Alterations of Heart Rate and of Heart Rate Variability After Radiofrequency Catheter Ablation of Supraventricular Tachycardia

Delineation of Parasympathetic Pathways in the Human Heart

Dusan Z. Kocovic, MD; Tomoo Harada, MD; Julie B. Shea, MS, RN; Daniel Soroff, MS; Peter L. Friedman, MD, PhD

Background. Persistent inappropriate sinus tachycardia has been reported as a complication after radiofrequency (RF) ablation of the fast atrioventricular (AV) nodal pathway. The purpose of this study was to evaluate the prevalence of this complication and its mechanism using heart rate variability analysis.

Methods and Results. Time and frequency domain analysis of heart rate was performed in the electrophysiology laboratory immediately before and immediately after RF ablation in 64 patients with supraventricular tachycardia. Ablation targets in these 64 patients included the fast AV nodal pathway (n = 3), the slow AV nodal pathway (n = 14), a posteroseptal accessory pathway (n = 23), and a left lateral accessory pathway (n = 24). A control group of 21 patients undergoing diagnostic study but not ablation underwent identical analysis immediately before and at the conclusion of their procedure. Patients undergoing ablation also had time and frequency domain analysis performed on ambulatory 24-hour Holter tapes recorded before ablation and at 1 day, 1 month, and 6 months after ablation. Compared with preablation values, time domain analysis immediately after ablation revealed a significant increase in mean heart rate and significant reductions in heart rate variability expressed as SD, MSSD, and PNN50 in patients undergoing AV nodal modification or posteroapical accessory pathway ablation. Frequency domain analysis revealed marked attenuation of high frequency (0.15 to 0.40 Hz) components, indicating parasympathetic denervation. These acute changes were not seen after ablation of left lateral accessory pathways or after diagnostic study without ablation. Time and frequency domain analysis of 24-hour ambulatory Holter monitors performed serially after ablation revealed resolution of abnormalities of heart rate and of heart rate variability 1 to 6 months after ablation, with reappearance of the high frequency parasympathetic component suggestive of reinervation.

Conclusions. RF ablation in the anterior, mid, and posterior regions of the low interatrial septum may disrupt preganglionic or postganglionic parasympathetic fibers located in these regions that are destined to innervate the sinus node. Such fibers become more scarce along the left AV groove with increasing distance from the posteroseptal space. Parasympathetic denervation may be one mechanism for persistent inappropriate sinus tachycardia after RF ablation. (Circulation. 1993;88[part 1]:1671-1681.)

Key Words • nervous system • arrhythmias • denervation • atrioventricular node • accessory pathways

Catheter ablation using radiofrequency (RF) energy is rapidly becoming the treatment of choice in patients with recurrent supraventricular tachycardia caused by the presence of an accessory atrioventricular (AV) connection or reentry within the AV node. The popularity of this approach is a reflection of the high success rate of the procedure, the remarkably low rate of procedure-related acute morbidity, and the apparent low risk of long-term adverse consequences.1-7 One complication that has been reported after RF ablation of the fast AV nodal pathway in patients with AV nodal reentry is the development of persistent inappropriate sinus tachycardia.8 In some cases, this complication has been mild and transient, whereas in others, it has produced debilitating symptoms lasting many months.8 Neither the prevalence nor the mechanism of this complication has been clarified. The present study was undertaken to determine the prevalence of persistent inappropriate sinus tachycardia after RF catheter ablation in different subsets of patients with supraventricular tachycardia and to shed light on the mechanism of this complication using the technique of heart rate variability analysis.
Methods

Patients

The study population comprised 64 patients with recurrent, symptomatic supraventricular tachycardia who had been referred to the Brigham and Women's Hospital for diagnostic electrophysiological studies and RF catheter ablation of their arrhythmia. A separate group of 21 patients with supraventricular tachycardia who had been referred for diagnostic electrophysiological studies but not catheter ablation served as the control group. For the control group of patients, the mean age was 39 years (range, 24 to 68 years). Among the patients in the control group, 11 had typical Wolff-Parkinson-White syndrome with orthodromic AV reciprocating tachycardia, 4 patients had orthodromic AV reciprocating tachycardia using a concealed accessory pathway as the retrograde limb of the reentrant circuit, and 6 patients had typical AV nodal reentrant supraventricular tachycardia. For the 64 ablation patients, the mean age was 41 years (range, 22 to 74 years). Among the ablation patients, 40 had Wolff-Parkinson-White syndrome with orthodromic AV reciprocating tachycardia, 7 patients had orthodromic AV reciprocating tachycardia with a concealed accessory pathway, and 17 patients had AV nodal reentrant tachycardia. Six patients had associated coronary artery disease (2 control patients and 4 ablation patients). The remaining 79 patients were free of structural heart disease.

Electrophysiological Studies

All patients underwent study in the absence of antiarrhythmic drugs. The method of study used in our laboratory for patients with supraventricular tachycardia has been described in detail previously. Each patient gave written informed consent to undergo a diagnostic electrophysiological study. In cases where a catheter ablation procedure was planned, patients also signed an additional research consent form to undergo catheter ablation according to a protocol approved by the hospital's Committee for the Protection of Human Subjects From Research Risks. Under local anesthesia and light sedation with diazepam and/or fenatyl, multipolar electrode catheters were advanced from the femoral veins and positioned in the right atrium, coronary sinus, right ventricular apex, and the His recording position. Bipolar electrograms from various sites in the right atrium, multiple sites in the coronary sinus, the His bundle region, the right bundle branch region, and the right ventricular apex were filtered between 40 and 500 Hz and displayed along with multiple surface ECG leads. All signals were recorded continuously on FM tape (TEAC T50) at a speed of 1.4 cm/s as well as on an ink jet paper recorder at paper speeds of 100 or 200 mm/s. Programmed stimulation of the right and left atrium, the latter by means of the coronary sinus catheter, as well as of the right ventricle, was performed using a standard extrastimulus stimulation protocol previously described for our laboratory. Supraventricular tachycardia was reproducibly inducible in all patients during their diagnostic study. Tachycardias were classified as AV nodal reentry or AV reciprocating tachycardia using an accessory pathway as one limb of the reentrant circuit, based on standard criteria. In patients with accessory pathways, the accessory pathway was localized anatomically on the basis of the site of earliest ventricular activation during manifest preexcitation or earliest atrial activation during retrograde accessory pathway conduction.

Radiofrequency Ablation

Radiofrequency energy was delivered to selected ablation sites from a custom-built electrosurgical unit (Radionics model RFG-3C, Burlington, Mass), the output of which was a continuous, unmodulated sine wave with a frequency of 500 KHz. The generator could deliver energy at a constant preset voltage for a variable time and provide a continuous registration of delivered current, voltage, and electrode tip impedance. Twenty to 35 W of energy was used for ablation; this was delivered between the ablation catheter tip electrode positioned at various target sites and an indifferent patch electrode (R2, Darox Corp, Niles, Ill) positioned on the posterior chest.

For ablation of accessory pathways, the ablation catheter was positioned against the AV groove in the ventricle to record earliest ventricular activation during manifest preexcitation or earliest atrial activation during retrograde accessory pathway conduction. Accessory pathway potentials were sought but were not required in the choice of target sites for ablation. Once a target site was chosen, RF energy was applied for 15 seconds. If accessory pathway conduction was not abolished during this time, the current was turned off and the catheter was repositioned. If accessory pathway conduction disappeared during the 15-second test applications, current was delivered to this site for a total of 60 seconds.

In the 17 individuals with AV nodal reentry, the slow pathway was targeted for ablation in 14 patients and the fast pathway in 3 patients. Methods of ablation in these patients were similar to those previously described. In general, fast pathway ablation was performed while the patient was in sinus rhythm to monitor changes in AV conduction during delivery of current. During slow pathway ablation, the preferred method was to deliver current during reentrant tachycardia and to reposition the catheter if tachycardia was not interrupted during a 15-second test application of current.

In all patients, a successful ablation procedure was defined as one that rendered supraventricular tachycardia noninducible and abolished all evidence of accessory pathway conduction. Noninducibility and absence of accessory pathway conduction was required in the basal state and also during infusion of isoproterenol. Once ablation was thought to be successful, the patients were allowed to rest with catheters in place for an additional 30 minutes, after which programmed stimulation was repeated. If tachycardia was still noninducible and accessory pathway conduction was still absent after this 30-minute waiting period, the procedure was terminated.

Follow-up

Patients undergoing diagnostic electrophysiological study but not ablation were discharged from the hospital the day after their procedure. Patients who underwent RF ablation of their supraventricular tachycardia were kept in the hospital on an ECG telemetry ward for 24 to 36 hours in order to monitor them for AV
conduction disturbances or signs of recurrent ventricular preexcitation. In all patients, a resting 12-lead ECG was performed the morning after their procedure. Ablation patients were followed for an average of 12±6 months (range, 1 to 27 months). After hospital discharge, patients were seen as an outpatient at 1 month. Follow-up electrophysiological studies as an outpatient were performed at 3 months on all patients who had undergone ablation of an accessory pathway to confirm the success of their procedure. Only 2 of the patients who underwent RF modification of the AV node returned for a 3-month follow-up electrophysiological study.

Heart Rate Variability Analysis

Two methods of heart rate variability analysis were used. The first method was used to study acute changes in various parameters that occurred in the laboratory immediately after as compared with before the patient's diagnostic study or ablation. Periods of sinus rhythm recorded on magnetic tape during the patient’s procedure (see below) were subsequently fed by cable into the high-level inputs of a commercially available signal-averaging apparatus that digitized the signal at a sampling rate of 1000 Hz by means of an analog-to-digital converter and then analyzed the signal using commercially available software (PREDICTOR, Cofaxionix Corporation, Oklahoma City, Okla). During this process, the ECG was overread beat by beat by two cardiologists to detect ectopic beats. Heart rate variability analysis was performed only on segments at least 3 to 5 minutes in duration during which there were no ectopic beats. RR intervals during such segments were then stored on the computer hard disk for subsequent analysis. The time domain indices of heart rate variability that were measured and the definitions of these indices were as follows: mean RR interval, the mean of all coupling intervals between normal sinus beats expressed in milliseconds (this was then converted to mean heart rate, expressed in beats per minute); SD, the standard deviation about the mean RR interval expressed in milliseconds; MSSD, the root mean square of differences of successive RR intervals; PNN50, the percentage of adjacent RR intervals that differed by more than 50 milliseconds. Frequency domain analysis of heart rate variability was accomplished by means of fast Fourier transform of the RR intervals. Power, expressed as (beats per minute)^2, was summed within the following frequency bounds: very low frequency power (0.0 to 0.04), low frequency power (0.04 to 0.15), and high frequency power (0.15 to 0.50 Hz).

In all patients, an initial 3- to 5-minute period of sinus rhythm recorded after placement of the electrode catheters but before beginning programmed electrical stimulation was analyzed. This recording period was defined as the basal state. Patients who developed sustained supraventricular tachycardia during catheter placement were excluded from this analysis. In the control group of patients, the second period of sinus rhythm analyzed was recorded at the end of the diagnostic study, before removal of the electrode catheters. This recording period was defined as the postprocedure state. In patients who underwent RF catheter ablation, the second (postprocedure) period of sinus rhythm analyzed was recorded during the 30-minute waiting period after an apparently successful ablation.

The second method used to study heart rate variability was analysis of ambulatory 24-hour Holter tape recordings. This method of analysis was used only in subjects who underwent ablation of their supraventricular tachycardia. Holter recordings in patients obtained before initiation of the present study were reviewed retrospectively and were combined with Holter recordings obtained prospectively in the more recent patients. Only a few patients had 24-hour Holter recordings before as well as after ablation. However, technically suitable recordings obtained 24 hours after ablation were available in 40 patients. For comparison, 21 of these ablation patients also had technically suitable 24-hour Holter tapes recorded 1 and/or 6 months after ablation.

Holter monitoring was performed using a two-channel bipolar recorder and was evaluated semiautomatically on a Marquette 8000 system (Marquette Electronics, Inc, Milwaukee, Wis). For each hour, the following data were computed and tabulated on printout: heart rate, total number of ventricular premature beats, number of couplets, ventricular tachycardia runs, ventricular tachycardia beats, and time analyzed. During the analysis, only beats that had normal morphology and whose cycle length duration was within 20% of the preceding cycle length were measured to assure the rejection of ectopic beats. This beat classification was verified, manually overread, and corrected where appropriate by an experienced technician or cardiologist. Less than 5% of all available RR intervals were excluded because of ectopic beats.

Heart rate variability was analyzed from the Holter recordings using a commercially available software algorithm (Marquette Heart 1.00). The indices measured included mean RR interval, SD, MSSD, and PNN50, as previously defined. In addition, the Marquette software performed power spectral analysis using fast Fourier transformation. This program integrates the following frequency bands: 0.01 to 1.0 Hz (area 1); low frequency, 0.04 to 0.15 Hz (area 2); and high frequency, 0.15 to 0.40 Hz (area 3). This integration is done under the power spectral density curve, yielding power expressed as milliseconds squared. However, for the purposes of pictorial presentation, this software gives the square root of these power values (expressed in milliseconds) along with a graph of the amplitude spectrum rather than of the power spectrum. Frequency analysis measurements were available for every hour of monitoring, but only average 24-hour values were used for statistical analysis.

Statistical Methods

Comparisons of the continuous data among the groups were made by one-way ANOVA with Bonferroni correction for comparison between means. A χ^2 test was used to compare dichotomous data between groups. Comparison of data within a group over time was obtained first by ANOVA for repeated measures and then by the paired Student's t test with Bonferroni correction. A value of P<.05 was required for statistical significance.
Results
Prevalence of Sinus Tachycardia

Radiofrequency ablation was deemed a primary success in all 64 patients who underwent the procedure. None of the patients developed AV block as a consequence of the procedure or experienced any other procedure-related acute complications. The prevalence of inappropriate sinus tachycardia was determined on the basis of resting sinus rate in the 12-lead ECG that was recorded with the patient supine the morning after the procedure. Using the standard definition of sinus tachycardia as a rate greater than 100 beats per minute, only 5 of the 64 ablation patients (7.8%) had an inappropriate sinus tachycardia. These 5 individuals included 1 patient who had undergone ablation of a fast AV nodal pathway and 4 patients who had undergone ablation of a posteroseptal accessory pathway. The most striking example of inappropriate sinus tachycardia occurred in the patient who had ablation of the fast AV pathway. This patient, a 30-year-old woman, had a resting sinus rate of 120 to 140 beats per minute that increased to 190 beats per minute with assumption of upright posture. If a slightly more liberal definition of inappropriate sinus tachycardia was used, ie, a resting sinus rate greater than 96 beats per minute, then an additional 3 patients were positive. The targets of ablation in these 3 additional patients included the slow AV nodal pathway in 1 patient, a posteroseptal accessory pathway in 1 patient, and a left lateral accessory pathway in 1 patient. None of the 21 control patients who underwent diagnostic electrophysiological study but not ablation had a resting sinus rate greater than 96 beats per minute the morning after their procedure.

Acute Change in Heart Rate Variability

Among the 21 control patients who underwent diagnostic electrophysiological study but not ablation, time domain indices of heart rate variability were not significantly changed at the end of the procedure as compared with the basal state (Table 1). In contrast, significant acute changes in these indices occurred in the patients who underwent RF catheter ablation (Fig 1). The 64 ablation patients were divided into 3 groups based on the target of ablation. Seventeen patients had AV nodal modification, 23 had ablation of a posteroseptal accessory pathway, and 24 had ablation of a left lateral accessory pathway (Table 1). Among the 17 individuals who had AV nodal modification, the postablation mean heart rate was significantly higher, accompanied by a significant reduction in SD, MSSD, and PNN50 (Table 1). Patients undergoing ablation of a posteroseptal accessory pathway also had a significant increase in the postprocedure mean heart rate (Table 1). SD, MSSD, and PNN50 in these patients also declined acutely after their ablation. The changes in SD and MSSD achieved statistical significance (Table 1). None of the changes in time domain indices of heart rate variability observed in patients after ablation of left lateral accessory pathways achieved statistical significance (Table 1).

Acute changes in the power spectrum of heart rate also were seen immediately after RF ablation (Table 2). These changes mirrored the changes that were seen in time domain indices of heart rate variability. The most striking change was a decrease in the high frequency components, indicating a decrease in parasympathetic influence. This was most obvious in patients undergoing AV nodal modification, although changes of lesser magnitude were also seen after ablation of posteroseptal accessory pathways (Table 2 and Fig 2). Control patients did not demonstrate significant changes in the heart rate power spectrum after their diagnostic study (Table 2).

As mentioned above, slight differences were observed in time domain indices of heart rate variability in the control patients after as compared with before their electrophysiological study, although these changes were not statistically significant. In individual patients, time domain indices of heart rate variability are influenced by the resting sinus rate. To correct for this influence, normalized values were calculated for the change that occurred in various indices of heart rate variability in the control patients as follows (HR indicates heart rate).

\[
\text{Normalized } \Delta \text{ mean HR} = \frac{\text{mean HR basal} - \text{mean HR postprocedure}}{\text{mean HR basal}}
\]
FIG1. Plots of RR interval duration immediately before (left) and immediately after (right) radiofrequency ablation of a posteroseptal accessory pathway. Note wide variations of RR intervals before ablation and markedly reduced variability of RR intervals immediately after ablation.

Normalized $\Delta$ SD = $\frac{SD_{basal} - SD_{postprocedure}}{SD_{basal}}$

Normalized $\Delta$ MSSD = $\frac{MSSD_{basal} - MSSD_{postprocedure}}{MSSD_{basal}}$

These normalized values, expressed as the percent change that occurred compared with the basal state in each patient, were then used to calculate mean normalized values for the entire group of 21 control patients. The calculated mean normalized time domain indices of heart rate variability for the control group were as follows: normalized $\Delta$ mean HR = $3\% \pm 10\%$, normalized $\Delta$ SD = $2\% \pm 20\%$, normalized $\Delta$ MSSD = $2\% \pm 25\%$.

Using the mean normalized values for mean heart rate and MSSD in the control group, the responses of patients undergoing ablation were separated into two categories referred to as normal or abnormal. Patients with abnormal responses were arbitrarily defined as individuals in whom normalized mean $\Delta$ heart rate and normalized $\Delta$ MSSD fell more than 2 SD away from the normalized values in the control patients. These data are presented in Table 3. As can be seen, 10 patients undergoing RF modification of the AV node had an abnormal degree of change in mean heart rate and MSSD after ablation, whereas the remaining 7 individuals who underwent ativoventricular nodal modification had a degree of change in these parameters that fell within the normal range (Table 3). Approximately half of the 23 patients who underwent ablation of a posteroseptal accessory pathway had an abnormal degree of

| TABLE 2. Acute Changes in Frequency Domain Indices of Heart Rate Variability |
|-----------------|-----------------|-----------------|-----------------|
|                 | Power (bpm²)    | Basal           | Postprocedure*  | $P^\dagger$     |
| Control (n=21)  | VLF             | 4897±3176       | 4647±3235       | NS              |
|                 | LF              | 1872±1739       | 1743±1569       | NS              |
|                 | HF              | 793±668         | 784±596         | NS              |
| AVN (n=17)      | VLF             | 3159±2229       | 2950±2340       | .05             |
|                 | LF              | 1302±774        | 775±698         | .01             |
|                 | HF              | 562±472         | 263±218         | .03             |
| Postero septal AP (n=23) | VLF | 5675±3300       | 5036±3098       | NS              |
|                 | LF              | 2186±1948       | 1802±1848       | <.04            |
|                 | HF              | 850±727         | 652±732         | <.04            |
| Left lateral AP (n=24) | VLF | 3991±2552       | 3747±2384       | NS              |
|                 | LF              | 1760±1617       | 1714±2052       | NS              |
|                 | HF              | 738±671         | 665±626         | NS              |

AVN indicates atrioventricular nodal modification; AP, accessory pathway; bpm, beats per minute; VLF, very low frequency (0.0 to 0.04 Hz); LF, low frequency (0.04 to 0.15 Hz); and HF, high frequency (0.15 to 0.50 Hz).

All values are expressed as mean±SD. *Values measured at end of diagnostic study for control patients and at end of ablation procedure for all other patients; †paired t test.
change in mean heart rate and MSSD after ablation (Table 3). Most patients who underwent ablation of a left lateral accessory pathway had changes in mean heart rate and MSSD that fell within the normal range. However, 3 patients had an abnormal degree of change in these parameters after ablation of a left lateral accessory pathway (Table 3). The prevalence of normal and abnormal responses among the three groups of ablation patients was statistically significant.

Chronic Changes in Heart Rate Variability

Ambulatory 24-hour Holter monitoring was used to study the changes that occurred in time and frequency domain indices of heart rate variability at various stages after RF ablation. For the purposes of this analysis, a group of patients whose mean heart rate and MSSD were unchanged acutely (group 1, normal response as defined above) was compared with a group whose mean heart rate and MSSD were significantly changed acutely after ablation (group 2, abnormal response as defined above). Table 4 presents time domain indices of heart rate variability in these two groups derived from ambulatory 24-hour tapes recorded 24 hours and 1 month after ablation. Patients judged as abnormal on the basis of acute changes in mean heart rate and MSSD at the conclusion of their ablation procedure had a higher mean heart rate and had reduced values for SD, MSSD, and PNN50 on the Holter monitor recorded 24 hours after ablation compared with patients whose mean heart rate and MSSD were unchanged acutely after ablation (Table 4). In the group judged abnormal, a significant increase in heart rate variability as reflected by MSSD was observed between 24 hours and 1 to 6 months after ablation (Table 4). A significant change in this parameter between 24 hours and 1 month after ablation was not seen in the group of patients judged to have been normal acutely (Table 4).

Power spectral analysis of heart rate obtained from ambulatory 24-hour Holter monitors revealed striking abnormalities in some patients after RF ablation. Most notable was a decrease in the high frequency components of heart rate variability, indicative of a loss of parasympathetic influence (Fig 3). Patients judged as abnormal based on their acute changes in mean heart rate and MSSD (group 2) had a reduced high frequency content of their heart rate power spectrum 24 hours after ablation compared with the patients classified as normal after ablation (group 1, Table 5). In the group 2 patients, a significant increase in the high-frequency components was noted 1 and 6 months after ablation as compared with 24 hours after ablation (Table 5 and Fig 4). Patients judged to be normal acutely after ablation (group 1) did not demonstrate such changes in the high-frequency components over time (Table 5).

The changes in time and frequency domain indices of heart rate variability that were observed in patients undergoing RF catheter ablation of supraventricular tachycardia did not appear to be related to the amount of myocardium destroyed during the ablation procedure or to the difficulty of achieving success during the procedure (Table 6). Ablation procedures directed against the AV node produced more dramatic changes

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**TABLE 3. Prevalence of Abnormal Degree of Change in the Time Domain Indices of Heart Rate Variability Among Subsets of Patients After Radiofrequency Ablation**

<table>
<thead>
<tr>
<th>Group</th>
<th>Normal</th>
<th>Abnormal</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>AVN</td>
<td>7</td>
<td>10</td>
<td>17</td>
</tr>
<tr>
<td>Posteroventral AP</td>
<td>12</td>
<td>11</td>
<td>23</td>
</tr>
<tr>
<td>Left lateral AP</td>
<td>21</td>
<td>3</td>
<td>24</td>
</tr>
<tr>
<td></td>
<td>40</td>
<td>24</td>
<td>64</td>
</tr>
</tbody>
</table>

AVN indicates atrioventricular nodal modification; AP, accessory pathway.

Values represent number of patients in each category; $\chi^2=10.74, P=.004$. 

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**FIG 2.** Power spectra of heart rate (bpm, beats per minute) immediately before (left) and immediately after (right) radiofrequency ablation of a posteroseptal accessory pathway. Data are from some patient illustrated in Fig 1. Note marked attenuation of a high-frequency parasympathetic (0.15 to 0.40 Hz) component after ablation.
TABLE 4. Chronic Changes in Time Domain Indices of Heart Rate Variability After Radiofrequency Ablation

<table>
<thead>
<tr>
<th></th>
<th>24 Hours</th>
<th>1 Month</th>
<th>P*</th>
<th>6 Months</th>
<th>P†</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HR, bpm</strong></td>
<td>82.0±9.6</td>
<td>80.0±10.7</td>
<td>NS</td>
<td>83.0±11.0</td>
<td>NS</td>
</tr>
<tr>
<td><strong>SD, milliseconds</strong></td>
<td>122.0±40.0</td>
<td>127.0±40.0</td>
<td>NS</td>
<td>130.0±39.0</td>
<td>NS</td>
</tr>
<tr>
<td><strong>PNN50, %</strong></td>
<td>9.23±13.0</td>
<td>9.77±9.0</td>
<td>NS</td>
<td>10.1±11.0</td>
<td>NS</td>
</tr>
<tr>
<td><strong>MSSD, milliseconds</strong></td>
<td>45.2±21.8</td>
<td>50.7±28.7</td>
<td>NS</td>
<td>51.3±29.6</td>
<td>NS</td>
</tr>
<tr>
<td><strong>HR, bpm</strong></td>
<td>86.0±11.7</td>
<td>76.0±9.0</td>
<td>NS</td>
<td>74.0±3.4</td>
<td>NS</td>
</tr>
<tr>
<td><strong>SD, milliseconds</strong></td>
<td>113.0±27.8</td>
<td>137.8±26.0</td>
<td>NS</td>
<td>140.0±29.0</td>
<td>NS</td>
</tr>
<tr>
<td><strong>PNN50, %</strong></td>
<td>8.6±9.4</td>
<td>12.2±9.8</td>
<td>NS</td>
<td>12.4±11.2</td>
<td>NS</td>
</tr>
<tr>
<td><strong>MSSD, milliseconds</strong></td>
<td>37.0±17.0</td>
<td>51.2±20.0</td>
<td>&lt;.05</td>
<td>52.3±21.2</td>
<td>&lt;.05</td>
</tr>
</tbody>
</table>

HR indicates heart rate; bpm, beats per minute; SD, standard deviation about mean RR interval; PNN50, percentage of adjacent RR intervals that differed by more than 50 milliseconds; and MSSD, root mean square of differences of successive RR intervals.

All values are expressed as mean±SD. P value determined by ANOVA for repeated measures was <.05. *1 month compared with 24 hours; †6 months compared with 24 hours (values determined by paired t test with Bonferroni correction).

Discussion
Prevalence of Sinus Tachycardia
Persistent inappropriate sinus tachycardia after RF ablation, defined as a resting sinus rate >100 beats per minute in the absence of typical physiological precipitants, was first described in 3 of 8 (37.5%) patients who had undergone ablation of the fast AV nodal pathway. A subsequent report, using the same definition of persis-
TABLE 5. Chronic Changes in Frequency Domain Indices of Heart Rate Variability After Radiofrequency Ablation

<table>
<thead>
<tr>
<th></th>
<th>24 Hours</th>
<th>1 Month</th>
<th>6 Months</th>
<th>6 Months</th>
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<tbody>
<tr>
<td></td>
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<tr>
<td><strong>Group 1 (n=9)</strong></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Total spectrum (0.01-1.0 Hz)</td>
<td>37.4±15.9</td>
<td>39.5±16.8</td>
<td>NS 40.1±20.1</td>
<td>NS 40.1±20.1</td>
</tr>
<tr>
<td>Low frequency (0.04-0.14 Hz)</td>
<td>23.1±11.8</td>
<td>25.3±12.2</td>
<td>NS 26.4±13.1</td>
<td>NS 26.4±13.1</td>
</tr>
<tr>
<td>High frequency (0.15-0.40 Hz)</td>
<td>12.9±7.3</td>
<td>15.2±7.5</td>
<td>NS 16.7±8.2</td>
<td>NS 16.7±8.2</td>
</tr>
<tr>
<td><strong>Group 2 (n=12)</strong></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Total spectrum (0.01-1.0 Hz)</td>
<td>37.4±14.6</td>
<td>45.6±13.2</td>
<td>NS 48.6±9.8</td>
<td>NS 48.6±9.8</td>
</tr>
<tr>
<td>Low frequency (0.04-0.14 Hz)</td>
<td>23.9±10.1</td>
<td>29.3±9.6</td>
<td>NS 32.3±8.5</td>
<td>NS 32.3±8.5</td>
</tr>
<tr>
<td>High frequency (0.15-0.40 Hz)</td>
<td>12.2±5.9</td>
<td>17.4±6.5</td>
<td>&lt;.05 16.5±3.9</td>
<td>&lt;.05 16.5±3.9</td>
</tr>
</tbody>
</table>

Values are expressed in milliseconds as mean±SD and were calculated as the square root of the area under the power spectrum within the defined range. *P* value determined by ANOVA for repeated measures was <.05. **1 month compared with 24 hours; 6 months compared with 24 hours (values determined by paired *t* test with Bonferroni correction). We observed persistent inappropriate sinus tachycardia, strictly defined as above, in 5 of 64 patients undergoing RF ablation. Importantly, this complication was observed not just in patients undergoing AV nodal modification but was also seen after RF ablation of posteroseptal accessory pathways.

The strict definition of inappropriate sinus tachycardia used in the present study and in previous reports
probably yields an underestimate of the actual number of patients who develop disturbances of sinus rate after RF ablation. In addition to a rapid resting sinus rate with the patient lying supine, we observed profound increases in sinus rate to 190 beats per minute in one of our patients with assumption of upright posture or with minimal activity. Such an inappropriate increase in sinus rate with minimal activity may be a more sensitive marker of patients with disturbances of sinus rate after ablation. However, it would be extremely difficult to use such a marker to distinguish such patients from other normal individuals who develop sinus tachycardia during their normal daily activities.

Parasympathetic Denervation After Ablation

The anatomy of parasympathetic innervation in the human heart has not been well delineated. In contrast, elegant studies in dogs have led to a much clearer understanding of cardiac parasympathetic innervation in this species. Ardell and Randall have shown in the dog heart that the intrapacrical projections of the left vagus to the sinus and AV nodes penetrate the epicardium in the region of the common pulmonary vein complex. The projections of the right vagus are more diffuse but appear to penetrate epicardium adjacent to the first bifurcation of the right pulmonary artery and the origin of the right pulmonary vein. The subepicardial neural projections of the preganglionic parasympathetic fibers from both vagi are less clearly defined, but these fibers are thought to terminate near the right pulmonary vein fat pad and tissues along the sulcus terminalis. Postganglionic fibers then penetrate to the AV node or extend their course across the right atrium and sulcus terminalis to innervate the sinus node. A few parasympathetic postganglionic fibers also extend dorsally around the superior vena cava to the sinus node.

Assuming that the parasympathetic innervation of human and canine hearts is similar, our hypothesis in the present study was that RF lesions in the region of the anterior or posterior atrial septum or in the region of the proximal coronary sinus could result in destruction of parasympathetic ganglia in these regions or postganglionic fibers originating in these regions that are destined to innervate the sinus node, thereby resulting in partial or total parasympathetic denervation of the sinus node. Parasympathetic denervation of the sinus node could occur in this fashion even though the RF lesions were being made several centimeters away from the sinus node. If such a hypothesis were correct, one would expect after ablation to see an immediate increase in heart rate and an immediate decrease in heart rate variability, specifically of the parasympathetic components that govern heart rate variability. One would also expect to see a slow resolution of these abnormalities occurring with a time course consistent with reinnervation. In animal models, parasympathetic reinnervation typically requires 6 weeks.

Heart rate variability analysis is a well-established tool in studies of autonomic physiology and has been used clinically in various patient populations. Mean heart rate may be increased and heart rate variability may be decreased as a consequence of elevated sympathetic tone, decreased parasympathetic tone, or a combination of both factors. Although certain time domain parameters of heart rate variability like PNN50 and particularly MSSD are said to reflect predominantly vagal influences on heart rate, most studies suggest that the best differentiation of parasympathetic from sympathetic influence is obtained using frequency domain analysis in addition to time domain analysis.

In the present study, both time domain and frequency domain analyses of heart rate variability were used, and both methods indicated the occurrence of parasympathetic denervation after RF ablation. Increases in heart rate, decreases in heart rate variability, and attenuation of the parasympathetic component of heart rate variability were seen immediately after ablation as compared with preablation values as predicted by our hypothesis. Furthermore, these abnormalities resolved over a time course suggestive of reinnervation. The most striking abnormalities of heart rate and heart rate variability observed in the present study occurred in patients undergoing RF modification of the AV node. Disturbances of lesser magnitude also occurred after ablation of posteroventral accessory pathways, whereas ablation of left lateral accessory pathways only rarely caused such abnormalities of heart rate and heart rate variability. These observations suggest that the greatest density of parasympathetic ganglia and postganglionic parasympathetic fibers may lie in the mid and anterior portions of the low interatrial septum and that these fibers become more sparse as one moves posteriorly toward the coronary sinus and more sparse still as one moves laterally to the left away from the posterior interatrial septum. None of the patients in the present study underwent ablation of the right posterior or right lateral accessory pathway. Therefore, we cannot speculate about the density of parasympathetic fibers in these regions.

Limitations of the Study

Our method of data analysis warrants further comment. No previous study has examined the effects of cardiac catheterization or programmed stimulation of the heart on heart rate variability. Although most
laboratories, like ours, administer sedatives liberally during electrophysiological study to allay patient anxiety, it is still possible that anxiety and cardiac pacing could cause an increase in sympathetic tone, which, in turn, would increase heart rate and decrease heart rate variability. This speculation prompted us to include a control group of patients who underwent diagnostic electrophysiological study but not ablation. These control patients demonstrated changes in heart rate and heart rate variability, which, although not statistically significant, enabled one to determine how much of a change one could reasonably expect to see merely as a consequence of undergoing a diagnostic electrophysiological procedure. Normalizing data based on initial values for heart rate and heart rate variability also enabled one to group together patients who, in the basal state, had widely disparate resting heart rates and indices of heart rate variability.

The most serious limitation of the present study is that it was conducted both prospectively and retrospectively. Thus, we do not have 24-hour ambulatory Holter data on every control and every ablation patient before their procedure and at each follow-up interval after their procedure. Nevertheless, the observations made in the present study cannot be explained as artifact. Using commercially available and widely used software for heart rate variability analysis, the time and frequency domain indices were consistent with one another with regard to changes in heart rate variability that occurred acutely after ablation. Furthermore, these time and frequency domain analyses were entirely concordant with time and frequency domain analyses of 24-hour Holter data performed the day after ablation using a completely different commercially available and widely used software. Finally, the evolution in time and frequency domain indices of heart rate variability observed over time in a fashion that was predicted for a biological phenomenon, ie, reinnervation, argues strongly against artifact.

An increase in sympathetic tone as the cause of postablation increases in heart rate and decreases in heart rate variability was not excluded in the present study. Such an increase in sympathetic tone could be related to the amount of myocardium destroyed during ablation, akin to myocardial infarction patients in whom the magnitude of myocardial necrosis is a major determinant of the level of sympathetic tone. However, this explanation is not plausible because the changes in heart rate and heart rate variability observed in the present study were related only to the anatomic site of ablation and not to the duration of the procedure or the amount of RF current applied. Alternatively, sympathetic tone could have been elevated by autonomic reflexes activated by ablation along the low interatrial septum. However, in the first 3 patients reported with persistent inappropriate sinus tachycardia after RF ablation of a fast AV nodal pathway, 24-hour urinary metanephrines were not elevated. Furthermore, sinus tachycardia was not well controlled with β-adrenergic blocking agents. This lack of efficacy of β-blockers was also observed in one of our patients. Clearly, demonstration of a possible role of the sympathetic nervous system will require more careful study of catecholamine metabolism in a larger group of patients.

One other plausible explanation for our observations is that not all ablation causes parasympathetic denervation by actual destruction of these fibers but rather that there is reflexogenically mediated parasympathetic withdrawal. This could be the result of stimulation of an afferent limb of such a reflex by inflammation or mechanical irritation at the site of ablation. Resolution of such inflammation over time could thereby give the appearance of reinnervation.

Clinical Implications

Patients recovering from acute myocardial infarction who have diminished heart rate variability are at increased risk of sudden death and have higher all-cause mortality. There is no evidence that this is also a characteristic of patients undergoing RF ablation, nor is there any reason to suspect that it might be true. Indeed, all available evidence suggests that patients undergoing RF ablation have an excellent prognosis. However, it is possible that parasympathetic denervation after RF ablation renders patients more susceptible to developing arrhythmia, particularly atrial arrhythmia, during the month or two necessary to establish reinnervation. Inhomogeneity of parasympathetic innervation in the atria could lead to regional differences in repolarization and conduction velocity, thus setting the stage for reentry. A recent report of atrial tachycardias occurring in the month after ablation of an accessory pathway is of interest in this regard. A variety of studies have also described a decrease in refractoriness of the fast AV nodal pathway after successful RF ablation of the slow pathway. One wonders whether this enhancement of fast pathway function might in part be a reflection of parasympathetic denervation after ablation.

References

Alterations of heart rate and of heart rate variability after radiofrequency catheter ablation of supraventricular tachycardia. Delineation of parasympathetic pathways in the human heart.

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