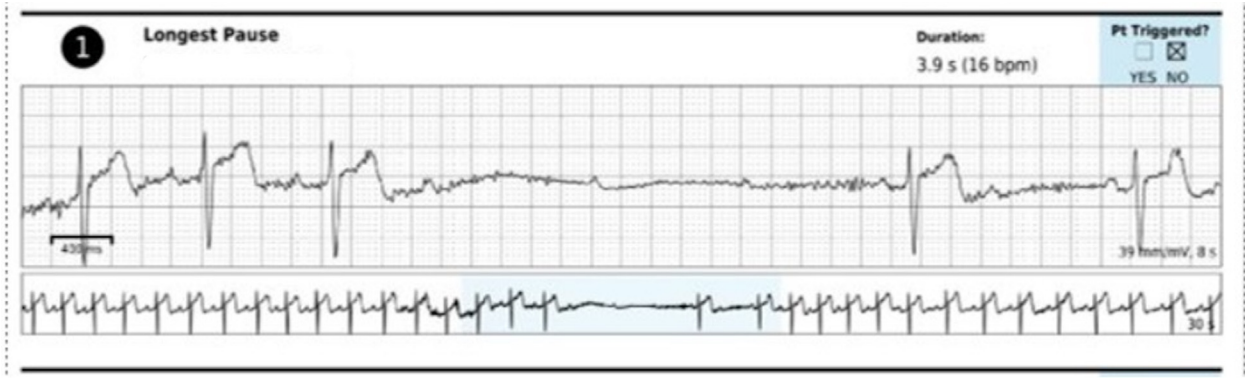
A 5.2-second pause, likely atrioventricular block, is revealed.

FIGURE 2 Baseline Electrocardiogram



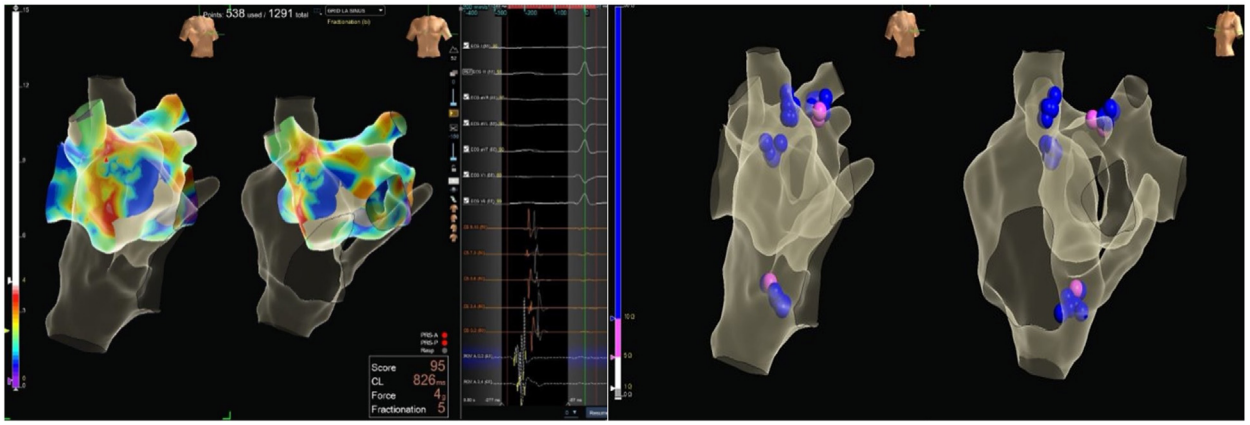
superior pulmonary veins (superior left atrial GP), posterior coronary sinus ostium (inferior paraseptal ganglionated plexus), and between the anterior superior vena cava and aorta (superior paraseptal ganglionated plexus) with a net decrease in sinus cycle length from 890 to 715 milliseconds, a decrease in AH interval from 284 to 110 milliseconds, but no change in the HV interval post-ablation (Figure 4). AV nodal Wenckebach cycle length at baseline under anesthesia was 590 milliseconds and post-ablation was 420 milliseconds. Although atropine was considered after ablation to assess vagal denervation, the procedure was done under general anesthesia due to the patent's anxiety and confounding effects of this on her vagal tone may have made the results difficult to interpret. Additionally, there was a

FIGURE 3 Outpatient Rhythm Monitor After Conservative Treatment



A 3.9-second pause consistent with atrioventricular block is revealed. The slowing of the P-P interval is suggestive of a vagal etiology.

FIGURE 4 Mapping and Ablation Sites



(A) Left atrial fractionation mapping revealing probable sites of parasympathetic ganglia (red). (B) Sites of radiofrequency ablation anterior to the right and left superior pulmonary veins, posterior CS ostium, and anterior superior vena cava. CS = coronary sinus.

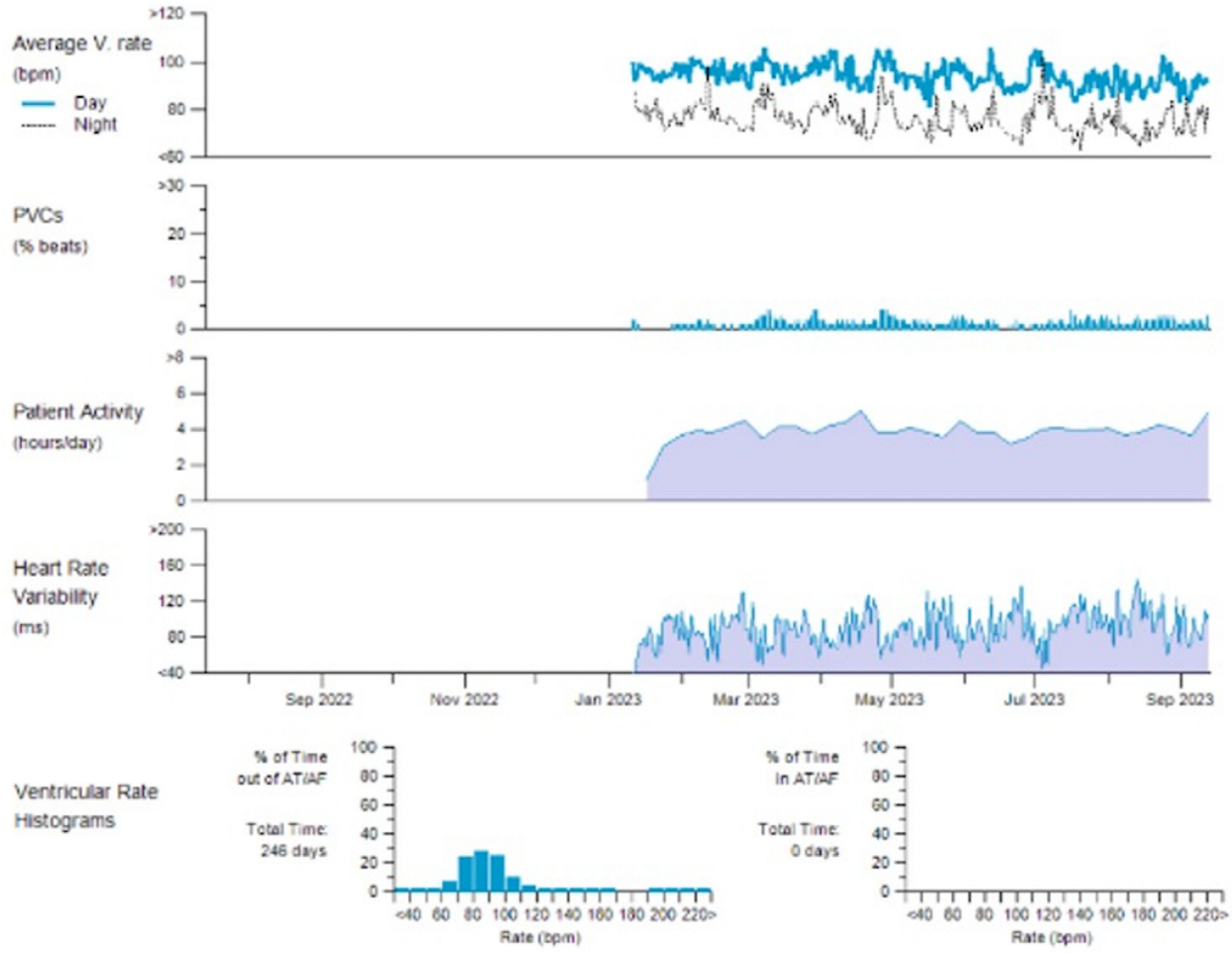
marked reduction in both the sinus cycle length and AH interval under general anesthesia suggesting a strong vagolytic effect. An ILR was placed at the end of the procedure. Her prior 1- to 2-week external monitors had shown sinus rates of 40 to 170 beats/min with an average heart rate of 72 beats/min and transient drops to 12 to 30 beats/min due to AV block. Since her ablation, the average heart rate by ILR has been 80 to 100 beats/min with no pauses (3 or more seconds) or heart block (**Figure 5**).

DISCUSSION

Autonomic dysfunction has been described in 2.5% of patients with long COVID and could be presented with postural tachycardia syndrome, orthostatic hypotension, or VVS.[1] The exact pathophysiological mechanisms remain unclear but may include direct neural tissue damage, immune and hormonal dysregulation, elevated cytokine levels, and persistent low-grade inflammation.[1] In some patients, overactivation of the vagal afferents which sense proinflammatory cytokines, and an abnormally increased vagal efferent output which has an anti-inflammatory effect, might lead to abnormal autonomic balance.[2] VVS is a heterogeneous condition which can be caused by either decreased systemic vascular resistance or decreased cardiac output.[3] The two main pathophysiological mechanisms in VVS are the following: 1) vasodepression, in which insufficient sympathetic vasoconstriction results in hypotension; and 2) cardioinhibition, when bradycardia or asystole predominates, suggesting parasympathetic overactivation.[3] Presentation may be dizziness or syncope due to hypotension, vagally mediated sinus node dysfunction, and/or AV block.[3] Traditional management includes increased salt and water intake, counterpressure maneuvers, pharmacologic options (eg, midodrine, fludrocortisone), and in refractory cases, pacemaker implantation. Response to these therapies is variable and many patients remain symptomatic. Although pacemaker therapy may prevent the cardioinhibitory component, it cannot prevent the vasodepressor reflex due to afferent vagal signaling leading to inhibition of sympathetic output and loss of vasomotor tone.[3]

CNA has emerged as an effective therapeutic alternative that may be superior to traditional measures to prevent VVS.[4] CNA involves identifying sites of cardiac parasympathetic ganglia by empirical anatomical localization, high-frequency stimulation, fractionation mapping,[5] computed tomography,[6] intracardiac echocardiography,[7] or ^{123}I-*meta*-iodobenzylguanidine imaging followed by radiofrequency ablation of these sites. GP are commonly located near the ostium of the left and right superior pulmonary veins, the ostium of the right inferior pulmonary vein, the inferior septal portion of the right atrium outside the coronary sinus, and between the distal superior vena cava and proximal aorta.[8] A vagal response (eg, decrease in heart rate with high-frequency stimulation) may assist in identifying

FIGURE 5 **Implantable Loop Monitor Report Up to 9 Months After Cardioneuroablation**



AT/AF = atrial tachycardia/atrial fibrillation; PVC = premature ventricular contraction; V. = ventricular.

location of the GP but is not uniformly used.[7] After ablation, an increase in sinus heart rate and decrease of the AH interval is suggestive of successful ablation.[5] Notably, the optimal methods to identify GP, procedural efficacy readouts, assessment methods of vagal input to the heart, and the order and extent of GP ablation are under debate. A recent randomized controlled trial showed that CNA is superior to nonpharmacologic treatments in patients with cardioinhibitory VVS.[7] Both types of VVS (vasodepressor and cardioinhibitory) were shown to respond in the first description of CNA by Pachon et al,[4] and this was supported by a subsequent study by Aksu et al,[5] in which 31 patients with functional or vagally mediated AV block were successfully treated with CNA. Recent data indicate that the clinical benefit of CNA persists more than 2 years after the procedure.[9] Nevertheless, the long-term effects of CNA on cardiac and autonomic function remain unclear. Interestingly, a preclinical study showed increased risk for ventricular arrhythmias and impaired autonomic function after CNA; therefore, further studies are needed to assess CNA long-term safety and efficacy.[10]

Although CNA has been described to successfully treat VVS, to our knowledge, this is the first case to describe its use in this type of dysautonomia after COVID-19 infection. Additionally, one of the unique features of this case was intermittent AV block as opposed to sinus node slowing, indicating functional AV block.

FOLLOW-UP

The patient has been off medications for 9 months with no symptoms and no pauses recorded by her ILR, and she is back to full duty police work (**Figure 5**). She noted that both fatigue and decreased exercise tolerance prior to the procedure have completely resolved. The patient has a long-term follow-up plan with us and is seen in-person or by video every 6 months with monthly ILR checks, which will be for at least 3 years.

CONCLUSIONS

CNA has been shown to be effective for the treatment of cardioinhibitory VVS in patients in which conservative management for cardioinhibitory VVS has been ineffective. CNA may be considered in patients experiencing this type of persistent dysautonomia after COVID-19 infection. Larger randomized trials are needed to confirm the utility and optimal strategies for using CNA in these patients.

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