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Utility of Head up Tilt Table Testing to Demonstrate Selective Denervation of the Sinus Node after Cardioneuroablation

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Abstract

A 65-year-old female who underwent cardioneuroablation for recurrent vasovagal syncope presented for 6 month follow-up visit. She had no further syncope after the procedure. A follow up tilt table testing (TT) demonstrated sinus tachycardia and variable degrees of atrioventricular block (AVB) after sublingual glyceryl trinitrate. She had no syncope during the test. As per existing knowledge, the occurrence of AVB during vasovagal reaction induced by TT should be preceded by sinus rhythm slowing. In this patient, sinus tachycardia during TT demonstrates highly specific denervation of ganglion cells which send postganglionic fibers directly to the sinus node without obvious influence on the atrioventricular node

Introduction

Cardioneuroablation (CNA) was proposed to modify the behavior of the cardiac autonomic nervous system to prevent the autonomic processes occurring in vasovagal syncope (VVS).[1] In a recently published study, we demonstrated that fractionated electrogram based CNA may decrease the procedure and fluoroscopy times without affecting efficacy when compared with previously defined high frequency stimulation and spectral analysis in patients with refractory VVS.[2] Experimental studies indicated that parasympathetic innervations of the sinus and the atrioventricular (AV) nodes are provided by different ganglionated plexi (GPs).[3] We tried to demonstrate selective denervation of sinus node with CNA by using tilt testing (TT) for the first time.

Case Report

A 65-year-old female with recurrent cardioinhibitory VVS, confirmed by reproducible syncope with a 10-s asystole during non-provoked TT (Figure 1A, 2A), underwent CNA 6 months ago after the patient refused pacemaker implantation. Baseline pre-procedure heart rate was 59 bpm.

Key Words

Syncope; Ablation; Neurocardiogenic syncope; Pacemaker; Vasovagal syncope; Bradycardia.

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Procedure Details:

The procedure was performed under conscious sedation with intravenous administration of midazolam and fentanyl. The patient underwent fractionated electrogram guided CNA. The sites demonstrating high or low amplitude fragmentation pattern in the regions that are consistent with probable GP locations were targeted. Ablation was started from fragmented electrograms on the left superior GP. Radiofrequency application caused a significant vagal response (VR) with sinus bradycardia. AA intervals increased from 1050 ms to 2160 ms during the left superior GP ablation. Ablation was continued until all targeted EGMs were eliminated. We then continued the ablation on the left inferior GP but no vagal response was seen during ablation at that site. The right superior GP was next. During ablation on the right superior GP, AA interval decreased from 1420 msec to 1100 msec. The ablation catheter was retracted along the interatrial septum and all fragmented areas were ablated on the right inferior GP. Next, we targeted right atrial part of GPs according to our ablation order. In the right atrium, the aorta– superior vena cava GP and right part of the right superior GP was targeted and ablated. AA interval decreased from 1098 msec baseline value to 659 msec (Movie 1). The inferior vena cava-left atrial GP which provides vagal innervations of AV node was not ablated because desired heart rate response was achieved with ablation of other GPs (Figure 2).

Link For Movie 1

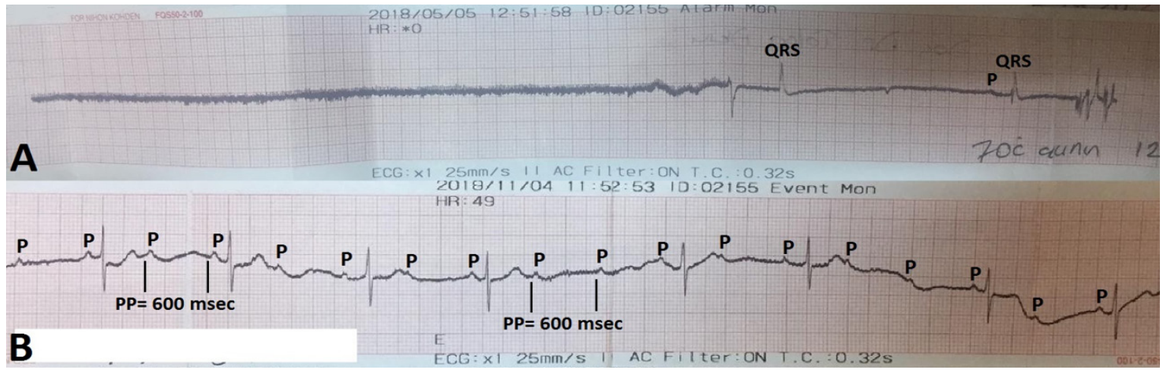

Figure 1A,1B : **Electrocardiogram recording during tilt testing before the procedure (A) and at 6 months of follow-up after cardioneuroablation (B)**

A. Electrocardiogram recording demonstrates 10-s asystole during non-provoked tilt testing. B. Electrocardiogram recording demonstrates variable degree atrioventricular block with sinus tachycardia without syncope after sublingual glyceryl trinitrate administration. Please see that PP interval is 600 msec during atrioventricular block.

Follow-up:

The frequency of syncopal episodes was twice a month before CNA and at 6 months following the procedure, she did not have any further recurrence of syncope. Follow-up resting ECG confirmed durable effect on sinus rate which was now 95 bpm. On routine follow-up TT, variable degree atrioventricular (AV) block with sinus tachycardia was detected without syncope after sublingual glyceryl trinitrate administration (Figure 1B, 2). Because the patient was totally asymptomatic, we decided to continue to observe the patient without any treatment. No new syncope or bradyarrhythmia related symptoms were noted during an additional 12-month follow-up.

Discussion

The main findings of the present case report are as follows: (1) different GP sites provide vagal innervation of the sinus and AV nodal regions, respectively; (2) although ablation of the right superior GP or the aorta– superior vena cava GP causes a significant increase in sinus rate, AV block may still be seen due to selective innervation principles of the sinus and AV nodal regions; (3) bi-atrial approach may be needed to get desired increase of the sinus rate (4) fractionated EGMs might be used to define anatomical location of GPs without using any additional equipment during electrophysiological study; and (5) fractionated electrogram based CNA can effectively prevent recurrent spontaneous syncopal episodes in a patient with refractory VVS.

Although the AV block induced by TT is a rare phenomenon, it was reported both in patients with VVS and in healthy volunteers.[4,5] The main feature of AV block related to the neurocardiogenic reflex provoked by TT was the substantial slowing of sinus rhythm and the presence of significant variability in PP intervals. A similar pattern of sinus bradycardia and AV block was also present during spontaneous syncopal episodes documented by implantable loop recorder.[6] The patients with non-neurocardiogenic reflex etiology of AV block do not appear to have this feature. In the present case, existence of such a response demonstrates highly specific denervation of ganglion cells which send postganglionic fibers directly to the sinus nodal region without obvious influence upon the AV nodal region.

In a recently published study, Hu et al 7 studied heart rate response characteristics of different GPs by using left-sided approach. During ablation of the right superior GP, heart rate increased from 61.3 ± 12.2 bpm to 82.4 ± 14.7 bpm, whereas during ablation of other GPs only vagal responses were observed. Based on this unique phenomenon, potential role of the right superior GP as the primary target of CNA was hypothesized by the authors. In the present case, targeted heart rate increase was achieved only after right-sided ablation.

The difference between heart rate response of left-sided approach of Hu et al[7] and the present case may have several explanations. Because great majority of GPs demonstrate subepicardial clustering, bi-atrial ablation might be needed to eliminate a significant number of post-ganglionic neurons in some cases. Because GPs usually regulate the sinus and AV nodes via interconnecting nerve fibers, theoretically, ablation of the right superior GP which was proposed to be the "head station" between the extrinsic and intrinsic cardiac autonomic nervous system may seem as valuable target in CNA.[8,9] However, selective vagal innervation of sinus and AV node was previously studied in animal studies.[3, 10,11] In an animal study, Randall et al3 demonstrated that the great majority of GPs supplying sinus node reside in aorta– superior vena cava GP and right superior GP. In contrast, GPs supplying AV node are found within a smaller fat pad overlying epicardium at the junction of the inferior vana cava-left atrial GP. The authors concluded that these vagal pathways to either sinus or AV nodes may be selectively ablated without interfering with vagal regulation of the remaining intact system. A similar experience was recently showed in humans by Pachon et al[12] by using extracardiac vagal stimulation. By this way, status of vagal denervation may be evaluated as many times as necessary.

In the current case, although the patient developed AV block with heart rate slowing down to less than 40 bpm during follow up TT, implantation of a pacemaker was not recommended because the patient was completely asymptomatic. In our previous works, no procedure related complication was seen. [13-15] Inappropriate sinus

Figure 2A, 2B: **Electroanatomical mapping views before (A) and after (B) cardioneuroablation**

Most efferent vagal fibers to the atria travel through the aorta (Ao)-superior vena cava (SVC) ganglionated plexus or fat pad (Ao-SVC GP) located between the medial SVC and aortic root. Vagal fibers to the sinus and atrioventricular nodes converge at this fat pad before projecting to following selective innervation sites. The right superior ganglionated plexus (RSGP) is located between SVC and the right superior pulmonary vein. It is also called as the right anterior ganglionated plexus. Theoretically, RSGP mainly provides vagal innervations of sinus node. The right inferior ganglionated plexus (RIGP) is located between the right pulmonary veins and the right atrium. It is also called as the posterior right ganglionated plexus. The posteromedial left ganglionated plexus (PMLGP) is located in the posterior aspect of the interatrial septum, between the posterior wall of the left atrium (LA), the inferior vena cava (IVC), and coronary sinus (CS) ostium. It is also called as IVC-LA GP. Some part of neuronal bodies related to this GP is in the left atrial side. Vagal innervation of atrioventricular node is provided by PMLGP. The left superior ganglionated plexus (LSGP) is located between the left atrial appendage and the left superior pulmonary vein. The left inferior ganglionated plexus (LIGP) is located within the fat pad anterior to the left inferior pulmonary vein. It is also called as the Marshall tract GP by different groups.
Spheres demonstrate ablation points in GP sites based on fractionated electrograms.
Intracardiac electrograms are seen at the bottom of figure. Please see that cycle length increases from 1307 msec to 638 msec after cardioneuroablation.

tachycardia was observed in 2 of all included patients during follow-up.[15] In one, there was no symptom associated with sinus tachycardia and the heart rates gradually decreased during follow-up. Although the other case was asymptomatic during the first 12 months, she had EHRA class 2 symptoms thereafter which completely resolved with ivabradine treatment.

Pre-ablation TT of the present case demonstrated an increase in total peripheral resistance while the vagal tone went up and sympathetic drive reduced (Figure 3A). However, after CNA, vagal tone remained stable, heart rate dropped down due to AV block and sympathetic tone went up, but total peripheral resistance remains the same (Figure 3B). In patients with VVS, the total peripheral resistance during the positive response period is significantly higher than the total peripheral resistance before this period.[16] Benditt et al.[17] showed that catecholamine levels significantly increased at both 2–3 and 4–6 minutes before syncope in children with VVS. The authors suggested that a change in the total peripheral resistance from the supine position to the positive response period positively correlated with syncope frequency, which suggested that abnormal total peripheral resistance might be responsible for the occurrence of VVS.

Conclusions:

Existence of sinus tachycardia with AV block during TT may demonstrate selective denervation of ganglion cells which send postganglionic fibers directly to the sinus node without obvious influence on the AV node. Understanding of different inputs to both the sinus node and AV node will help in planning ablation and a better outcome.

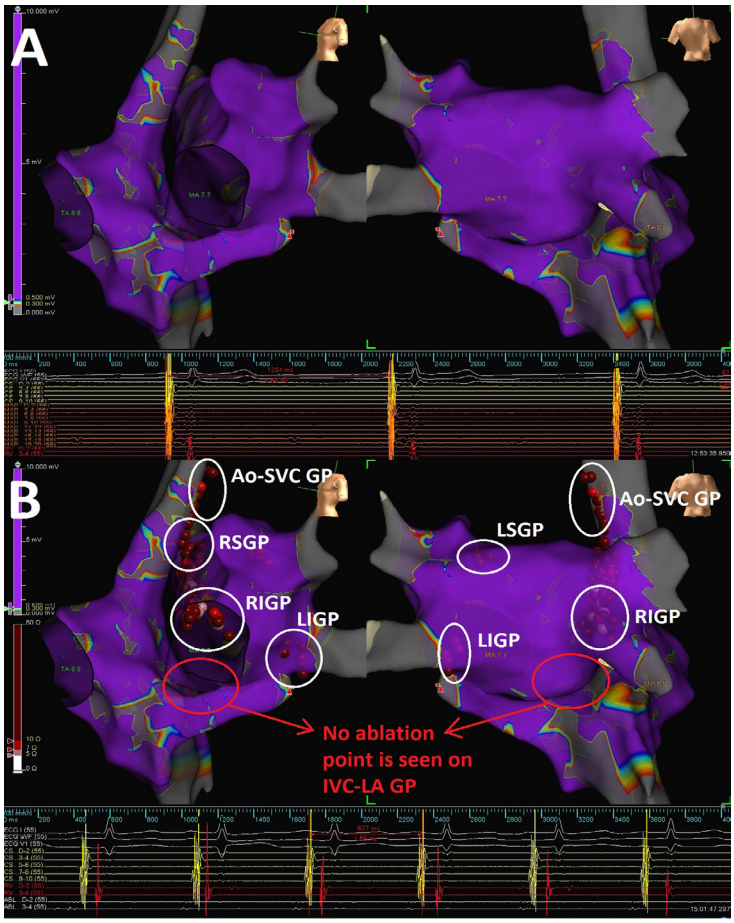

Figure 3A, 3B: **Hemodynamical results of the case during tilt testing before the procedure (A) and at 6th months of follow-up after cardioneuroablation (B)**

Top trace shows the heart rate curve; bottom trace shows continuous blood pressure curves. Blood pressure stabilizes shortly after the assumption of the upright position with no changes for the duration of the preparatory phase; the heart rate immediately rises, then stabilizes. The vertical red line indicates the time of onset of the vasovagal reaction, which is characterized, at first, by a mild decrease in blood pressure with a steep fall in heart rate and syncope occurs. The total duration of the vasovagal reaction is about 4 min. HR=heart rate; BP=blood pressure

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