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

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Background—Vasovagal syncope (VVS) is the most common 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 symptomatic VVS.

Methods and Results—Ten consecutive patients (mean age, 50.4 ± 6.4 years; 7 women) with a median of 3.5 (range, 2–20) recurrent episodes of VVS during the preceding year and positive head-up tilt testing in whom standard therapies were ineffective or poorly tolerated were enrolled. Ganglionated plexi (GP) in the LA, identified by high-frequency stimulation, was targeted by radiofrequency catheter ablation. The patients were then followed up at 3, 6, 12, 24, and 36 months, including repeated head-up tilt testing and Holter at 3 and 12 months. Radiofrequency energy was applied at the left superior GP in 10 patients, right anterior GP in 5, and left inferior GP in 3, using an 8-mm ablation catheter. Vagal response, defined as transient ventricular asystole, atrioventricular block, or an increase in R-R 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 (range, 13–55) months of follow-up, no patient had any recurrence of syncope and all patients had significant improvement in symptoms, but 5 of 10 patients reported transient prodromes. No complications occurred.

Conclusions—Comprehensive endocardial autonomic denervation of the LA demonstrates the feasibility of treating VVS in medium-term follow-up. (Circ Arrhythm Electrophysiol. 2012;5:279-286.)

Key Words: ablation ■ vasovagal syncope ■ autonomic denervation ■ ganglionated plexi

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.1 It is associated with an increased risk of physical injury and reduced quality of life when isolated or recurrent syncope occurs, despite 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 the 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 conventional therapy. Multicenter, placebo-controlled trials published to date have shown 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 endeavor to identify an alternative therapy in alleviating symptoms 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 (PV) ostia was greater than that at other atrial sites because of the particular rich autonomic innervation at the PV antra.9–11 In the present study, we evaluate the feasibility and efficacy of endocardial denervation of the ganglionated plexi (GP) in left atrium (LA) around the antra of the PVs 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 LA vagal denervation. All patients had more than 3 syncopal episodes preceding the procedure or at least 1 recurrence of syncope within 6 months before catheter ablation and positive response (defined in the Head-Up Tilt Testing section) to passive head-up tilt or the nitroglycerin (NTG) phase of HUT. All patients failed treatment 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 counterpressure maneuvers. Seven patients had been unrespiratory or intolerant to 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 cardiologic, neurologic, and psychiatric assessments. Other causes of syncope, namely, orthostatic hypotension, sinus hypersensitivity, sinus node and atrioventricular conduction disturbances, ventricular tachyarrhythmia, aortic stenosis, pulmonary hypertension, hypertrophic cardiomyopathy, transient ischemic attack, seizure disorders, subclavian steal syndrome, and drug-induced syncope, were excluded.1 Patients with recent myocardial infarction (<6 months), severe heart failure (New York Heart Association class III or IV), concomitant severe chronic diseases (eg, diabetes mellitus, neurologic diseases, terminal diseases), previous heart surgery and catheter ablation, and permanent pacemaker were also excluded.

A routine conventional electrophysiological 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.

Preablation Treatment
A detailed history with respect to VVS was 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 radiography, 12-lead ECG, 24-hour ambulatory monitoring (Holter), and echocardiography. Computed tomography scan of the chest was performed in all patients to delineate the LA and PV anatomy.

The 2 patients who had concomitant paroxysmal atrial fibrillation (AF) were anticoagulated with warfarin, with an international normalized ratio within the therapeutic window for more than 4 weeks before the procedure. All arrhythmic drugs other than amiodarone were discontinued for at least 5 half-lives (1 patient was on amiodarone). The anticoagulation method that we used has been reported elsewhere.13 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
HUT 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° 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).13 Continuous ECG monitoring and noninvasive blood pressure measurements were performed. The end point of the test was reproduction of syncope in the presence of hypotension, bradycardia, or both.

A positive response was defined as syncope or development of presyncope in association with an abrupt hypotension (systolic blood pressure <70 mm Hg or diastolic blood pressure <40 mm Hg) or bradycardia (heart rate <40 bpm) 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 VASIS (Vasovagal Syncope International Study) classification.13

Electrophysiological Study
All procedures were carried out under conscious sedation with intravenous administration of midazolam and flurbiprofen axitil. Three right femoral venous access was obtained by means of the Seldinger technique, through which a decapolar 6F steerable electrode catheter was inserted and placed in the coronary sinus, a quadripolar electrode catheter was placed in the right ventricle, and an 8-mm-tip deflectable catheter (Bard Electrophysiology, Lowell, MA, or IBI, St Jude Medical, Irvine, CA) was introduced into the LA through a transseptal puncture. After the transseptal puncture, intravenous heparin was administered to maintain an activated clotting time of 200–300 seconds. A 3-dimensional geometry of the LA was created by dragging the steerable catheter along the endocardial surface of the LA, using the Ensite Array/NavX mapping system (St Jude Medical Inc, St Paul, MN). Surface ECG and bipolar endocardial electrograms were continuously monitored and recorded (Bard Electrophysiology, Lowell, MA). Intracardiac electrograms were filtered from 30–500 Hz and measured at a sweep speed of 100 mm/s. Blood pressure and pulse oximetry were monitored throughout the procedure.

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

More attention was paid when stimulating the 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 R-R interval by 50%.14

Mapping and Radiofrequency Ablation
After GP mapping, radiofrequency energy was applied at the identified GP sites through an 8-mm-tip radiofrequency ablation catheter. The appropriate ablation site was confirmed by vagal response and hypotension observed within a few seconds after radiofrequency 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 2 planes and tagged on the 3-dimensional map of the LA created by the Ensite 3000 system. The maximal setting of power and temperature were 60 W and 60°C, respectively. The end point of the procedure was inhibition of the vagal response at each target during radiofrequency after at least 60 seconds of radiofrequency energy delivery. Right ventricular pacing was applied if necessary. The patients with AF were then treated with stepwise linear catheter ablation as previously described.12

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

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

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

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>50.4±6.4</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>7 (70%)</td>
</tr>
<tr>
<td>Syncope history, y</td>
<td>2.8±1.8</td>
</tr>
<tr>
<td>Symptom burden</td>
<td></td>
</tr>
<tr>
<td>Total No. of syncopal episodes, median (range)</td>
<td>6.5 (3–100)</td>
</tr>
<tr>
<td>No. of syncope in preceding 12 mo, median (range)</td>
<td>3.5 (2–20)</td>
</tr>
<tr>
<td>Reported prodromes, patients, n (%)</td>
<td>7 (70%)</td>
</tr>
<tr>
<td>Syncope-related physical injury, patients, n (%)</td>
<td>7 (70%)</td>
</tr>
<tr>
<td>Head-up tilt test</td>
<td></td>
</tr>
<tr>
<td>Time to tilt syncope, min</td>
<td>34.8±8.2</td>
</tr>
<tr>
<td>Syncope during nitroglycerin provocative phase, patients, n (%)</td>
<td>8 (80%)</td>
</tr>
<tr>
<td>Heart rate decreased, bpm</td>
<td>37.4±11.3</td>
</tr>
<tr>
<td>Systolic blood pressure decreased, mm Hg</td>
<td>48.3±24.2</td>
</tr>
<tr>
<td>Diastolic blood pressure decreased, mm Hg</td>
<td>36.2±15.5</td>
</tr>
<tr>
<td>Supine blood pressure, mm Hg</td>
<td>106.2±9.7/65.7±8.9</td>
</tr>
<tr>
<td>Supine heart rate, bpm</td>
<td>70.8±12.1</td>
</tr>
<tr>
<td>Left atrium diameter, mm</td>
<td>32.3±3.5</td>
</tr>
<tr>
<td>Left ventricular ejection fraction, %</td>
<td>63.0±3.1</td>
</tr>
</tbody>
</table>

Patients were not receiving any medical therapy except for 2 patients who had AF. All patients received aspirin for a period of 3 months, with the exception of the 2 patients who had concomitant AF ablation, and warfarin was given. Inappropriate sinus tachycardia was defined as a resting sinus rate >100 bpm without physiological or hemodynamic causes, based on Holter monitor and ECG.15 The symptoms indicating delayed gastric emptying were carefully observed, such as nausea, abdominal pain, and distension a 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 and the number of syncope or prodromes before and after the procedure were compared, using a paired Wilcoxon signed rank test evaluated with exact probability values. A value of \( P<0.05 \) was considered statistically significant for all statistical determinations. All analysis was performed with the use of SPSS software version 13.0 (SPSS, Chicago, IL).

Results

Patient Characteristics
Ten consecutive patients (mean age, 50.4±6.4 years; 7 women) 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 disease.

Before 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 syncope spells were particularly frequent, with at least 10 episodes over the preceding year, ranging between 10–20. Seven patients had physical injury caused by syncope.

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

All patients underwent conventional electrophysiological 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 LA
High-frequency stimulation through the 8-mm-tip catheter was performed at the endocardial LA wall, including the 4 typical GP sites, at the vicinity of the antra of the PVs in all patients. Figure 1 is a schematic representation of all the locations of the vagal responses induced in the LA during the procedure in the 10 patients. A positive 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

Figure 1. Schematic left atrial representation of the locations of ganglionated plexi (GP) identified in all 10 patients. Yellow dots represent the GP in the left atrium (LA) of the 10 patients. Each dot represents the approximated GP site identified. Radiofrequency energy was applied at the left superior GP (LSGP) in 10 patients, right anterior GP (RAGP) in 5, and left inferior GP (LIGP) in 3. The sites LSPG located were between the root of the left superior pulmonary vein (LSPV) and the LA in 9 patients, between the LSPV and left auricular appendage (LAA) in 8, and both in 7. RAGP is located between the anterior root of right superior pulmonary vein (RSPV) and the LA. LIGP is located between inferior aspect of left inferior pulmonary vein (LIPV) and the LA.
patients (50%), and between left inferior PV and LA (LIGP) in 3 patients (30%). The LSGP located were from 2 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 PV and LA in any patient. Thus, 1 of 10 (10%) patients had 3 identified GPs and 6 of 10 (60%) had 2 GPs (mean, 1.8 ± 0.6 identified GPs per patient).

LA Vagal Denervation

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

An average of 9 ± 1 radiofrequency 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 radiography time was 11.2 ± 1.7 minutes. There were no complications related to the ablative procedure, including vascular injury, thromboembolic events, tamponade, and others.

Outcome

During the follow-up of 30 ± 16 (range, 13–55) months, none of the patients had an 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 symptoms, especially for the 4 patients who had frequent VVS (≥ 10 syncopal episodes over 12 months), but 5 patients had prodromes (Figure 3).

HUT was repeated 3 months after LA vagal denervation in all patients. HUT was negative in 6 patients and positive in 4 patients. Interestingly, the average time to the onset of symptoms in the 4 patients in whom HUT remained positive was postponed by 8.8 ± 5.2 minutes, and in 1 patient the syncopal episode 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 with that at 3 months in these 6 patients (Table 2).

HR and HRV parameters showed significant changes at 3 months and persisted for 12 months after the ablation (except for maximum heart rate, shown in Table 3). The mean and minimum HR increased and time- and frequency-domain HRV parameters decreased at 3 months compared with before ablation and persisted at 12 months in postablation studies.

Inappropriate sinus tachycardia or symptoms 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 LA 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 repeat HUT after catheter ablation.

The present study is our initial experience to demonstrate the efficacy of preventing frequent VVS by comprehensive LA 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 interatrial septum guided by HFS in a single patient with frequent episodes of VVS.8

Previous Studies
Pachon et al16 reported that the cardiac autonomic modulation through catheter ablation guided by Fast-Fourier Transform analysis was an alternative treatment for refractory neurally mediated syncope. In this study, 6 patients who underwent this procedure had symptomatic relief at a follow-up period up to 9 months. Scanavacca et al8 reported a 15-year-old

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>Prodomes</th>
<th>Time to Tilt Syncope, Minutes</th>
<th>No. of Syncope Episodes</th>
<th>Time to Tilt Syncope at 3 Months, Minutes</th>
<th>Time to Tilt Syncope at 12 Months, Minutes</th>
<th>Follow-Up, Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5</td>
<td>LSGP/RAGP</td>
<td>+</td>
<td>20</td>
<td>35*</td>
<td>+</td>
<td>0</td>
<td>55</td>
</tr>
<tr>
<td>2</td>
<td>5</td>
<td>LSGP/RAGP</td>
<td>+</td>
<td>12</td>
<td>37.5*</td>
<td>+</td>
<td>0</td>
<td>55</td>
</tr>
<tr>
<td>3</td>
<td>1.3</td>
<td>LSGP</td>
<td>–</td>
<td>3</td>
<td>40*</td>
<td>–</td>
<td>0</td>
<td>42</td>
</tr>
<tr>
<td>4</td>
<td>3</td>
<td>LSGP</td>
<td>+</td>
<td>2</td>
<td>40*</td>
<td>–</td>
<td>0</td>
<td>36</td>
</tr>
<tr>
<td>5</td>
<td>1</td>
<td>LSGP/LIGP</td>
<td>+</td>
<td>3</td>
<td>42.5*</td>
<td>+</td>
<td>0</td>
<td>24</td>
</tr>
<tr>
<td>6</td>
<td>0.3</td>
<td>LSGP/RAGP</td>
<td>–</td>
<td>10</td>
<td>27.5</td>
<td>+</td>
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<td>37.5* 40* 24</td>
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<tr>
<td>7</td>
<td>5</td>
<td>LSGP</td>
<td>–</td>
<td>2</td>
<td>40*</td>
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<td>0</td>
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</tr>
<tr>
<td>8</td>
<td>3</td>
<td>LSGP/LIGP</td>
<td>+</td>
<td>3</td>
<td>32.5*</td>
<td>–</td>
<td>0</td>
<td>37.5* 40* 16</td>
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<tr>
<td>9</td>
<td>2</td>
<td>LSGP/RAGP/LIGP</td>
<td>+</td>
<td>4</td>
<td>37.5*</td>
<td>–</td>
<td>0</td>
<td>37.5* 40* 14</td>
</tr>
<tr>
<td>10</td>
<td>2</td>
<td>LSGP/RAGP</td>
<td>+</td>
<td>10</td>
<td>15</td>
<td>+</td>
<td>0</td>
<td>37.5* 40* 13</td>
</tr>
</tbody>
</table>

GP indicates ganglionated plexi; LIGP, left inferior GP; LSGP, left superior GP; RAGP, right anterior GP.

*Positive head-up tilt test (HUT) during nitroglycerin phase.

†Unwilling to have repeated postablation HUT.
female patient with frequent episodes of VVS in whom selective vagal denervation on the atrial septum guided by HFS was performed. Although the syncope recurred 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 radiofrequency 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 any patients at a medium-term follow-up of 30±16 months (ranging from 13–55 months).

Mechanism of Vagal Denervation
VVS is thought to be elicited in response to the 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 the cardioinhibitory type, our study interestingly revealed that extensive LA GP denervation benefited the vasodepressor and the mixed type also.

The observation that both cardioinhibitory and vasodepressor reactions could be modulated by LA vagal denervation in our study is intriguing. The underlying mechanism of this phenomenon cannot be fully explained by the current available body of literature. Thompson et al.17 suggested that an interconnection between afferent and effluent neurons of the intrinsic cardiac autonomic system and the GP receives inputs from both mechanosensory and chemosensory receptors. Thus, it is conceivable that denervation of the GP in the LA might affect the effluent pathway involved in the initiation and regulation of the Bezold-Jarisch reflex, preventing both cardioinhibitory and vasodepressor reactions during VVS, and in turn prevent recurrence of syncope.

GP Identification and Denervation
Studies of the anatomy of the intrinsic cardiac nerve system indicate that the LA 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 fewer ganglia than the left and right superior PVs.20 The endocardial sites where vagal response was induced in our procedure were consistent with these anatomic 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 AF) were heterogeneous. Pappone et al.18 and Scanavacca et al.22 have observed the return in autonomic innervation at 3–6 months, after catheter ablation in treating AF. Another report from Scanavacca et al.8 however, showed relatively long-lasting autonomic denervation effects in the frequent symptomatic VVS patient assessed by HRV and time- and frequency-domain data on Holter. Taking into consideration the 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 (8-mm tip) with a higher radiofrequency power setting (60 W). We did not observe any complications with the use of this approach. Furthermore, in our study, the effects of the denervative procedure possibly persisted at least 12 months after the ablation, evidenced by findings from repeated HUT and time- and frequency-domain analyses from Holter monitoring and 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 has been known that patients with multiple episodes of frequent syncope and presyncope had a major adverse effect...
to quality of life, which was particularly marked in older and female patients. Although conventional therapy, including lifestyle modification, pharmacological treatment, 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 et al followed up a large group of patients with VVS induced by HUT and developed a predictive model that 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-month follow-up period in our study supported that, apart from the effect of HUT itself, autonomic denervation in the LA contributed to the reduced frequency of syncope events. Although 50% of patients reported to have recurrences of minor prodromal symptoms, the frequency and extent of these symptoms were significantly improved compared with before denervation, and, more importantly, there was no recurrence of syncope in any patients during follow-up after the ablative procedure. Furthermore, the time to tilt-triggered syncope/symptoms was postponed in 4 patients after denervation raised the possibility that denervation had a favorable augmentative effect on baroreflex. The mechanism of this interesting phenomenon is unclear and needs further elucidation.

The results of the present study indicate that radiofrequency 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 performed in a small number of patients without a control group. A larger patient cohort is needed to confirm the safety and efficacy of this new treatment option in patients with VVS—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 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 are still lacking. Despite these limitations, the results of our study provide important contributions to the literature with respect a new treatment modality for patients with frequent VVS.

Conclusions
Comprehensive autonomic denervation in the LA by ablation of the GP endocardially may prevent recurrent episodes of syncope in patients with VVS. The approach demonstrates the feasibility from 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, controlled studies are required to investigate this treatment option further.

Disclosures
None.

References
In this report, we evaluated the feasibility of selective endocardial autonomic denervation in the left atrium (LA) as an alternative treatment strategy in patients with highly systematic vasovagal syncope. Ten consecutive patients (mean age, 50.4±6.4 years; 7 women) with recurrent episodes of vasovagal syncope and positive head-up tilt testing were enrolled. Ganglionated plexi in the LA, identified by high-frequency stimulation, were targeted by radiofrequency catheter ablation using an 8-mm, solid-tip ablation catheter. The end point of procedure was the inhibition of the vagal response at target sites. The results from this early human experience seems very encouraging in that the procedure was able to eliminate the symptom of syncope in all 10 patients at 30±16 (13–55) months of follow-up, without any procedure-related complication. This study suggests that radiofrequency current application for LA autonomic denervation in patients with highly symptomatic recurrent vasovagal syncope is feasible and may be a valuable adjunctive therapy in patients who cannot be adequately treated with conventional treatment modalities.
Endocardial Autonomic Denervation of the Left Atrium to Treat Vasovagal Syncope: An Early Experience in Humans
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 sínì v léčbě vazovagální synkopy
První zkušenosti u lidí

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Kontext — Vazovagální synkopa (VVS) představuje nejčastější příčinu recidivující synkopy, která může být i přes optimální klasickou léčbu pro pacienta vysilující. Cílem této studie bylo zhodnotit proveditelnost a účinnost selektivní endokardiální autonomní denervace v levé sínì jako alternativní léčebné strategie 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 standardně podávané léky účinné, nebo je pacienti netolerovali. Radiofrekvenční katetrační ablace byla provedena v ganglionových pleteních (ganglionated plexi, GP) v levé sínì, identifikovaných vysokofrekvenční stimulací. Pacienti byli následně vyšetřeni po 3, 6, 12, 24 a 36 měsících, kdy byl proveden test na nakloněné rovině a holterovo monitorování EKG po 3 a 12 měsících. Radiofrekvenční energie byla pomocí 8mm ablačního katetu aplikována v levé horní GP u 10 nemocných, v pravé přední GP u 5 a v levé spodní GP u 3. Během ablace byla pozorována ve všech GP odpověď n. vagus, popisovaná jako přechodná komorová asystolie, atrioventrikulární 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 stavky. Nevyskytovaly se žádné komplikace.

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

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

Editorial k tomuto abstraktu článku naleznete na straně 7

SOUHRN PRO KLINICKOU PRAXI

V této studii jsme hodnotili proveditelnost selektivní endokardiální autonomní denervace v levé sínì (LS) jako alternativní léčebnou strategii u pacientů s vysoce symptomatickou vazovagální synkopou. Do studie bylo zařazeno 10 po sobě jdoucích pacientů (průměrný věk 50,4 ± 6,4 roků; 7 žen) s recidivujícími epizodami vazovagální synkopy a s pozitivním výsledkem testu na nakloněné rovině. Radiofrekvenční katetrační ablace byla provedena v ganglionových pleteních v LS, identifikovaných vysokofrekvenční stimulací pomocí 8mm ablačních katetrů s pevným hrotem. Sledovaným parametrem výkonu byla inhibice odpovědi n. vagus na 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, odstranit u všech 10 pacientů symptomy synkopy bez jakýchkoli komplikací v souvislosti s výkonem. Na základě výsledků publikované studie lze domnívat, že použití radiofrekvenční energie k autonomní denervaci v levé sínì u nemocných s vysoce symptomatickou recidivující vazovagální synkopou je možné a může se stát cennou formou přidatné léčby pacientů, u nichž selhala klasická léčba.

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