Cardioneuroablation for vasovagal syncope alters head-up tilt test response and reduces cardiac deceleration capacity

Simin Cai, MD,*† Lihui Zheng, MD, PhD,† Yan Yao, MD, PhD, FHRS†

*From the *Center of Arrhythmia, Huazhong Fuwai Hospital, Heart Center, Henan Provincial People's Hospital, The People's Hospital of Zhengzhou University, Henan, China, and †Cardiac Arrhythmia Center, Fuwai Hospital, National Center for Cardiovascular Diseases, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China.*

Introduction

Vasovagal syncope (VVS) is the most frequent etiology of transient loss of consciousness in young people and has complex mechanisms, which are yet to be deciphered.[1] Head-up tilt test (HUTT) is a diagnostic tool that documents the hemodynamic changes associated with the syncopal episode of the patient and is used to differentiate 3 VVS patterns: cardioinhibitory, vasodepressor, and mixed (proposed by the Vasovagal Syncope International Study).[2] In the tilt-evoked VVS context, the cardioinhibitory pattern is closely associated with vagal activation and the vasodepressor pattern is related to vasodilation.[3] The deceleration capacity (DC) of heart rate represents the capacity of the cardiac vagal nerve for dynamic regulation while responding to physical and psychological stimuli.[4] DC can be ascertained by processing the sequences of 24-hour R-R intervals with the phase-rectified signal averaging technique which helps in the diagnosis and treatment planning for VVS.[5,6]

Cardioneuroablation (CNA) is an emerging interventional treatment that can keep patients with refractory VVS free from syncope by denervation of the cardiac vagal nerve plexi.[7] CNA may affect the type of vasovagal reaction, resulting in a negative response or in changing of mixed and cardioinhibitory patterns to a vasodepressor pattern. However, both responses have shown an improvement of syncope.[8,9] Few studies have attached importance to this situation. In this study, we describe a change of pattern in the HUTT response related to vagal denervation and report the successful denervation of the cardiac vagus nerve, as confirmed by the reduced DC.

KEYWORDS Vasovagal syncope; Cardioneuroablation; Tilt test; Deceleration capacity of heart rate; Vagal activity
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Address reprint requests and correspondence: Dr Yan Yao, Fuwai Hospital and Cardiovascular Institute, 167 Beilishi Rd, Xicheng, Beijing 100037, China. E-mail address: ianyao@263.net.cn; or Dr Lihui Zheng, Fuwai Hospital and Cardiovascular Institute, 167 Beilishi Rd, Xicheng, Beijing 100037, China. E-mail address: zhenglihui@263.net.

KEY TEACHING POINTS

- Cardioneuroablation is an emerging interventional treatment that can allow patients with refractory vasovagal syncope to become free of syncope by denervation of the cardiac vagal nerve plexus.
- The deceleration capacity (DC) of heart rate is a new indicator of vagal excitability. Measuring DC from 24-hour ambulatory electrocardiograms is simple and cost-effective and should be added to autonomic assessment. This can be useful in building a better understanding of the autonomic mechanisms leading to vasovagal reactions.
- Changes in the head-up tilt test response after denervation may be associated with a potential abnormality of the patient's baroreflex or characteristics of nonspecific nerve ablation within a specific range of cardioneuroablation.

Case report

A 21-year-old man had experienced at least 10 episodes of syncope for 8 months prior to hospitalization. He had undergone transcatheter closure of the patent foramen ovale to treat syncope but apparently failed to achieve the expected outcome. The first syncope event occurred while walking, and subsequent episodes were mainly caused by emotional excitement or physical training. Approximately 5 minutes before syncope, he experienced intolerable prodromes, including dizziness, palpitations, numbness of the hand, weakness, and pallor. Loss of consciousness usually lasted for 1–3 minutes, without convulsions or incontinence. When the patient recovered fully and spontaneously from fainting, a mild headache ensued. The patient denied any relevant medical history related to the VVS spectrum of illnesses.

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Physical examination and laboratory investigation results were within the normal limits. Echocardiography, computed tomography, and magnetic resonance imaging revealed no organic heart lesions. A 12-lead electrocardiogram (ECG) showed sinus bradycardia at 52 beats per minute (bpm) with a PR interval of 160 ms (Figure 1A). Holter monitoring (24-hour ECG) recorded an average heart rate (HR) of 54 bpm, accompanied by increases in parameters related to vagal activity, such as root mean square of successive differences in normal cardiac cycle, high-frequency power (HF) of heart rate variability (HRV), and DC. The DC value was high enough to achieve the diagnostic indication for VVS (DC $\geq$7.5 ms) and the recommended indication for CNA (nighttime DC $\geq$10 ms).[5,6] The DC value was determined by using the software MIC-12H Analysis Platform (Jinke Instruments, Beijing, China). The average baseline values of blood pressure (BP) and HR at preprocedural HUTT (Figure 2A) were 105/60 mm Hg and 64 bpm, respectively. Initially, the patient was undergoing a drug-free passive orthostatic phase (up to 30 minutes at 70° angles); subsequently, 0.35 mg nitroglycerin was administered sublingually. Five minutes later, the patient complained of dizziness, blurred vision, weakness, and hearing loss without experiencing syncope. Considering the positive HUTT response, both BP and HR declined to the extent of achieving the classification criteria of a mixed VVS type pattern. The young patient refused permanent pacemaker implantation and chose to undergo CNA therapy over medication.

After transseptal puncture of the lateral side of the inferior edge of the foramen ovale occluder, 3-dimensional electroanatomical mapping of the left atrium and pulmonary veins was performed. Ganglionated plexi (GP) mapping was guided by anatomical observation and high-frequency stimulation (drivetrains of 30 Hz, 20 V, with 2-ms pulse width). Vagal reflexes (transient ventricular asystole, atrioventricular block, or a 50% increase in R-R interval) were observed only in the left inferior GP and posteromedial left GP (PMLGP). Ablation was performed in the order of GPs: left superior GP, left inferior GP–right inferior, and GP–posteromedial left GP, using a radiofrequency ablation catheter with preset parameters (upper limits of power and temperature were 40 W and 60°C, respectively) (Figure 3A). Ablation of the right anterior GP significantly shortened the P-P interval (Figure 3B and 3C), and the HR increased to 110 bpm after ablation of the corresponding site on the superior vena cava. Immediate postprocedure ECG showed HR values up to 99 bpm with a PR interval of 156 ms (Figure 1B).

Eight months after CNA, the patient experienced 2 transient syncopal episodes (less than 1 minute each), and the duration of the prodromal symptoms was prolonged. The positive HUTT results resulted in a vasodepressor pattern of response. The average HR value increased to 79 bpm.

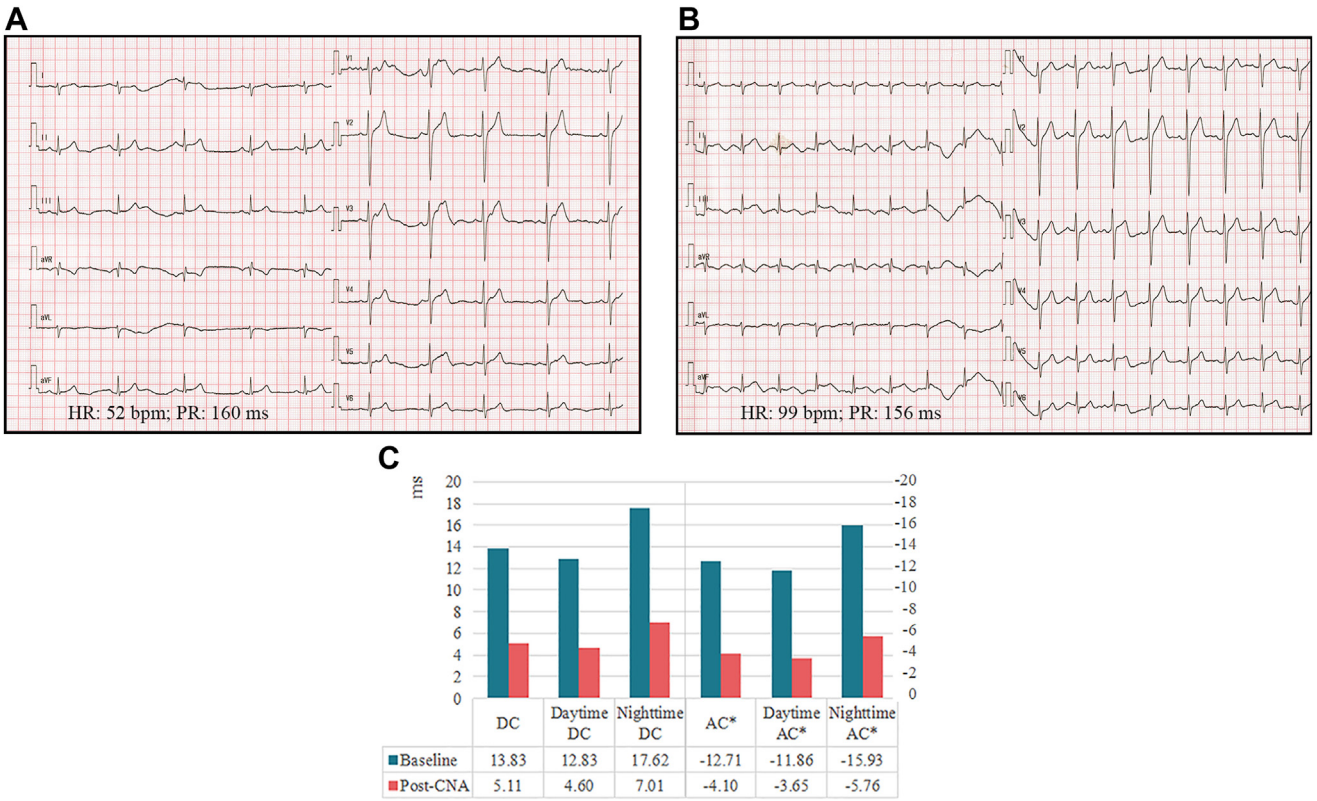

Figure 1 Comparison of resting electrocardiogram (ECG) and autonomic-related indexes at baseline and month 8 after cardioneuroablation. **A:** Baseline ECG. **B:** Postprocedure ECG. **C:** Deceleration capacity (DC) and acceleration capacity (AC) of heart rate. *Value of AC reflects sympathetic nerve tensility. HR = heart rate; PR = P-R interval.

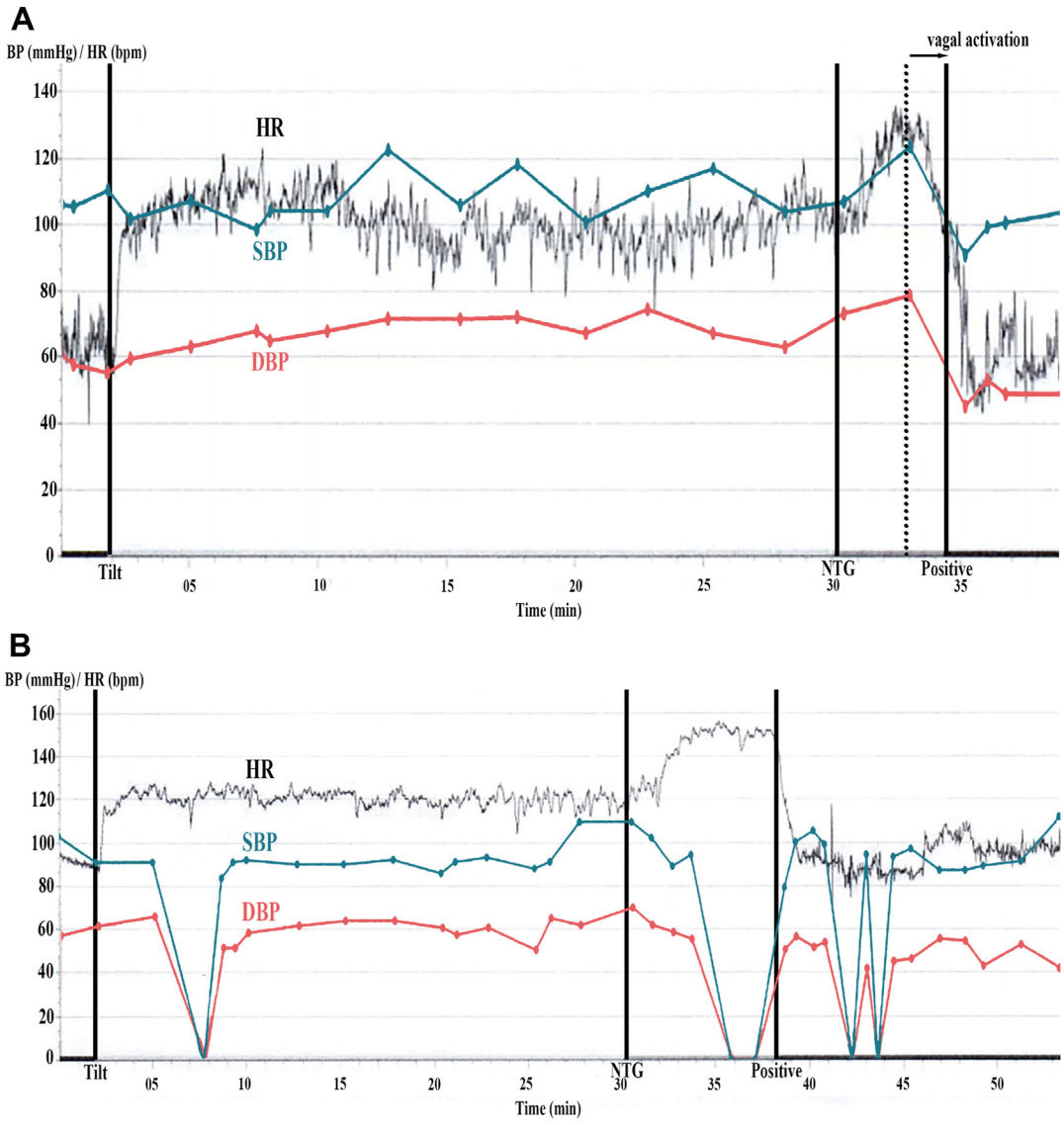

Figure 2 Dynamic changes in blood pressure (BP) and heart rate (HR) during head-up tilt test (HUTT). **A:** HUTT before ablation. **B:** HUTT at 8 months after ablation. The 3 vertical solid lines in A and B represent the beginning of the orthostatic phase, the drug-provocative phase, and the occurrence of symptoms, respectively. DBP = diastolic blood pressure; NTG = nitroglycerin; SBP = systolic blood pressure.

The differences in the magnitude of DC between baseline and follow-up are shown in Figure 1C. A significant reduction was noted in vagal-related HRV parameters and DC, both of which represent effective vagal denervation.

Discussion

Numerous studies[7,10] have reported a striking success for CNA in eliminating or reducing syncope recurrence in cardioinhibitory and mixed VVS and have confirmed the role of inappropriate vagal activation in the occurrence of VVS. According to previous small cohort studies, overall syncope recurrence rate was lower than 10% after CNA.[10] Recently, a meta-analysis and a randomized controlled trial demonstrated that freedom from syncope after CNA exceeds 90% during 2 years of follow-up.[7,11] Similar dramatic improvements were recorded in the present report. In our case, the 24-hour ECG in the 8th month after CNA visually reflected the effectiveness of vagal denervation through decreases in several objective indices, such as root mean square of successive differences in normal cardiac cycle, HF, and DC. Thus, it is clear that the changes in DC reveal the mechanism of CNA treatment in this case and suggest that CNA may alter the autonomic reflex mechanism of VVS.

At present, the pathophysiological mechanism of VVS is related to hyperactivation of the parasympathetic division that could be triggered by prolonged standing, emotional stress, or high-intensity exercise, representing paradoxical vasodilation and bradycardia, and leading to further hypotension and loss of consciousness.[1] The process associated with a vagal-mediated relative or absolute reduction in HR is known as cardioinhibition and is the main component that

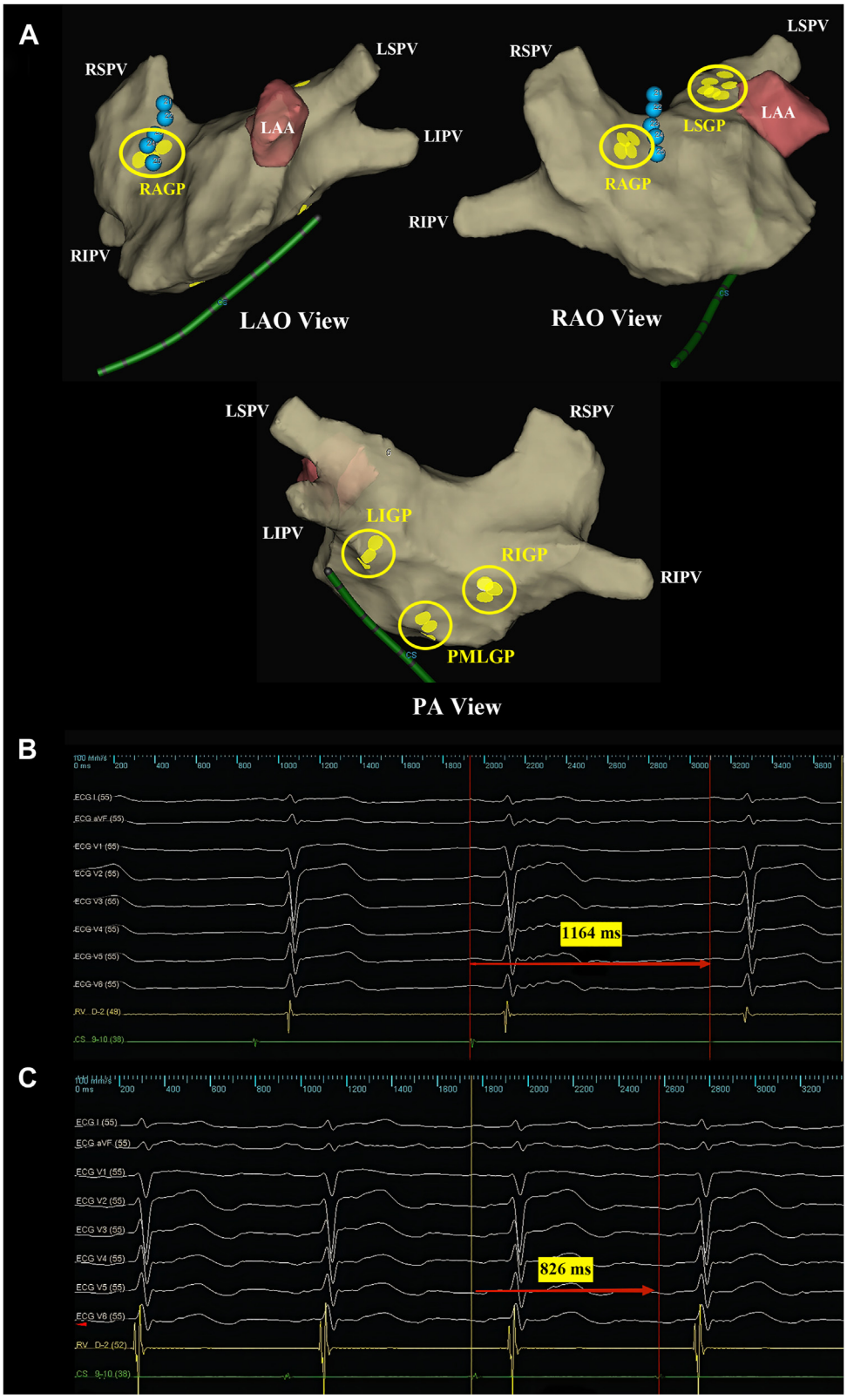

Figure 3 Cardioneuroablation procedure. **A:** Three-dimensional endocardial surface of the left atrium, locations of ganglionated plexi (*yellow points*), and the ablation lesions of right atrium (*blue points*). **B, C:** Preablation (**B**) and postablation (**C**) intracardiac electrogram of right anterior ganglionated plexus (RAGP). R-R interval decreased from 1164 to 826 ms. CS = coronary sinus; LAA = left atrial appendage; LAO = left anterior oblique; LIGP = left inferior ganglionated plexus; LIPV = left inferior pulmonary vein; LSGP = left superior ganglionated plexus; LSPV = left superior pulmonary vein; PA = posterior-anterior; PMLGP = posteromedial left ganglionated plexus; RAO = right anterior oblique; RIGP = right inferior ganglionated plexus; RIPV = right inferior pulmonary vein; RSPV = right superior pulmonary vein.

could be ameliorated by CNA. Serving as a functional biomarker for cardiac vagal tone, DC has shown superior diagnostic value for patients with VVS; it not only increases the success rate of ablation but also increases the opportunity for treating these patients, who were once thought to respond ineffectively to CNA.[5,6] Naturally, chronic vagal activation during the asymptomatic period can also be measured with HRV; however, there are inherent defects affecting the resulting analysis. On one hand, the phase-rectified signal averaging algorithm of DC can extract periodic deceleration-related components of the vagal nerve modulation process[5]; in HRV analysis, it is difficult to separate parasympathetic modulators from the mixed autonomic effect.[12] On the other hand, DC individually quantifies vagal activity by removing nonperiodic interference (data noise/artifacts or arrhythmias)[4]: HRV is more susceptible to external factors owing to the absence of this characteristic.

HUTT is usually applied to assess the adaptive reactions to positional changes of the autonomic nervous system when the clinical history is insufficient to make a conclusive explanation for syncope.[1] In a recent meta-analysis report comprising a total of 465 patients across 14 studies, 440 patients (94.6%) underwent preoperative HUTT; of these, 236 patients were classified into the cardioinhibitory group (66.1%).[7] Most of the studies have taken positive HUTT as an indication for screening candidates for CNA, especially if the response pattern is accompanied by a significant decrease in HR (which suggests inappropriate activation of the vagus nerve). The unsatisfactory sensitivity and specificity of HUTT[13] cannot be overlooked. The European syncope guidelines note that not only patients with VVS but also some patients with arrhythmic syncope will be HUTT positive.[14] However, the magnitude of DC showed no difference in patients with VVS with or without positive HUTT at baseline.[5] Therefore, relying solely on the results of HUTT can be challenging for elucidating autonomic nervous system abnormalities in patients, and DC will be a useful indicator in this context.

By comparing the HUTT results before and after treatment, we noted that CNA affected the type of vasovagal reaction. However, studies on the effects of CNA on the hemodynamic response to HUTT are scarce. In a study reported by Aksu and colleagues,[9] syncope recurrence after CNA was observed in only 3 cases, of which 2 cases had mixed responses in preprocedural HUTT. Repeating HUTT after a new syncopal episode showed a vasodepressor response, indicating that these patients may have an accompanying, potentially inappropriate, reflex response resulting in vasodilation.[9]

In our case, the pre-CNA HUTT results showed a classic hemodynamic sequence of a mixed-type response (Figure 2A). High vagal excitability was further confirmed by an increase in the magnitude of DC. After denervation of the cardiac vagal nerve, DC descends to a normal level, and the relatively dominant sympathetic excitation can increase HR and myocardial contractility, thereby maintaining BP to prevent fainting. There were 3 significant decreases in BP during post-CNA HUTT (Figure 2B). The first fluctuation occurred in the early orthostatic phase, with BP not being measured, where HR decreased briefly and slightly but did not trigger symptoms. We speculate that the effect of the baroreflex was sufficient to maintain cerebral perfusion at that time; however, the cause of the sudden drop in BP was not clear. BP dropped again after administration of the drug. As the second fluctuation occurred, the compensatory HR value increased and remained at approximately 150 bpm until the symptoms appeared. Symptom onset was followed by a third BP fluctuation, and the patient experienced syncope. These hemodynamic changes in our case demonstrate that the potentially abnormal baroreflex makes it impossible to maintain BP under the dual stimulation of a prolonged upright posture and a vasodilator pattern—although CNA altered the excessively inhibitory effect of the cardiac vagus nerve. It may be difficult to avoid the destruction of adjacent sympathetic nerve fibers when ablating vagus nerve fibers; therefore, hemodynamic changes may be associated with the characteristics of nonspecific nerve ablation within a specific range and/or incomplete sympathetic nerve regeneration.[15]

Conclusion

CNA is emerging as a novel treatment for refractory VVS, and DC is a new indicator for assessing vagal tone. These advances will help guide the selection of patients suitable for CNA in the future. The reduction of postoperative DC and syncope burden in our case confirmed the effectiveness of CNA in treating VVS by modulating cardiac vagal tone. We reason that the pattern change in postoperative HUTT may be related to treatment efficacy or abnormal baroreflex.

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