Endocardial Autonomic Denervation of the Left Atrium to Treat Vasovagal Syncope: An Early Experience in Human

Running title: Yao et al.; Autonomic Denervation for Vasovagal Syncope

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Abstract:

Background - Vasovagal syncope (VVS) is the commonest cause of recurrent syncope that can be debilitating despite optimal conventional therapy. The aim of this study was to evaluate the feasibility and efficacy of selective endocardial autonomic denervation in left atrium (LA) as an alternative treatment strategy in patients with highly systematic VVS.

Methods and Results - Ten consecutive patients (mean age 50.4±6.4 years, 7 females) with a medium of 3.5 (2-20) recurrent episodes of VVS during the preceding year and positive head-up tilt testing (HUT) in whom standard therapies were ineffective or poorly tolerated were enrolled. Ganglionic plexi (GP) in the LA, identified by high-frequency stimulation, was targeted by radiofrequency (RF) catheter ablation. The patients were then follow-up at 3, 6, 12, 24 and 36 months including repeated HUT and Holter at 3 and 12 months. RF energy was applied at the left superior GP in 10 patients, right anterior GP in 5, left inferior GP in 3 using an 8mm ablation catheter. Vagal response, defined as transient ventricular asystole, atrioventricular block, or an increase in RR interval by 50%, was observed during ablation in all GP sites. The end point of procedure was the inhibition of the vagal response at target sites. At 30±16 (13-55) months follow-up, no patient had any recurrence of syncope, all patients experienced significant improvement in symptom albeit 5 of 10 patients reported transient prodromes. No complication occurred.

Conclusions - Comprehensive endocardial autonomic denervation of the LA demonstrates the feasibility of treating vasovagal syncope in medium term follow-up.

Key words: ablation, vasovagal syncope, autonomic denervation, ganglionic plexi
Introduction

Vasovagal syncope (VVS), the most common cause of sudden and transient loss of consciousness due to cerebral hypoperfusion, represents a disorder of the autonomic cardiovascular regulation. It is associated with an increased risk of physical injury and reduced quality of life when isolated or recurrent syncope occurred despite of the benign prognosis from the syncope itself.1,2

The mechanism of VVS has not been fully elucidated. Nonetheless, an enhanced parasympathetic tone as a result of the dysregulation of Bezold-Jarisch reflex together with a decrease in sympathetic tone play important roles in the induction of cardioinhibitory and vasodepressor reaction of VVS.2

The treatment of VVS is challenging particularly in patients who have frequent episodes of syncope despite of conventional therapy. Multicenter placebo-controlled trials published to date showed that the efficacy of pharmacological therapies and cardiac pacing remain limited (31.6% - 67% of success in prevention of recurrence of syncope).3-7 Consequently, we sort to identify an alternative therapy in alleviating symptom of syncope in highly symptomatic subjects who failed conventional treatment.

A recent case report showed that vagal denervation by catheter ablation of selected areas of interatrial septum can attenuate vagal activity and reduce symptom of syncope.8 Previous animal and human studies have demonstrated that the incidence of ablation induced vagal reflex at the vicinity of pulmonary venous ostia was greater than that at other atrial sites because of the particular rich autonomic innervation at the pulmonary venous antra.9-11 In this study we sort to evaluate the feasibility and efficacy of endocardial denervation of the ganglionated plexi (GP) in left atrium (LA) around the antra of pulmonary veins in the treatment of VVS.

Methods

Patients

Ten consecutive patients with recurrent frequent episodes of VVS and positive head-up tilt testing (HUT) were enrolled and underwent left atrial vagal denervation. All patients had more
than 3 syncopal episodes preceding the procedure or at least one recurrence of episode syncope within 6 months before catheter ablation and positive response (defined as below in the Head-up Tilt Testing section) from passive head-up tilt or nitroglycerin (NTG) phase of HUT.

All patients failed to be treated by conventional therapies. Failure was defined as the recurrence of syncope. All patients were given the optimal fluid intake and dietary advice, and were shown the physical counter-pressure manoeuvres. Seven patients had been unresponsive or intolerant of 80 mg daily of propranolol, 2 patients failed 0.2 mg daily of fludrocortisones. Previous medications were all discontinued before and after denervation.

Before the ablation, all patients underwent thorough cardiological, neurological and psychiatric assessments. Other cause of syncope namely orthostatic hypotension, sinus hypersensitivity, sinus node and atrioventricular conduction disturbances, ventricular tachyarrhythmia, aortic stenosis, pulmonary hypertension, hypertrophic cardiomyopathy, transient ischaemic attack, seizure disorders, subclavian steal syndrome and drug-induced syncope were excluded.1 Patients with recent myocardial infarction (<6 months), severe heart failure (NYHA class III or IV), concomitant severe chronic diseases (eg, diabetes mellitus, neurological diseases, terminal diseases), previous heart surgery and catheter ablation, permanent pacemaker were also excluded.

A routine conventional EP study was performed in all patients including sinus atrial node recovery time assessment, which intended to rule out any possible other underlying arrhythmia and sick sinus syndrome before the ablation.

Pre-ablation management

Detail history with respect to VVS were carefully taken from all patients including frequency, precipitating factors, prodromes and associated physical injury during the syncopal
spells.

The baseline investigations were performed before the procedure in all patients including chest X-ray, 12-lead electrocardiography, 24 hour ambulatory monitoring (Holter), and echocardiography. Computed tomography scan of the chest were performed in all patients to delineate the left atrial and pulmonary vein anatomy.

The two patients who had concomitant paroxysmal atrial fibrillation (AF) were anticoagulated with warfarin with an international normalized ratio (INR) within the therapeutic window for more than 4 weeks before the procedure. All antiarrhythmic drugs other than amiodarone were discontinued for at least 5 half-lives (one patient was on amiodarone). The anticoagulation method we used had been reported elsewhere.\textsuperscript{12}

All patients gave written informed consent before the stimulation and ablation procedures. The study was approved by the local ethical research committee.

**Head-up tilt testing**

Head-up tilt testing was performed in the morning in patients in a fasting state. An electronically controlled tilt table with a footboard for weight bearing and restraining belts was used for the procedure. Subjects were initially tilted at $70^\circ$ for 30 minutes (passive tilt testing). If no symptoms occurred, participants were treated with 0.25 mg NTG sublingually, and continued to be tilted for an additional 20 minutes (NTG tilt testing).\textsuperscript{13} Continuous ECG monitoring and noninvasive blood pressure measurements were preformed. The end point of the test was reproduction of syncope in the presence of hypotension, bradycardia, or both.

The positive response was defined as syncope or development of pre-syncope in association with an abrupt hypotension (systolic blood pressure $<70$ mmHg or diastolic blood pressure $<40$ mmHg) or bradycardia (heart rate $<40$ beats/min) during passive or NTG induced
HUT, as well as reproduction of the patient’s relevant clinical symptoms. The reaction type of positive HUT was reported according to the VASIS (Vasovagal Syncope International Study) classification.13

**Electrophysiological Study**

All procedures were carried out under conscious sedation with intravenous of Midazolam and flurbiprofen axitil. Three right femoral venous access were obtained using Seldinger technique through which a decapolar 6F steerable electrode catheter was inserted and placed in the coronary sinus (CS), and a quadripolar electrode catheter was placed in the right ventricle, and a 8-mm-tip deflectable catheter (Bard Electrophysiology, Lowell, MA, or iBI, St. Jude Medical, Irvine, CA) was introduced into the LA via a transseptal puncture. After the transseptal puncture, intravenous heparin was administered to maintain an activated clotting time of 200 to 300 seconds. A three dimensional geometry of the LA was created by dragging the steerable catheter along the endocardial surface of the LA using Ensite Array/NavX mapping system (St. Jude Medical Inc., St. Paul, Minnesota). Surface ECG and bipolar endocardial electrograms were continuously monitored and recorded (Bard Electrophysiology, Lowell, MA). Intracardiac electrograms were filtered from 30 to 500 Hz and measured at a sweep speed of 100 mm/s. Blood pressure, pulse oximetry were monitored throughout the procedure.

**Identification of ganglionated plexi**

The ganglionated plexi (GP) was located by high frequency stimulation (HFS) through 8-mm-tip catheter in the LA (HFS: 20 Hz, 10-20V, pulse width 5 ms; MicroPace EPS320, Australia). This technique has been reported elsewhere.14 We particularly focused at the regions between the root of the left superior pulmonary vein and LA or the left auricular appendage (left
superior GP, LSGP), inferior to the left inferior pulmonary vein (left inferior GP, LIGP),
anterior to the right superior pulmonary vein (right anterior GP, RAGP), and inferior to the right
inferior pulmonary vein (right inferior GP, RIGP).

More attention was paid when stimulating catheter tip near the mitral valvular annulus to
avoid ventricular capture during HFS. A positive vagal response was defined as transient
ventricular asystole, atrioventricular (AV) block, or an increase in mean RR interval by 50%.14

Mapping and Radiofrequency ablation

Following GP mapping, the radiofrequency (RF) energy was applied at the identified GP
sites through an 8-mm-tip RF ablation catheter. The appropriate ablation site was confirmed by
vagal response and hypotension observed within a few seconds after the RF application. The
GP sites were localized and ablated in the sequence of LSGP followed by LIGP, RAGP and
RIGP.

Each target was recorded fluoroscopically in two planes and tagged on the
three-dimensional map of the LA created by the Ensite 3000 system. The maximal setting of
power and temperature were 60W, 60°C, respectively. The end point of the procedure was
inhibition of the vagal response at each target during RF after at least 60 seconds of RF energy
delivery. Right ventricular pacing was applied if necessary. The patients with atrial fibrillation
were then treated with stepwise linear catheter ablation as previously described.12

Post-ablation Follow-up

After the procedure, all the patients were observed as an in-patient for at least 24 hours.
HUT and Holter monitor were repeated 3 and 12 months later after ablation, respectively. In
addition, a clinical visit or telephone follow-up was performed at 3, 6, 12, 24 and 36 months
after left atrial denervation. All clinical events were carefully documented including symptom
of syncope and related physical injury, and prodromes such as dizziness, fatigue, diaphoresis were not considered the recurrent episode of syncope.

Heart rate (HR), time- and frequency-domain heart rate variability (HRV) were analyzed from 24-hour Holter data before ablation, 3 months and 12 months later after ablation with specific software (Mortara Rangoni Europe, Bologna, Italy).15

Patients were not receiving any medical therapy except two patients who had atrial fibrillation. All patients received Aspirin for a period of 3 months with the exception of the two patients who had concomitant AF ablation and warfarin was given. Inappropriate sinus tachycardia was defined as a resting sinus rate more than 100 beats per minute (bpm) without physiological or haemodynamic causes based on Holter monitor and ECG.15 The symptoms indicating delay gastric emptying were carefully observed, such as nausea, abdominal pain and distension in few days after ablation.

Statistical Analysis

All data are reported as mean±SD for continuous variables and number of subjects (%) for categorical variables. Comparisons of changes of HR and HRV, the number of syncope or prodromes before and after the procedure were compared using a paired Wilcoxon signed rank test evaluated with exact p-values. P<0.05 was considered statistically significant for all statistical determinations. All analysis was performed using SPSS software version 13.0 (SPSS, Chicago).

Results

Patient characteristics

Ten consecutive patients (mean age 50.4±6.4 years, 7 females) with frequent recurrent
episodes of VVS were enrolled. Their clinical characteristics are shown in Table 1. All patients had normal left ventricular systolic function. No patient had hypertension or structured heart diseases.

Prior to catheter ablative denervation, patients had a median of 6.5 (range 3-100) syncope spells over an average of 2.8±1.8 years. Over the preceding 12 months, they had a median of 3.5 (range 2-20) syncope spells. In 4 patients, the syncopal episodes were particularly frequent, at least 10 episodes over the preceding year ranging between 10-20. Seven patients had suffered physical injury due to syncope.

The HUT of the 10 patients were all positive before the procedure. During the HUT, all the patients experienced a rapid decrease of blood pressure and sinus rhythm. The heart rate decreased by 37.4±11.3 beats per minute, systolic and diastolic blood pressure decreased by 48.3±24.2 mmHg and 36.2±15.5 mmHg, respectively. The average time to the onset of symptom was 34.8±8.2 minutes.

All patients underwent conventional electrophysiologic study at the beginning of the procedure including the sinus node recovery time assessment and no patient had any evidence of sick sinus syndrome.

**Localization of GP in the left atrium**

High frequency stimulation through the 8mm-tip-catheter was performed at the endocardial left atrial wall including the 4 typical GP sites, at the vicinity of the antra of the pulmonary veins (PV) in all patients. Figure 1 is a schematic representation of all the locations of the vagal responses induced in LA during the procedure in the 10 patients. A positive vagal response was seen in at least one region of the LA in all patients. The most common endocardial left atrial sites where vagal response was elicited were near the left superior PV (LSGP) in 10 patients.
(100%), between the right superior PV and LA (RAGP) in 5 patients (50%), and between left inferior PV and LA (LIGP) in 3 patients (30%). The LSGP located were from two main areas 1) between root of the left superior PV and the LA in 9 patients and 2) between the left superior PV and the left auricular appendage (LAA) in 8 patients. We were not able to elicit a vagal reflex between right inferior pulmonary vein and LA in any patient. Thus, 1/10 (10%) patient had identified three GPs and 6/10 (60%) had two GPs (mean 1.8 ± 0.6 identified GPs per patient).

**Left Atrial Vagal Denervation**

The RF energy was applied at LSGP in 10 patients, RAGP in 5, LiGP in 3. Within a few seconds of the onset of RF application, evoked vagal reflex and hypotension were observed in all patients during catheter ablation. Left atrial vagal denervation was accomplished by radiofrequency lesions delivered at these sites. The end point of procedure was inhibition of the vagal response at each target during RF after delivery energy at least for 60 seconds. Figure 2 shows an example of the RF application at the target sites.

An average of 9 ± 1 RF pulses per patient was needed to completely eliminate the induced vagal response at all sites in the 10 patients. The mean procedure time was 50.2 ± 3.8 minutes, and mean x-ray time was 11.2 ± 1.7 minutes. There were no complications related to the ablative procedure including vascular injury, thrombo-embolic events, tamponade and others.

**Outcome**

During the follow-up of 30 ± 16 (13-55) months, none of the patient experienced any episode of syncope or related physical injury (P=0.002) and the number of prodromes per year after the autonomic denervation was significantly decreased (P=0.016). All patients reported obvious improvement of symptom, especially for the 4 patients who suffered from frequent
VVS (≥10 syncopal episodes over 12 months) albeit 5 patients experienced prodromes (Figure 3).

HUT was repeated 3 months after left atrial vagal denervation in all patients. HUT was negative in 6 patients, while positive in 4 patients. Interestingly, the average time to the onset of symptoms in the 4 patients where HUT remained positive was postponed by $8.8 \pm 5.2$ minutes, and in 1 patient the syncopal during HUT was delayed from the passive tilt phase to the NTG phase (table 2). In the absence of further syncope, only 6 patients were willing to have another HUT at 12 months. There were no discernable changes of the HUT finding at 12 months compared to that at 3 months in these 6 patients (table 2).

Heart rate (HR) and heart rate variability (HRV) parameters showed significant changes in 3 months and persisted in 12 months after the ablation, except the maximum heart rate, which were showed in table 3. The mean and minimum HR increased, time- and frequency-domain HRV parameters decreased at 3 months compared to before ablation and persisted at 12 months post-ablation studies.

Inappropriate sinus tachycardia or symptom related to delay in gastric emptying were not observed in any of the 10 patients.

Discussion

Major findings

The main finding of this study is that the left atrial autonomic denervation guided by HFS could improve symptoms and prevent the recurrence of syncope in patients with VVS. None of the patients in the study had recurrence of syncope or any associated physical injury in a medium term follow-up (30 ± 16 months). Although 4 patients in our study reported positive
HUT after denervation, the time to the onset of symptoms was delayed during the repeat HUT after catheter ablation.

This study is our initial experience to demonstrate the efficacy of preventing frequent VVS by comprehensive left atrial autonomic denervation guided by HFS. The study concurred with the observation from a previous case report showing a beneficial effect of selective vagal denervation focused on inter-atrial septum guided by HFS in a single patient with frequent episodes of VVS.8

**Previous studies**

Pachón et al16 reported that the cardiac autonomic modulation through catheter ablation guided by Fast-Fourier Transform analysis was an alternative treatment for refractory neural mediated syncope. In this study 6 patients who underwent this procedure had symptomatic relief at follow-up period up to 9 months. Scanavacca et al8 reported a fifteen years old female patient with frequent episodes of VVS performed selective vagal denervation on atrial septum guided by HFS. Although the syncope reoccurred late after the procedure which is consistent with autonomic activity recovery, the patient reported significant improvement in quality of life and remained asymptomatic for the first 9 months after denervation.

In our study, we elected to target all the GP sites in the LA and use a large solid-tip RF ablation catheter with high power with the intention to comprehensively denervate all the identifiable GP sites and to minimize the chance of the regeneration of the autonomic innervation of the ablated sites. In this preliminary series there was no recurrence of syncope in all patients at a medium-term follow-up of 30±16 months (ranging 13-55 months).

**Mechanism of vagal denervation**

The vasovagal syncope is thought to be elicited in response to a Bezold-Jarisch reflex,
involving a combination of parasympathetic enhancement (bradycardia) and sympathetic suppression (hypotension). It is surmised that the effects of vagal denervation could break the vicious cycle that maintains the ongoing vasovagal reflex. Although intuitively the cardiac GP denervation would provide benefit only in cardioinhibitory type, our study interestingly revealed that extensive left atrial GP denervation benefitted the vasodepressor and the mixed type also.

The observation that both cardioinhibitory and vasodepressor reactions could be modulated by left atrial vagal denervation in our study is intriguing. The underlying mechanism of this phenomenon can not be fully explained by the current available body of literature. Thompson et al.\(^{17}\) suggested a interconnection between afferent and efferent neurons of intrinsic cardiac autonomic system and GP receive inputs from both mechano- and chemo- sensory receptors. Thus, it is conceivable that denervation of GP in LA might affect the efferent pathway involved in the initiation and regulation of Bezold-Jarisch reflex, preventing both cardioinhibitory and vasodepressor reactions during VVS in turn prevent recurrence of syncope.

**GP identification and denervation**

The studies from anatomy of intrinsic cardiac nerve system indicate that the left atrial autonomic ganglia are distributed mainly around the PV antra.\(^{18,19}\) LSGP is located on the roof junction of left superior PV (LSPV) and often extends to the medial aspect of left atrial appendage (LAA). RAGP is located anterior to the right superior PV (RSPV) and often extends inferiorly.\(^{19}\) In addition, The left and right inferior PVs involve a less number of ganglia than the left and right superior PVs.\(^{20}\) The endocardial sites where vagal response induced in our procedure were consistent with these anatomical findings. The most common sites were at the roof or LAA junction of the left superior PV (LSGP) and the anterior surface of right superior
PV (RAGP). All GPs identified by HFS were ablated and bradycardia-hypotension reaction was observed in all patients during ablation. Elimination of vagal reflex followed by sinus tachycardia occurred in all patients.

The medium to long-term effects of autonomic denervation by catheter ablation are not fully elucidated. Although the animal study in dogs showed that the effects of vagal denervation after fat pad ablation were reversed within 4 weeks,21 the findings from early human studies (left atrial ablation in patients with atrial fibrillation) were heterogeneous. Pappone15 group and Scanavacca22 group have observed the return in autonomic innervation at 3 to 6 months respectively, after catheter ablation in treating atrial fibrillation. Another report from Scanavacca et al,8 however, showed a relative long lasting autonomic denervation effects in the frequent symptomatic VVS patient assessed by HRV, time- and frequency-domain data on Holter. Taking into the consideration of potential recovery of autonomic innervation late after catheter ablation, in our study we elected to adopt an extensive LA denervation protocol in addition to using large tip catheters (8mm tip) with higher RF power setting (60W). We did not observe any complications using this approach.

Furthermore, in our study the effects of the denervative procedure possibly persisted at least 12 months after the ablation evidence by findings from repeated HUT, time- and frequency-domain analyses from Holter monitor and last but not the least, the clinical symptomatic status. Future studies with longer term follow-up are paramount to allow better understanding of the ‘durability’ of this interventional approach in treating VVS.

**Effect and clinical implications**

It was known that patients with multiple episodes of frequent syncope and pre-syncope had a major adverse effect to the quality of life, which was particularly marked in older and
female patients. Although conventional therapy including life style modification, pharmacological or cardiac pacing can be effective in symptom alleviation in some VVS patients, a significant proportion of patients continue to be highly symptomatic despite receiving the optimal currently available therapy.

Our study demonstrated that an alternative treatment strategy in denervating the autonomic innervation to the LA percutaneously could be effective in the prevention of syncope in a group of patients who had highly symptomatic recurrent VVS. Sheldon and colleagues followed up a large group of patients with VVS induced by HUT and developed a predictive model which revealed the recurrence risk in the follow-up cohort without intervention was 0.03 per month. The observation of no recurrence of syncope after a mean 30±16 follow-up period in our study supported that, apart from the effect of HUT itself, autonomic denervation in LA has contributed to the reduced frequency of syncope events.

Although 50% of patients reported to have recurrences of minor prodromal symptoms, the frequent and extent of these symptoms were significantly improved compared to before denervation and more importantly there was no recurrence of syncope in all patients during follow-up after the ablative procedure. Furthermore, the time to tilt triggered syncope/symptoms was postponed in 4 patients after denervation raises the possibility that the denervation had a favorable augmentative effect of baroreflex. The mechanism of this interesting phenomenon is unclear and needs further elucidation.

The results of the present study indicate that RF current application for LA autonomic denervation in patients with VVS is feasible and may be a valuable adjunctive therapy in patients who cannot be adequately treated by conventional treatment modalities.
Limitations

This was a single center early series included a small number of patients without a control group. A larger patient cohort is needed to confirm safety and efficacy of this new treatment option in patients with VVS and perhaps followed by a randomized, controlled trial to further define the role of this approach. In addition, the effect of vagal denervation between different hemodynamic types based on HUT was not compared in this preliminary study.

We have shown that at least autonomic denervation is effective in the prevention of syncope in highly symptomatic VVS patients at a medium term follow-up period but the long-term follow-up data of this procedure is still lacking. Despite of those limitations, the results of our study provide important contribution to the literature with respect a new treatment modality for patients with frequent VVS.

Conclusion

Comprehensive autonomic denervation in the left atrium by ablating at the ganglionated plexi endocardially may prevent recurrent episode of syncope in patients with vasovagal syncope. The approach demonstrates the feasibility from this our early experience, and may be offered as an alternative interventional treatment to a selective group of patients with highly symptomatic recurrent VVS. Further larger randomized control study is required to investigate this treatment option further.

Conflict of Interest Disclosures: None

References:


Table 1. Baseline Characteristics of the Patients (n=10)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
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<tr>
<td>Age (yrs)</td>
<td>50.4 ± 6.4</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>7 (70%)</td>
</tr>
<tr>
<td>Syncope history (yrs)</td>
<td>2.8 ± 1.8</td>
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<tr>
<td><strong>Symptom burden</strong></td>
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<tr>
<td>Total Number of syncopal episodes, median (range)</td>
<td>6.5 (3-100)</td>
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<tr>
<td>Number of syncope in preceding 12 months, median (range)</td>
<td>3.5 (2-20)</td>
</tr>
<tr>
<td>Reported prodromes, pts (%)</td>
<td>7 (70%)</td>
</tr>
<tr>
<td>Syncope-related physical injury, pts (%)</td>
<td>7 (70%)</td>
</tr>
<tr>
<td><strong>Head-up tilt test</strong></td>
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<tr>
<td>Time to tilt syncope, min</td>
<td>34.8 ± 8.2</td>
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<tr>
<td>Syncope during NTG provocative phase, pts (%)</td>
<td>8 (80%)</td>
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<td>Heart rate decreased, bpm</td>
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<td>48.3 ± 24.2</td>
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<tr>
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<td>36.2 ± 15.5</td>
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<tr>
<td>Supine blood pressure, mmHg</td>
<td>106.2 ± 9.7 / 65.7 ± 8.9</td>
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<tr>
<td>Supine heart rate, bpm</td>
<td>70.8 ± 12.1</td>
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<tr>
<td>Left atrium diameter, mm</td>
<td>32.3 ± 3.5</td>
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<tr>
<td>Left ventricular ejection fraction, (%)</td>
<td>63.0 ± 3.1</td>
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bpm=beats per minute; mm=millimeter
Table 2. Catheter ablation and Follow-up Results of Study Population

<table>
<thead>
<tr>
<th>Patient #</th>
<th>History, years</th>
<th>GP Ablation</th>
<th>Pre-ablation Pro-dromes</th>
<th>No. of Syncope</th>
<th>Time to Tilt Syncope, min</th>
<th>Post-ablation Pro-dromes</th>
<th>No. of Syncope</th>
<th>Time to Tilt Syncope</th>
<th>Follow-up Months</th>
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<td>#1</td>
<td>5</td>
<td>LSGP/RAGP</td>
<td>+</td>
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<td>+</td>
<td>12</td>
<td>37.5*</td>
<td>0</td>
<td>0</td>
<td>-</td>
<td>55</td>
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<td>1.3</td>
<td>LSGP</td>
<td>-</td>
<td>3</td>
<td>40*</td>
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<td>-</td>
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<td>21</td>
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<td>3</td>
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<td>-</td>
<td>0</td>
<td>40*</td>
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</table>

GP = Ganglionated plexi; LIGP = left inferior GP; LSGP = left superior GP; RAGP = right anterior GP.
* Positive HUT during Nitro phase. †Unwilling to have repeated post ablation HUT.
Table 3. Comparison of changes of HR and HRV before and after ablation

<table>
<thead>
<tr>
<th></th>
<th>Pre-ablation (n=10)</th>
<th>3 months after ablation (n=10)</th>
<th>12 months later after ablation (n=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MD ± SD</td>
<td>MD ± SD</td>
<td>MD ± SD</td>
</tr>
<tr>
<td>SDNN, ms</td>
<td>129.1 ± 14.3</td>
<td>104.2 ± 8.8</td>
<td>100.1 ± 7.4</td>
</tr>
<tr>
<td>rMSSD, ms</td>
<td>29.7 ± 9.0</td>
<td>21.2 ± 6.1</td>
<td>19.4 ± 5.6</td>
</tr>
<tr>
<td>ln LF, ms²</td>
<td>5.53 ± 0.22</td>
<td>5.22 ± 0.19</td>
<td>5.18 ± 0.17</td>
</tr>
<tr>
<td>ln HF, ms²</td>
<td>5.11 ± 0.23</td>
<td>4.69 ± 0.19</td>
<td>4.59 ± 0.17</td>
</tr>
<tr>
<td>Minimum HR, bpm</td>
<td>51.2 ± 4.6</td>
<td>56.2 ± 5.1</td>
<td>56.8 ± 4.8</td>
</tr>
<tr>
<td>Maximum HR, bpm</td>
<td>121.5 ± 13.4</td>
<td>118.8 ± 14.4</td>
<td>120.0 ± 11.8</td>
</tr>
<tr>
<td>Mean HR, bpm</td>
<td>70.9 ± 5.4</td>
<td>80.3 ± 5.9</td>
<td>81.2 ± 5.2</td>
</tr>
</tbody>
</table>

*Compared with pre-ablation; SDNN, standard deviation of all NN intervals; rMSSD, root mean square of the successive differences; LF, low-frequency; HF, high-frequency; HR, heart rate; bpm, beats per minute.
**Figure Legends:**

**Figure 1** shows the schematic left atrial representation of the locations of GPs identified in all 10 patients. The yellow dots represent the schematically ganglionated plexi (GP) in left atrium (LA) of the 10 patients. Each dot represents the approximated GP site identified. The Radiofrequency energy was applied at the left superior GP (LSGP) in 10 patients, right anterior GP (RAGP) in 5, left inferior GP (LIGP) in 3. The sites LSPG located were between root of the left superior pulmonary vein (LSPV) and the LA in 9 patients, between the LSPV and left auricular appendage (LAA) in 8, both in 7. RAGP located between the anterior root of right superior pulmonary vein (RSPV) and the LA. LIGP located between inferior aspect of left inferior pulmonary vein (LIPV) and the LA.

**Figure 2** shows an example of denervation at the target sites. A three-dimensional computed tomography reconstruction of the left atrium (LA) fused within the NavX environment. The yellow dots represent the ganglionated plexi (GP) sites identified by HFS and denervated by radiofrequency (RF) ablation. Positive vagal responses were provoked when RF energy was delivered to the root of the left superior pulmonary vein (LSPV), anterior to the right superior pulmonary vein (RSPV), inferior to the left inferior pulmonary vein (LIPV). When RF applications through an 8mm tip catheter were delivered, vagal reflex was observed within seconds.

**Figure 3** shows the numbers of syncope and prodromes per year before and after denervation.
Endocardial Autonomic Denervation of the Left Atrium to Treat Vasovagal Syncope: An Early Experience in Human

Yan Yao, Rui Shi, Tom Wong, Lihui Zheng, Wensheng Chen, Long Yang, Wen Huang, Jingru Bao and Shu Zhang

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Endokardiální autonomní denervace v levé síně v léčbě vazovagální synkopy
První zkušenosti u lidí

Yan Yao, MD, PhD*; Rui Shi, MD*; Tom Wong, MBChB, MD, FRCP; Lihui Zheng, MD, PhD; Wensheng Chen, MD; Long Yang, MD; Wen Huang, MD; Jingru Bao, MD; Shu Zhang, MD, PhD

Kontext — Vazovagální synkopa (VVS) představuje nejčastější příčinu recidivující synkopy, která může být i přes optimální klasicckou léčbu pro pacienta vysilující. Cílem této studie bylo zhodnotit proveditelnost a účinnost selektivní endokardiální autonomní denervace v levé síně jako alternativní léčebnou strategii u nemocných s vysoce symptomatickou VVS.

Metody a výsledky — Do studie bylo zařazeno 10 po sobě jdoucích pacientů (průměrný věk 50,4 ± 6,4 let; 7 žen) s průměrně 3,5 (rozmezí 2–20) recidivujícími epizodami VVS v předchozím roce a s pozitivním výsledkem testu na nakloněné rovině, u nichž nebyly standardní methode podávané léky účinné, nebo je pacienti netolerovali. Radiofrekvenční katetrační ablaci byla provedena v ganglionových pleteniích (ganglionated plexi, GP) v levé síně, identifikovaných vysokofrekvenční stimulací. Pacienti byli následně vyšetření po 3, 6, 12, 24 a 36 měsících, kdy byl proveden test na nakloněné rovině a holterovo monitorování EKG po 1 a 12 měsících. Během ablace byla pozorována ve všech GP odpověď n. vagus, popisovaná jako přechodná komorová asystolie, atriointrikulární blokáda nebo prodloužení R-R intervalu o 50%. Sledovaným parametrem výkonu byla inhibice odpovědi n. vagus na místech intervence. Po 30 ± 16 (rozmezí 13–55) měsících následného sledování nedošlo u žádného z pacientů k recidivě synkopy a u všech pacientů bylo zaznamenáno významné zmírnění symptomů, nicméně 5 z 10 pacientů uvedlo přechodné prodromální stavě. Nevyšlykly se žádné komplikace.

Závěry — Komplexní endokardiální autonomní denervace v levé síně prokázala při střednědobém sledování proveditelnost léčby VVS. (Circ Arrhythm Electrophysiol. 2012;5:279-286.)

Klíčová slova: ablaci ■ vazovagální synkopa ■ autonomní denervace ■ ganglionové pletení

SOUHRN PRO KLINICKOU PRAXI

V této studii jsme hodnotili proveditelnost selektivní endokardiální autonomní denervace v levé síně (LS) jako alternativní léčebnou strategii u pacientů s vysoce symptomatickou vazovagální synkopou. Do studie bylo zařazeno 10 pacientů (průměrný věk 50,4 ± 6,4 let; 7 žen) s recidivujícími epizodami VVS a s pozitivním výsledkem testu na nakloněné rovině. Radiofrekvenční katetrační ablaci byla provedena v ganglionových pletenách v LS, identifikovaných vysokofrekvenční stimulací pomocí 8mm ablacií katetrů s pevným hrotem. Sledovaným parametrem výkonu byla inhibice odpovědi n. vagus v místech intervence. Výsledky této studie s prvními zkušenostmi u pacientů jsou velmi povzbudivé v tom smyslu, že popisovaný výkon dokázal během sledování v délce 30 ± 16 (13–55) měsíců, odstranil u všech pacientů symptamy synkopy bez jakýchkoliv komplikací v souvislosti s výkonem. Na základě výsledků publikované studie se lze domnívat, že použití radiofrekvenční energie k autonomní jedenervaci v levé síně u nemocných s vysoce symptomatickou recidivující vazovagální synkopou je možné a může se stát cennou formou přidatné léčby pacientů, u nichž selhala klasiccká léčba.