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BEGINNER

CASE REPORT: CLINICAL CASE

Catheter-Based Cardio-Neural Ablation for Refractory Vasovagal Syncope

First U.S. Report

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ABSTRACT

We highlight the feasibility and efficacy of a new application for catheter ablation to target atrial ganglionated plexi in a patient with refractory vasovagal syncope. We describe a physiologically guided technique and demonstrate 18-month freedom from syncope with 2 tilt-table tests to objectively assess reproducible elimination of symptomatology and underlying pathophysiology. (**Level of Difficulty: Beginner.**) (J Am Coll Cardiol Case Rep 2020;2:1161–5)

HISTORY OF PRESENTATION

A 52-year-old female patient presented with recurrent syncope since childhood, associated with both depression and anxiety. A tilt-table test with syncopal response was initially performed at an outside hospital, and she was given the diagnosis of vasovagal syncope (VVS).

PAST MEDICAL HISTORY

She had been on multiple medications over the past 10 years and was refractory to propranolol, midodrine, and droxidopa. She had taken venlafaxine and buproprion for depression, and accepted a dual-chamber pacemaker implantation 6 years before self-referral to our institution. But neither fluid-loading, behavioral, medical, nor pacemaker therapy (lower rate of 70 beats/min) prevented the refractory prodromes and syncope that occurred every 1 to 2 months.

DIFFERENTIAL DIAGNOSIS

VVS is associated with cardioinhibitory and/or vasodepressor responses, presenting as predominantly bradycardia and/or hypotension, respectively, which can be differentiated by formal tilt-table testing. Orthostatic hypotension is classically positional, and postural orthostatic tachycardia syndromes have stereotypic responses to tilt table testing. Seizure must be distinguished from syncope, and psychogenic causes of syncope may reflect underlying psychiatric diagnoses.

INVESTIGATION

During her first tilt-table test at our institution, her baseline heart rate (HR) was 77 beats/min with a

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ABBREVIATIONS AND ACRONYMS

AV = atrioventricular
BP = blood pressure
CS = coronary sinus
GP = ganglionated plexus
HFS = high-frequency stimulation
HR = heart rate
LA = left atrial/atrium
LSGP = left superior ganglionated plexus
RA = right atrial/atrium
RAGP = right anterior ganglionated plexus
RF = radiofrequency
SVC = superior vena cava
VVS = vasovagal syncope

blood pressure (BP) at 130/90 mm Hg. The head-up tilting provoked nausea followed by syncope within 5 min, and the procedure was concluded. BP dropped to 74/54 mm Hg, whereas the HR was 88 beats/min (Figure 1), consistent with neurocardiogenic syncope with vasodepressor response.

MANAGEMENT

The patient had extensively researched novel therapies for refractory vasovagal therapies performed outside of the United States and provided informed consent to proceed with attempted cardioneural ablation of atrial ganglionated plexi (GP), with a complete understanding of the experimental nature of this application. General anesthesia was administered, and an activated clotting time was maintained over 300 s with intravenous heparinization before transseptal puncture.

The GP were localized by high-frequency stimulation (HFS) (20 Hz, output 20 mA, pulse width 2 ms) delivered from a standard electrophysiology programmed stimulator (Micropace, GE Healthcare, Santa Ana, California) using a standard irrigated ablation catheter (TactiCath Quartz, Abbott, Abbott Park, Illinois) in both atria at anatomic sites consistent with GP locations. Transient atrial fibrillation was initiated by HFS, which self-terminated repeatedly. The definition of a positive vagal response was an incremental prolongation of the RR interval by 50%, transient ventricular asystole, or atrioventricular (AV) block (1). The pacemaker was programmed to VVI mode at 30 beats/min to allow for assessment of longer pauses.

The GP locations with positive provoked vagal responses were annotated on the 3-dimensional mapping geometry (Ensite-Precision, Abbott). Radiofrequency (RF) energy (30 to 40 W) was delivered to sites with positive HFS (left superior GP [LSGP], left inferior GP, coronary sinus [CS] ostium) as well as additional anatomically guided sites (right anterior GP [RAGP], superior vena cava [SVC], right atrial [RA] septum). The location of HFS provoked responses, ablation time and sequence are shown in Figure 2. No vagal reflexes or hypotension were observed during GP ablation. However, repeat HFS was performed immediately after ablation at positive response sites and were rendered unprovocable. The total ablation time was 18.8 min. The patient was discharged the following day after an uncomplicated 23-h observation and prescribed 1 month of anticoagulation.

LEARNING OBJECTIVES

- VVS is the manifestation of an abnormal cardioneural reflex arc (Bezold-Jarisch) that presents in 2 pathophysiological states: cardioinhibitory (bradycardia) and vasodepressor (vasodilatory hypotension). Pacemaker implantation is only indicated in those with predominantly cardioinhibitory responses.
- The efficacy of medical therapy for VVS is limited and inconsistent across randomized trials.
- VVS treatment via atrial GP ablation is a novel and promising catheter-based alternative therapy for refractory VVS with both cardioinhibitory and vasodepressor responses.
- HFS is feasible to physiologically localize GP anatomic sites in the RA and LA, and elimination of provoked vagal responses can be demonstrated after targeted ablation with repeat stimulation in the short term and in follow-up tilt table testing.

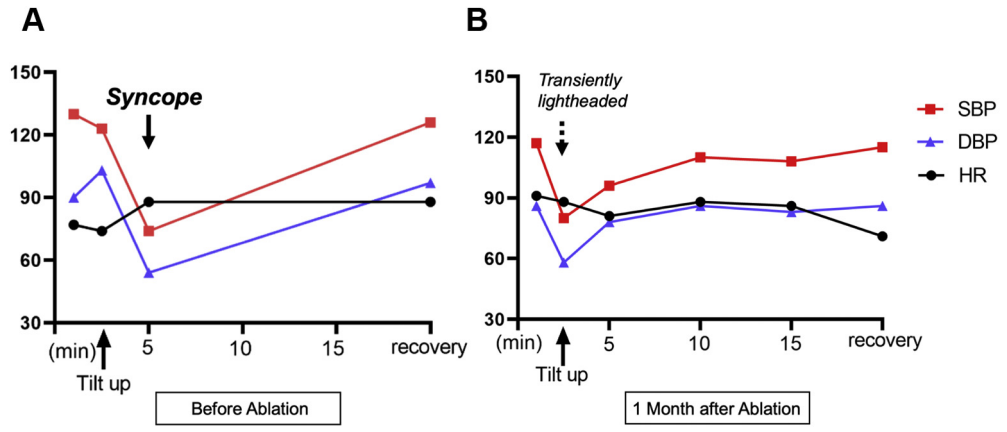
FOLLOW-UP

A formal tilt-table test (70°) was repeated at 1 month and 1 year after atrial vagal denervation (Figures 1 and 3) to objectively reassess elimination of the Bezold-Jarisch reflex. A hypotensive response was observed immediately upon tilt at 1 month, with transient lightheadedness, but no syncope, for 15 min. At 1 year, repeat tilt-table test was negative, and additional provocation was attempted with isoproterenol infusion (2 μg/min) for an additional 20 min without any symptoms. At 18 months after cardioneural ablation, the patient has remained free from any prodromal episodes and syncope.

DISCUSSION

Vasovagal syncope is typically managed by medical, device, and behavioral therapy, with the latter as most effective. This case report of a patient with continued symptoms of medically and device-refractory VVS demonstrates the feasibility and efficacy of a novel catheter-based approach to achieve vagal denervation. Although early cases of successful cardioneural ablation have been reported from Brazil, China, and Turkey, this is the first case reported from the United States, to the best of our knowledge. Further, is it the only report with subacute and longer-term repeat tilt-table testing to assess objective and reproducible changes in the reflex arc. The

FIGURE 1 Tilt-Table Testing: Initial and 1-Month Follow-Up



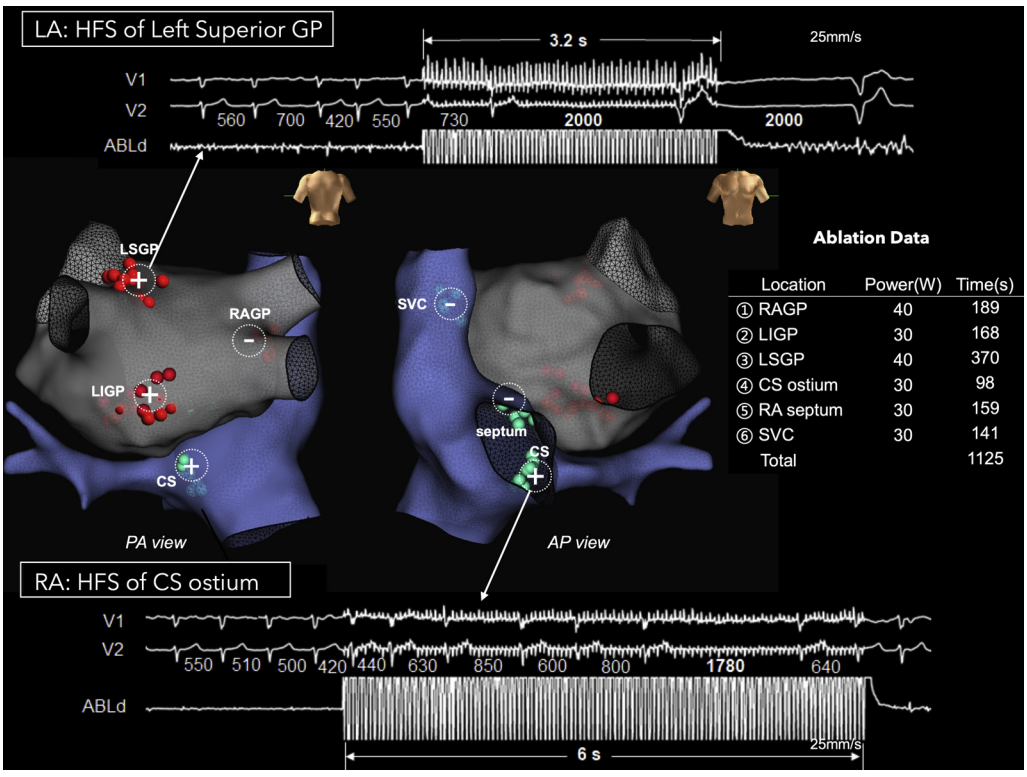
(A) The tilt-table test before ablation showed a rapid drop blood pressure without a drop in heart rate (vasodepressor response) followed by syncope within 5 min of upright positioning at 70°, prompting immediate conclusion of the study. **(B)** The repeat test 1 month after ablation procedure exhibited transient blood pressure decrease with mild lightheadedness without syncope. DBP = diastolic blood pressure; ISP = isoproterenol; SBP = systolic blood pressure.

vasodepressor response detected on initial tilt-table test without cardioinhibition indicates a type 3 pattern of VVS, which is unlikely to be corrected by pacemaker therapy, including rate-responsiveness algorithms, that is, closed-loop stimulation (2). Prior reports of cardioneural ablation have predominantly been performed for cardioinhibitory (bradycardia-predominant mechanism) and functional AV block.

VVS is a result of parasympathetic enhancement and/or sympathetic suppression in response to the Bezold-Jarisch reflex, presenting with bradycardia and/or hypotension. Vagal denervation is perhaps the most physiologically targeted therapy for this challenging clinical condition. Pachon et al. (3) were the first to report the successful vagal denervation by RF ablation targeting GP in 21 patients presenting with symptomatic functional bradyarrhythmias, including neurally mediated syncope (n = 6). Their updated report in 2011 (4) enrolled 43 patients with cardioinhibitory VVS (VASIS [Vasovagal Syncope International Study] type 1 and 2 included). The ablations were guided by spectral mapping and targeted on additional anatomic structures such as the CS, SVC junction, right pulmonary vein, and interatrial septum. Syncope recurred in only 3 cases during follow-up (2 vasodepressor, 1 undefined). Recently, more evidence (5-8) on the safety and efficacy of GP ablation for VVS has emerged, most of which were about type 1 or 2 syncope involving bradycardia or functional AV block. The anatomy or HFS-guided GP targets covering both the RA and left atrium (LA), including the left superior/inferior GP and right anterior/inferior GP, are consistent with our ablation locations (7). Type 3 patients (vasodepressor response) have been rarely attempted in previous studies, although mixed types (cardioinhibitory and vasodepressor) have shown favorable response (4,9). Variation between the types of syncopal patterns may be possible within the same patient.

Although anatomically guided approaches have been successfully employed based on stereotyped locations and local high-frequency electrogram characteristics, we pursued this initial case with the use of HFS to identify GP target sites, with 3 regions demonstrating positive provoked vagal responses. No bradycardia or hypotension occurred during GP ablation, and importantly, ablation eliminated the response to HFS, providing a physiological endpoint to this procedure. Prior studies have demonstrated evoked vagal reflex during RF energy application, which were performed under conscious sedation instead of general anesthesia (6). The LA GP denervation may also affect the efferent pathway in the initiation of vagal reflex (6,9), accounting for the subsequent lack of HFS response in the RA. Therefore, the ablation sequence of GP requires

FIGURE 2 GP Ablation



The examples of positive response to HFS were shown in the LSGP **(top)** and the CS ostium **(bottom)**, with a prolonged RR interval more than 50% of the average. The ablation targets **(dotted circle)** covered both the RA and LA, including 3 regions (LSGP, LIGP, CS ostium) with a positive HFS response and 3 anatomic locations (RAGP, RA septum, SVC) with a negative HFS response. The ablation setup and sequences marked with corresponding numbers are listed in the table **(right)** (contact force 10 to 30 g). + = positive HFS response; − = negative HFS response; AP = anteroposterior; CS=coronary sinus; GP = ganglionated plexus; HFS = high-frequency stimulation; LA = left atrial; LIGP = left inferior ganglionated plexus; LSGP = left superior ganglionated plexus; PA = posteroanterior; RA = right atrial; RAGP = right anterior ganglionated plexus; SVC = superior vena cava.

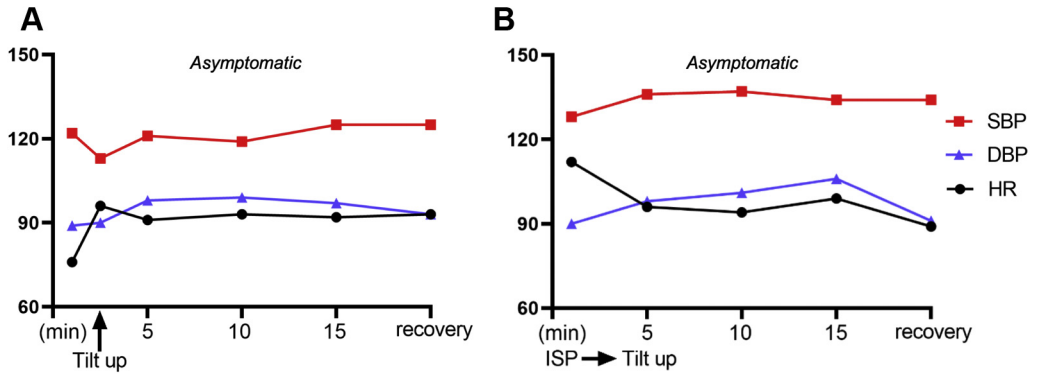
additional investigation. Although there is no current standardization for the selection of ablation targets (anatomically versus physiologically guided) and procedural endpoints, we opted for a physiological endpoint in this initial case for more definitive demonstration of denervation to titrate therapy.

Freedom from syncope and the negative tilt-table test during follow-up suggest that vagal denervation may eliminate the physiological reflex underlying VVS by affecting the efferent neuron fibers related to both cardioinhibitory and vasodepressor activation (10). However, it is difficult to locate the corresponding GP that primarily cause a vasodepressor response with current approaches. The success of our case might be a result of extensive GP ablation in both atria, and further studies are required to examine the extent of ablation necessary to achieve a therapeutic effect.

CONCLUSIONS

Vasovagal syncope refractory to medical, device, and behavioral therapy can be a debilitating cardiovascular condition. Selective ablation of GP within the RA and LA may be a promising catheter-based alternative therapy for refractory VVS. The nascent field of cardioneural catheter ablation signals a paradigm shift in the treatment of functional bradycardia and hypotensive syndromes. Further studies are warranted as successful vagal denervation may obviate the need for permanent pacemaker implantation in selected patients, and may be applicable to patients with predominantly vasodepressor responses. As

FIGURE 3 Tilt-Table Testing: 1 Year After Ablation



(A) The tilt-table test (70°) performed showed stable blood pressure and HR response and the patient remained asymptomatic throughout. **(B)** Therefore, isoproterenol was infused intravenously (2 μg/min) for further provocation, without any symptoms or vagal response for an additional 20 min. Abbreviations as in **Figure 1**.

medical therapy and pacemaker implantation have not been consistently demonstrated to be effective, there is sufficient clinical equipoise to pursue a randomized sham-controlled trial at experienced centers to assess the impact of this novel therapeutic approach in selected patients.

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