Selective Atrial Vagal Denervation Guided by Evoked Vagal Reflex to Treat Patients With Paroxysmal Atrial Fibrillation

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Background—The aim of this study was to evaluate whether selective radiofrequency (RF) catheter ablation of the atrial sites in which high-frequency stimulation induces vagal reflexes prevents paroxysmal atrial fibrillation (AF).

Methods and Results—Ten patients with episodes suggestive of vagal-induced paroxysmal AF and no heart disease were selected for percutaneous epicardial and endocardial mapping of the atria to search for sites in which high-frequency transcatheter stimulation (20 Hz) induced vagal reflexes. A vagal response defined as AV block of >2 seconds was elicited in 7 of 10 patients (70%) with an average of 5.2 sites per patient. RF pulses (21.0 ± 12.0 per patient) were applied at those sites to eliminate all evoked vagal reflexes. The 3 patients in whom evoked vagal reflexes were not obtained underwent circumferential pulmonary vein ablation with an average of 58.0 ± 13.9 RF pulses per patient (P = 0.022). Autonomic evaluation was performed before and 48 hours and 3 months after the procedure and was consistent with vagal withdrawal in all patients. Two of the 7 patients who underwent denervation remained asymptomatic without the use of antiarrhythmic medication at a mean follow-up of 8.3 ± 2.8 months (range, 5 to 15 months); 4 had frequent recurrences and were referred for circumferential pulmonary vein ablation; and 1 had few AF episodes without antiarrhythmic medication. One patient had acute delayed gastric emptying after atrial vagal denervation.

Conclusions—RF catheter ablation of selected atrial sites in which high-frequency stimulation induced vagal reflexes may prevent AF recurrences in selected patients with apparently vagal-induced paroxysmal AF. (Circulation. 2006;114:876-885.)

Key Words: catheter ablation • fibrillation • nervous system, autonomic

Atrial fibrillation (AF), the most common sustained cardiac arrhythmia, frequently is refractory to antiarrhythmic (AA) drugs.1,2 Pulmonary vein (PV) radiofrequency (RF) catheter ablation procedures have been performed as an alternative treatment for such patients. The effectiveness of catheter ablation is related to the extension of atrial lesions created around the PV ostia that aims empirically to eliminate the triggers and change the substrate for AF maintenance.3–7 However, these lesions create large areas of scarring in the atria that might be substrates for atrial tachycardias and depress left atrial contractility.8,9

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Vagal tone is a trigger for AF events in a subset of patients.10 In canine models, vagal stimulation shortens the effective atrial refractory period and triggers and maintains AF.11–13 Furthermore, selective vagal denervation prevents vagal-induced AF.14 In humans, some data suggest that adjunctive vagal denervation during PV ablation significantly reduces AF recurrences.7,15

We hypothesized that selective atrial vagal denervation alone could prevent vagal-induced paroxysmal AF.

Methods

Patients

We prospectively selected 10 patients with paroxysmal AF to receive selective vagal atrial denervation between November 2004 and June 2005. Inclusion criteria were documented episodes of symptomatic paroxysmal AF refractory to at least 2 AA drugs, age between 18 and 65 years, no heart disease, and onset of AF episodes suggesting vagal tone predominance such as documented episodes during sleep and rest, after meals, or after vasovagal syncope. Exclusion criteria were previous AF catheter ablation, persistent AF for >48 hours, sinus node and AV conduction disturbances, a permanent pacemaker, and diagnosis of any structural heart disease after clinical evaluation, ECG, echocardiography, Holter monitoring, and treadmill stress testing. Patients with thyroid dysfunction, diabetes mellitus, lung diseases, and renal and hepatic failure also were excluded. All patients provided written informed consent to take part in this study.
Autonomic Evaluation
AA drugs were discontinued for at least 5 half-lives; amiodarone was discontinued for 1 month. Heart rate variability (HRV) was used as an indicator of autonomic activity. Heart rate (HR) and time-domain and frequency-domain HRV were analyzed from 24-hour Holter monitoring and tilt-table testing before and 48 hours and 3 months after ablation. All 24-hour Holter ECG recordings were obtained in accordance with standard guidelines. After automatic analysis, the data file was visually reviewed and edited by one of the investigators. HRV was performed with Marquette Holter Analysis Software (Marquette Medical Systems, Milwaukee, Wis). Premature ventricular beats, electrical noise, or other aberrant ECG signals were excluded from HRV analysis. Time-domain measures were the SD of all normal R-R intervals in the 24-hour ECG recording (SDNN), the square root of the mean squared differences of successive NN intervals (rMSSD), and the percentage of sinus cycles differing from the preceding cycle by >50 ms over the entire 24-hour recording (pNN50). Power spectral analysis (computed by fast Fourier transformation) of all normal R-R intervals also was performed.

Time-domain measures and power spectral analysis (computed by fast Fourier transformation) also were analyzed during tilt-table testing with specific software (WinCPRS version 1.155, Absolute Aliens Ay, Turku, Finland) in 5-minute segments, ie, after the patient rested for 30 minutes in the supine position and after the first 5 minutes after orthostatic exposure. Three frequency-domain measures of HRV were obtained: very low-frequency (LF) power (0.00 to 0.04 Hz), LF power (0.04 to 0.15 Hz), and high-frequency (HF) power (0.15 to 0.40 Hz). The power of each frequency band was logarithmically transformed to avoid the undue influence of extreme values; this was expressed in milliseconds squared. The sympathetic-vagal balance evaluation was based on frequency-domain HRV analysis (LF/HF ratio).

Electrophysiological Study
Patients underwent electrophysiological study while in a fasting state and anesthetized. Three multipolar catheters were placed into the coronary sinus, around the tricuspid annulus, and on His bundle position, respectively. Intracardiac electrograms were filtered at band-pass settings from 80 to 500 Hz and displayed simultaneously with ECG leads I, II, III, V₁, and V₅ on a multichannel recorder (EP Tracer, CardioTek, Maastricht, the Netherlands). A programmed digital stimulator (EP Tracer) was used to deliver electrical impulses at 2-msec duration at twice the diastolic threshold. Programmed atrial stimulation was performed in the high right atrium and coronary sinus with up to 2 extrastimuli during 2 different pacing cycle lengths (600 and 400 ms), followed by continuously and decrementally reducing the pacing cycle length up to 200 ms to access supraventricular tachycardia, atrial flutter, and AF induction. Intravenous adenosine (18 mg) and isoproterenol (up to 30 μg) also were infused in bolus to evaluate AF induction.

Identification and RF Ablation of Autonomic Atrial Innervation
The left atrium was accessed from the epicardial and endocardial surfaces. One quadrupolar catheter with a 4-mm or 8-mm tip ( Biosense, Diamond Bar, Calif) was introduced into the pericardial space by the subxyphoid approach as previously described. An other 4-mm-tip catheter ( Biosense) was introduced into the left atrium through a long sheath by the transseptal approach. Heparin was infused (10 000-IU bolus) through the sheaths, and the activated clotting time was measured every 30 minutes to maintain the activated clotting time between 250 and 300 seconds.

Atrial ablation target sites were identified as the places where vagal reflexes evoked by transcatheter HF stimulation were obtained. Rectangular electrical stimuli were delivered at a frequency of 20 Hz, amplitude up to 100V, and pulse duration of 4 ms (Grass Stimulator S-48, Astro Med Inc, Grass Instruments Division, West Warwick, RI).

Vagal reflex was defined as AV block >2.0 seconds that occurred after HF stimulation (Figure 1). If a reflex was elicited, RF energy was delivered (60°C, 30 to 50 W for 60 seconds, Stokert, Biosense) at the epicardial or endocardial sites where HF stimulation induced evoked vagal reflexes. The end point of ablation was defined as the failure to reproduce vagal reflexes with repeated HF stimulation. Complete vagal denervation was defined arbitrarily as the abolition of all vagal reflexes evoked by HF stimulation.

Pulmonary Vein Isolation
PV isolation was performed in patients in whom a vagal reflex was not induced or in cases of late AF recurrences during follow-up after successful vagal denervation. A circular decapolar (Lasso, Biosense) catheter was introduced in the left atrium by a long sheath through the transseptal approach. One 7F 8-mm-distal-tip electrode ( Biosense) also was introduced into the left atrium by a second transseptal puncture. Heparin was infused (10 000-IU bolus) through the sheaths, and the activated clotting time was measured every 30 minutes to maintain the activated clotting time between 250 and 300 seconds. PV angiographies were performed by using one of the long transseptal sheaths, except for the right inferior PV, which was not systematically evaluated.

The Lasso catheter was placed on the PV ostia, and RF pulses (20 to 50 W, 55°C, 15 to 60 seconds) were applied to encircle the PVs 1 to 2 cm from their ostia. The end point was a reduction of at least 80% of atrial electrogram amplitude and PV disconnection. RF applications on the left posterior wall were monitored by an esophageal thermometer (Precision 4000A Thermometer, YSI Tem-
perature, Dayton, Ohio), and energy delivery was limited by esophageal temperature elevation up to 37.5°C. Adenosine (12 to 18 mg IV) and isoproterenol (10 to 30 μg IV) were infused in bolus to identify PV reconnection or ectopic triggers outside the veins.

**Postablation Follow-Up**

After ablation, patients received subcutaneous enoxaparin (0.5 mg/kg twice a day) started 6 hours after the end of the procedure and maintained until adequate levels of anticoagulation with oral warfarin were obtained (international normalized ratio, 2.0 to 3.0). Patients were discharged without AA therapy and instructed to report any symptoms. A Loop event record was recommended to document all possible symptoms of AF recurrence. Holter monitoring also was performed 48 hours and 3 months after the procedure. Recurrence of AF was defined as a sustained episode lasting >30 seconds. The end point of the study was considered freedom from late AF recurrence in patients with atrial vagal denervation.

**Data Analysis**

Data are presented as mean±SD. The power of each frequency band was logarithmically transformed to normalize the distribution. Comparisons within groups and different time sequences were done with a paired t test, whereas an unpaired 2-sample t test was used for comparisons between groups. Differences were considered significant at values of P<0.05.

The authors had full access to the data and take full responsibility for their integrity. All authors have read and agree to the manuscript as written.

**Results**

**Population Characteristics**

All 10 patients had frequent episodes of symptomatic paroxysmal AF documented by 12-lead ECG or 24-hour Holter monitoring. All patients had no other associated diseases, and most AF episodes were related to vagotonic tone (Figure 2). Clinical characteristics are shown in Table 1.

**Electrophysiological Study**

Anomalous pathways, AV reentrant tachycardia, and sustained atrial tachycardia were excluded by the electrophysiological test. Self-limited sustained AF was induced in 1 patient by intravenous adenosine and in another patient after intravenous isoproterenol. Programmed atrial stimulation induced sustained AF in 2 patients and atrial flutter in 2 others.

**Localization of Vagal Innervation Atrial Sites**

Atrial HF stimulation induced sustained AF in all patients. A vagal response was elicited in 7 of 10 patients (70%) with an average of 5±2.4 sites per patient. HF stimulation at these sites caused immediate vagal reflexes (Figure 3). We began eliciting vagal reflexes from the epicardium and attempted to eliminate the response by RF application at the same place. However, when that place was too close to the esophagus, phrenic nerves, aorta, or coronary arteries, we changed the site of ablation to the endocardium. The most common epicardial sites were the left atrial (LA) posterior wall (catheter inside the oblique sinus) and close to the right inferior PV in 7 patients (100%), right superior PV in 5 patients (71%), left inferior PV in 5 patients (71%), and left superior PV in 3 patients (42%). In 4 patients, vagal reflexes were elicited in the posterior region between the inferior PV and coronary sinus ostium and along the esophagus position. In 3 patients, vagal reflexes also were elicited on the anterior and superior LA wall with the catheter positioned inside the transverse sinus and less frequently on the lateral sites of PVs explored outside the oblique sinus (Figure 3A).

The most common endocardial sites where vagal response was elicited were between the right inferior PV and LA in 4 patients (57%), between the LA and right superior PV in 2 patients (28%), and between left inferior and superior PV in 2 patients (28%) (Figure 3B). In 2 patients, reflex sites were the interatrial septum, the LA roof, and the coronary sinus ostium.

We were not able to elicit a vagal reflex stimulating epicardial or endocardial sites in 3 patients (patients 2 through 4). However, HF stimulation induced sustained AF and elicited right and left phrenic stimulation in all these patients.

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One to eight (average, 4.3 ± 1.6) RF applications were required to eliminate the evoked vagal reflex at the same site, and an average of 21 ± 12 RF pulses per patient were needed to completely eliminate the response at all sites in the 7 patients with induced reflexes (10.1 ± 8.2 pulses at epicardial sites and 10.9 ± 8.2 pulses at endocardial sites; P = NS). In 1 patient (patient 1), RF pulses were applied just to the epicardial surface; in 2 patients (patients 6 and 10), just to the endocardium; and in 4 patients, to both. When evoked vagal reflex sites were too close to the esophagus, we delivered RF from the endocardium, positioning the epicardial catheter between the endocardial catheter and esophagus to avoid an increase in esophageal temperature. Evoked vagal reflexes were not observed during RF applications, except in 1 patient.

In general, either no change occurred or an increase occurred in mean HR during RF application. The mean procedure time was 265.7 ± 56.2 minutes, and mean x-ray time was 74.7 ± 7.5 minutes. No complications were observed at the end of the procedures.

Pulmonary Vein Isolation
A mean of 58.0 ± 13.9 RF pulses were applied to completely isolate the 4 independent PVs in patients 2 and 3 and the left trunk and 2 right PVs in patient 4. The mean procedure time and mean x-ray time were 240 ± 87.2 and 78.7 ± 5.5 minutes, respectively. Evoked vagal reflex was not observed in any patient during RF applications. No complications were observed at the end of the procedures. Significantly fewer RF pulses were applied to abolish vagal response than to isolate the PV (21.0 ± 12.0 versus 58.0 ± 13.9; P = 0.022).

Clinical Outcome
Patients had a mean follow-up of 8.3 ± 2.8 months (range, 5 to 15 months). Of the 7 patients in whom vagal denervation was obtained (average follow-up, 7.7 ± 3.2 months; range, 5 to 15 months), 5 (71.4%) had AF recurrence: 4 in the first week after the procedure and 1 after 4 months of follow-up (Figure 4). All 4 patients who had early recurrence of AF also had late

<table>
<thead>
<tr>
<th>TABLE 1. Baseline Characteristics of the Patients (n=10)</th>
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<tbody>
<tr>
<td>Age (range), y</td>
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<tr>
<td>Male sex, n (%)</td>
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<tr>
<td>Paroxysmal AF, n (%)</td>
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<tr>
<td>Vagal-induced AF, n (%)</td>
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<tr>
<td>Sleep, n (%)</td>
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<tr>
<td>After meal, n (%)</td>
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<tr>
<td>After vasovagal reflex, n (%)</td>
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<td>Table-tilt test response, n (%)</td>
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<tr>
<td>Positive mixed</td>
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<tr>
<td>Echocardiogram</td>
</tr>
<tr>
<td>Left atrium, mm</td>
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<tr>
<td>LV end-diastolic diameter, mm</td>
</tr>
<tr>
<td>LV end-systolic diameter, mm</td>
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<tr>
<td>LV ejection fraction, (%)</td>
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<tr>
<td>Holter</td>
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<tr>
<td>Heart rate</td>
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<tr>
<td>Minimum</td>
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<tr>
<td>Average</td>
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<tr>
<td>Maximum</td>
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<tr>
<td>Time-domain HRV</td>
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<tr>
<td>SDNN</td>
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<tr>
<td>pNN50</td>
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<tr>
<td>rMSSD</td>
</tr>
<tr>
<td>Frequency-domain HRV</td>
</tr>
<tr>
<td>LF, ms²</td>
</tr>
<tr>
<td>HF, ms²</td>
</tr>
<tr>
<td>LF/HF</td>
</tr>
<tr>
<td>Atrial ectopy, n/h</td>
</tr>
<tr>
<td>Ventricular ectopy, n/h</td>
</tr>
</tbody>
</table>

*AF induced after positive tilt-table test in 1 patient.

LV indicates left ventricular.
recurrences despite the AA drugs and were referred for PV isolation after 3 months. One patient continued under clinical observation without AA therapy for sparse, short episodes of AF. Two patients remained asymptomatic without AA and without AF episodes on Loop and Holter monitoring recordings. The 3 patients who underwent PV isolation remained free of recurrence without AA drugs. Inappropriate sinus tachycardia (HR ≥100 bpm at rest) was not observed in any patient. Patient 8 had acute delayed gastric emptying after atrial vagal denervation. Clinical manifestations began on the day after the procedure and persisted for 1 week. Stomach-emptying scintillography performed on the sixth day showed significant stomach emptying delays (78% retention after 4 days after the procedure and persisted for 1 week. Stomach-emptying scintillography performed on the sixth day showed significant stomach emptying delays (78% retention after 4

**Discussion**

The main findings of this study are that vagal reflexes can be induced by transcatheter HF stimulation of select epicardial and endocardial areas of the LA in most patients with paroxysmal AF. RF catheter ablation of these areas eliminates such responses and promotes autonomic changes, suggesting vagal tonus withdrawal. However, these parasympathetic changes obtained without PV disconnection were enough to prevent clinical AF episodes in few selected patients. Additionally, this study suggests that extensive PV antrum ablation itself promotes left atrial autonomic denervation even in patients in whom evoked vagal reflexes could not be elicited by HF atrial stimulation.

**Clinical and Autonomic Patterns of Atrial Denervation and AF Recurrence**

The autonomic characteristics of patients are shown in Tables 2 and 3. In the whole population, HR and HRV parameters changed significantly for all variables except maximal HR. Time-domain HRV parameters and frequency-domain parameters decreased after the procedure, and all differences persisted after 3 months. Patients who underwent PV antrum isolation and those who underwent vagal denervation that remained without AF recurrence had a significant increase in minimum HR (P=0.05) and a trend in decreasing natural logarithm of low-frequency (LnLF) power spectra (P=0.09) compared with patients with recurrences during the follow-up.

**Effects of Atrial Vagal Denervation**

Minimal and mean HRs significantly increased after vagal denervation. Table 2 and Figure 5 show changes in sinus rhythm rate after acute and chronic vagal denervation. After circumferential PV ablation (CPVA), minimal and mean HRs also changed significantly, indicating that extensive ablation of PV antrum also changes the autonomic tone. Minimal HR early after the procedure was higher after CPVA than after vagal ablation (P<0.05). Time-domain HRV parameters significantly decreased after vagal denervation; this difference also was observed after CPVA (Tables 2 and 3, Figures 5 and 6). After 3 months, time-domain and frequency-domain analysis remained different from baseline. Although the HF spectrum decreased on frequency-domain HRV analysis after the procedure, no difference was observed on sympathetic vagal balance analysis (LF/HF, 1.61, 2.02, and 1.89 before, soon after, and late after the procedure, respectively; P=0.18) because of a proportional decrease in LF spectrum components. These data suggest that sympathetic fibers also were destroyed after vagal denervation and CPVA.

**TABLE 2. Holter Monitoring Data of All Patients Before, Soon After, and Late After AF RF Catheter Ablation Guided by Evoked Vagal Reflex or PV Isolation**

<table>
<thead>
<tr>
<th></th>
<th>Before Mean±SD</th>
<th>Soon After Mean±SD</th>
<th>P*</th>
<th>Late After Mean±SD</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Heart rate, bpm</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minimum</td>
<td>42.4±6.5</td>
<td>62.0±15.6</td>
<td>0.005</td>
<td>56.0±7.3</td>
<td>0.0008</td>
</tr>
<tr>
<td>Average</td>
<td>64.3±5.4</td>
<td>82.0±14.5</td>
<td>0.006</td>
<td>76.3±4.6</td>
<td>0.0001</td>
</tr>
<tr>
<td>Maximum</td>
<td>111.6±20.0</td>
<td>124.8±25.3</td>
<td>0.251</td>
<td>131.1±18.0</td>
<td>0.054</td>
</tr>
<tr>
<td><strong>Time-domain HRV</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SDNN</td>
<td>164.6±8.2</td>
<td>71.8±45.3</td>
<td>0.0002</td>
<td>91.4±25.1</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>pNN50</td>
<td>29.4±19.1</td>
<td>2.1±3.0</td>
<td>0.032</td>
<td>1.5±1.6</td>
<td>0.030</td>
</tr>
<tr>
<td>rMSSD</td>
<td>55.2±24.0</td>
<td>15.6±8.2</td>
<td>0.018</td>
<td>19.0±6.8</td>
<td>0.026</td>
</tr>
<tr>
<td><strong>Frequency-domain HRV</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LnLF, ms²</td>
<td>6.85±0.82</td>
<td>3.97±1.85</td>
<td>0.003</td>
<td>5.33±1.33</td>
<td>0.035</td>
</tr>
<tr>
<td>LnHF, ms²</td>
<td>5.99±0.86</td>
<td>3.0±1.19</td>
<td>0.0003</td>
<td>4.1±0.75</td>
<td>0.004</td>
</tr>
<tr>
<td>LF/HF</td>
<td>1.6±0.3</td>
<td>1.9±0.7</td>
<td>0.29</td>
<td>2.0±0.7</td>
<td>0.18</td>
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<tr>
<td>Atrial ectopy, n/h</td>
<td>27.1±53.8</td>
<td>6.0±6.1</td>
<td>0.34</td>
<td>9.6±11.5</td>
<td>0.42</td>
</tr>
<tr>
<td>Ventricular ectopy, n/h</td>
<td>0.8±2.0</td>
<td>39.6±83.7</td>
<td>0.267</td>
<td>3.4±4.9</td>
<td>0.240</td>
</tr>
</tbody>
</table>

LnLF indicates natural logarithm of low-frequency power; LnHF, natural logarithm of high-frequency power.

*Compared with before ablation.
Selective Vagal Denervation Strategy for Paroxysmal AF Ablation

Clinical features and ECG monitoring of paroxysmal AF onset have strongly suggested that vagal activity increases before the initiation of the AF episodes in a select group of patients. Animal model studies have demonstrated that vagal activity increases vulnerability for AF by shortening the atrial effective refractory periods and increasing spatial atrial...
Reducing and maintaining AF. Therefore, vagal activity attenuation by selective ablation of vagal atrial innervation might be a logical strategy to treat select patients with vagal-induced AF.

**Vagal Denervation Guided by Elicited Vagal Reflex**

Transient sinus bradycardia, sinus arrest, and hypotension have been reported during RF-catheter PV ostial ablation. Such reflexes were initially reported as a complication of focal ablation, and thermal stimulation of afferent vagus nerve fibers was considered the cause. Its incidence was 15% when low-power and more localized RF ablation was performed inside the PV ostia but increased to 34% when high-power and extensive endocardial RF ablation was performed around the PV antrum. In our study, just 1 patient had vagal reflexes during RF delivery in areas selected by HF stimulation. The incidence was closer to that of Hsieh et al and Lemery et al, probably because we delivered lower RF power and the ablated area was more restricted. However, it was an unexpected find. Our initial expectation was that a very high incidence of vagal reflexes would be elicited during RF delivery at sites selected with vagal innervation identified by HF stimulation. In fact, during RF delivery, HR increased instead. This could be interpreted as an immediate withdrawal of vagal activity resulting from rapid inhibition of the atrial autonomic ganglia plexuses activity responsible for the autonomic control of the heart. This response was independent of endocardial or epicardial delivery of RF energy.

**Atrial Vagal Denervation Guided by HF Stimulation**

Schauerte et al demonstrated in dogs that the major parasympathetic pathways to the atria can be identified by transvenous HF stimulation. RF catheter ablation of these parasympathetic nerves prevented the induction and maintenance of AF during vagal stimulation. A preliminary report by Nakagawa et al suggests that patients randomized to PV isolation plus atrial denervation guided by HF stimulation experience a significant reduction in AF recurrence during follow-up compared with patients randomized to lone PV isolation. That observation is in accordance with observations of Pappone et al, who suggested that adjunctive vagal denervation during CPVA significantly reduces the recurrence of AF. The present study is the first attempt to promote selective vagal atrial denervation as a lone strategy to treat patients with paroxysmal AF. Our results confirm that this approach is feasible, but its effectiveness is low when applied as the only procedure in patients with paroxysmal AF. Because we selected patients with a clear vagal-induced AF, it is reasonable to suppose that vagal denervation guided by HF stimulation did not produce the necessary autonomic modification to prevent AF in our patients. In fact, patients without recurrences, including those in whom HF stimulation could not elicit a vagal reflex and who underwent PV antrum

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**TABLE 3. Table-Tilt Test Analysis of All Patients Before, Soon After, and Late After AF RF Catheter Ablation Guided by Evoked Vagal Reflex or PV Isolation**

<table>
<thead>
<tr>
<th></th>
<th>Before Mean±SD</th>
<th>Soon After Mean±SD</th>
<th>P*</th>
<th>Late After Mean±SD</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (average), bpm</td>
<td>60.8±6.7</td>
<td>78.3±14.6</td>
<td>0.012</td>
<td>72.5±9.7</td>
<td>0.008</td>
</tr>
<tr>
<td>SDNN</td>
<td>41.5±15.7</td>
<td>18.4±12.5</td>
<td>0.006</td>
<td>27.9±13.4</td>
<td>0.078</td>
</tr>
<tr>
<td>rMSSD</td>
<td>25.6±11.4</td>
<td>11.3±9.3</td>
<td>0.016</td>
<td>14.9±8.4</td>
<td>0.048</td>
</tr>
<tr>
<td>LF/HF</td>
<td>3.95±2.53</td>
<td>2.70±3.03</td>
<td>NS</td>
<td>3.88±4.33</td>
<td>NS</td>
</tr>
<tr>
<td>LnLF</td>
<td>5.83±1.15</td>
<td>2.69±2.08</td>
<td>0.003</td>
<td>4.62±1.49</td>
<td>NS</td>
</tr>
<tr>
<td>LnHF</td>
<td>4.65±1.02</td>
<td>2.46±1.60</td>
<td>0.007</td>
<td>3.84±1.03</td>
<td>NS</td>
</tr>
<tr>
<td>LF/HF</td>
<td>3.95±2.53</td>
<td>2.70±3.03</td>
<td>NS</td>
<td>3.88±4.33</td>
<td>NS</td>
</tr>
</tbody>
</table>

LnLF indicates natural logarithm of low-frequency power; LnHF, natural logarithm of high-frequency power.

*Compared with before ablation.
†All-period analysis of time-domain HRV.
‡Five-minute frequency-domain HRV analysis.
ablation, had more significant changes in HRV parameters compared with patients with AF recurrences. This observation suggests that some atrial sites with vagal innervation were not identified during HF stimulation once extensive empirical ablation of the PV antrum promoted a more significant autonomic change. Otherwise, a nonhomogeneous atrial denervation might also propitiate a favorable condition facilitating sustained AF. Olgin et al22 demonstrated that sympathetic stimulation blunts the decrease in effective refractory period induced with vagal stimulation in normal atrial myocardium. When innervation is made heterogeneous by regional sympathetic denervation, dispersion of refractoriness is increased, and AF can be sustained without vagal stimulation. In the present study, we attempted to selectively ablate the vagal fibers on the basis of vagal reflex induced by HF stimulation. However, recent anatomic studies have demonstrated that in human hearts the autonomic nervous system is organized in a complex network connecting fibers from the central nervous system with the ganglionated atrial plexuses that also are connected to the conduction system of the heart (sinus node and AV node). The atrial autonomic ganglia are distributed mainly around the PV antrum encompassing sympathetic and parasympathetic fibers that share the same ganglionated plexus.23 It seems that attempts to selectively ablate the vagal innervation on the atria cannot be performed without a simultaneous ablation of some sympathetic fibers.

Localization of Vagal Innervation Atria by HF Stimulation
We designed this study on the basis of anatomic distribution of autonomic ganglionated plexus of the atria as described by Armour et al.23 Because preganglionic parasympathetic and postganglionic sympathetic fibers come together in the fat pads on the epicardial surface of the LA posterior wall, we planned to initiate the mapping and ablation of the autonomic ganglia through the epicardial approach. Pericardial PV reflections form the oblique and transverse sinuses located at the posterior and superior left atrial walls and facilitate a stable catheter location on the epicardial atrial surface. Except in 3 patients in whom we could not elicit any vagal response by HF stimulation, we localized most of our targets for RF ablation in that area. Our findings are in accordance with those described by Pappone et al7 and Lemery et al21 and are comparable to the anatomic description of Armour et al,23 which shows autonomic ganglia distributions around the antrum of PV ostia in most patients. Although the epicardial approach was useful for localizing the ganglia position, we found some limitations to delivery of RF energy in some epicardial spots. In some locations, the absence of circulating

Figure 6. Changes in HRV on tilt-table test (rest and upright) before, soon after, and late after selective atrial vagal denervation guided by evoked vagal response (blue continuous line) and after CPVA (red dashed line). Data for probability values were obtained during different time sequences. *P<0.05, #P<0.10.
Effects of Atrial Ablation on Autonomic Parameters

Previous studies have demonstrated that focal PV ablation and CPVA may result in a transient increase in HR and a transient decrease in time-domain and frequency-domain HRV, suggesting parasympathetic nervous withdrawal, enhanced sympathetic activity, or a combination of both.7,19,20 Hsieh et al20 reported autonomic dysfunction with increases in HR and decreases in the HRV parameters after ablation of focal AF originating from PVs. Independently of the presence or absence of evoked-vagal response, all parameters recovered spontaneously after 1 month. Pappone et al7 reported that patients who had evoked vagal response during CPVA that was abolished by continuous RF delivery (vagal denervation) had a better outcome, and autonomic changes were more significant and remained for a longer time (3 to 6 months). In the present study, we observed autonomic changes similar to those reported by these authors. HRV parameters and minimum and mean HRs increased significantly after the procedure and remained elevated at the 3-month evaluation. Time-domain measure analysis decreased and persisted until the 3-month evaluation. Patients who underwent PV isolation also had similar behavior, but HR and HRV measurements had a more significant acute change. When patients with AF recurrences were compared, those free of recurrence had more significant decreases in HRV indexes that persisted after the 3-month evaluation, as described previously.7

Safety of Vagal Denervation

Three main concerns should be considered after vagal denervation: inappropriate sinus node tachycardia, fast AV node conduction during AF, and ventricular arrhythmias facilitated by vagal tone decrease in the ventricles. Hsieh et al20 reported 2 patients (6.7%) who had inappropriate transient sinus tachycardia after focal PV ablation. Pappone et al7 also reported 2 patients (8%) who developed inappropriate sinus tachycardia after CPVA. All these patients had signals of vagal denervation during the procedure that lasted up to 1 month. In our study, despite the significantly increased mean HR after ablation, no patient had criteria for inappropriate sinus tachycardia. The mean HR during AF also increased after vagal denervation, which could be a possible cause for worsening of patient symptoms when the vagal denervation procedure did not prevent AF recurrences. We did not specifically evaluate the negative effects of vagal denervation on the ventricular electrophysiological parameters. Chiou and Zipes24 reported that RF catheter ablation of 3 canine atrial fat pads abolished vagal modulated sinus arrhythmia, markedly decreased HRV, and eliminated baroreflex sensitivity without affecting vagal innervation of the ventricles or causing any ventricular arrhythmias. Acute delayed gastric emptying lasting 1 week was an unexpected complication observed in 1 patient after vagal denervation. The left vagus branch running on the esophageal anterior wall toward the stomach might be damaged during left posterior wall ablation. This complication was recently reported in 4 patients who underwent PV ablation, with 1 patient needing a surgical procedure to restore gastric emptying.25

Study Limitations

This study included a small number of patients. The high AF recurrence rate observed during follow-up did not allow us to continue the protocol. However, this premature study interruption did not disprove the hypothesis that AF induced by vagal activity could be treated by selective ablation of autonomic ganglia. Patients who underwent RF ablation guided by vagal reflex induced by HF stimulation who remained free of AF recurrence had an important autonomic change at noninvasive evaluation. On the contrary, patients without success did not have the same level of autonomic change. It also is possible that the methodology used to localize and eliminate such ganglia and vagal fibers was not completely effective. However, our observations suggest that the elimination of all evoked vagal reflexes induced by HF stimulation may prevent vagal-induced AF episodes in select patients. It seems that a critical change in cardiac autonomic behavior at the end of the procedure is necessary when selective autonomic denervation is proposed to treat patients with paroxysmal AF.

Conclusion

RF catheter ablation of select atrial sites in which HF stimulation induced vagal reflexes may prevent AF recurrences in selected patients with apparent vagal-induced paroxysmal AF.

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Disclosures

None.

References


**CLINICAL PERSPECTIVE**

A better understanding of the electrophysiological mechanisms of cardiac arrhythmias has allowed many clinical disorders to be effectively treated in recent years. More recently still, electrophysiologists have focused on the treatment of atrial fibrillation (AF). However, regular procedures promote unspcific and extensive ablation of pulmonary vein ostia and left atrial posterior wall. These lesions result in large areas of scarring in the atria, which might depress left atrial contractility and create substrates for atrial tachycardia. Clinical features and animal model studies have strongly suggested that vagal activity increases before the initiation of the AF episodes and that selective vagal denervation decreases the probability of inducing and maintaining AF. Therefore, vagal activity attenuation by selective ablation of vagal atrial innervation might be a logical and specific strategy to treat patients with vagal-induced paroxysmal AF. This study assessed this hypothesis in 10 patients. Two of these patients had AF recurrences prevented after radiofrequency ablation of select atrial sites in which high-frequency stimulation induced vagal reflexes. The success obtained in these 2 patients creates a perspective that, with the improvement of techniques of atrial vagal denervation, AF might be abolished with more preservation of the atria. As in the past when the knowledge of cardiac arrhythmia mechanisms guided the development of specific techniques to approach different mechanisms of supraventricular and ventricular tachycardias, a better understanding of AF mechanisms will guide the future development of effective and specific strategies that preserve the structure and function of the heart.
Selective Atrial Vagal Denervation Guided by Evoked Vagal Reflex to Treat Patients With Paroxysmal Atrial Fibrillation

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