

# Time Course and Predictors of Autonomic Dysfunction After Ablation of the Slow Atrioventricular Nodal Pathway

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**MARKOWITZ, S.M., ET AL.:** Time Course and Predictors of Autonomic Dysfunction After Ablation of the Slow Atrioventricular Nodal Pathway. *Withdrawal of parasympathetic tone has been reported after ablation in the posteroseptal right atrium and has been attributed to injury of vagal efferent fibers. The purpose of this study was to assess the time course and predictors of autonomic dysfunction after slow pathway ablation. In 30 patients with AV nodal reentrant tachycardia, time- and frequency-domain measures of heart rate variability (HRV) were measured before, 30 minutes after, and 1 day after slow pathway ablation. There were significant reductions in mean RR interval ( $724 \pm 163$  vs  $836 \pm 164$  ms,  $P < 0.05$ ), SD of RR intervals ( $29 \pm 17$  vs  $40 \pm 18$  ms,  $P < 0.05$ ), root mean squared difference ( $15 \pm 8$  vs  $29 \pm 17$  ms,  $P < 0.05$ ), and high frequency power ( $4.1 \pm 0.4$  vs  $4.5 \pm 0.6 \log_{10} \text{ms}^2$ ,  $P < 0.05$ ) 30 minutes after ablation. However, these parameters returned to baseline 1 day after ablation. Multivariate regression identified isoproterenol dose during the diagnostic study ( $P = 0.02$ ) and radiofrequency duration ( $P = 0.02$ ) as statistically significant predictors of heart rate change ( $R^2 = 0.45$ ). These findings suggest that changes in autonomic tone after ablation in the posteroseptal right atrium are transitory and resolve within 1 day of the procedure. These short-term changes may be related to procedural variables rather than direct injury to vagal efferent fibers. (PACE 2004; 27:1638–1643)*

**atrioventricular node, radiofrequency ablation, heart rate variability, isoproterenol**

## Introduction

Changes in autonomic function may occur after radiofrequency (RF) ablation in the right or left atria.<sup>1</sup> Several studies have documented reductions in heart rate variability (HRV) following ablation in the posteroseptal right atrium (RA), suggesting that withdrawal of parasympathetic tone occurs, and these changes may persist for weeks or months.<sup>2–5</sup> The etiology of parasympathetic withdrawal has been attributed to denervation of cardiac vagal efferent fibers that lie in the atrioventricular (AV) groove, and reinnervation is thought to account for the long-term recovery of parasympathetic tone. More recently, vagal denervation has been implicated after circumferential pulmonary vein ablation and has been proposed as a mechanism that contributes to reduction in atrial fibrillation.<sup>6</sup>

A growing body of evidence in animals and humans suggests that parasympathetic nerve fibers

accumulate in epicardial fat pads, one of which is located between the inferior vena cava and left atrium in the AV groove near the ostium of the coronary sinus (CS).<sup>7,8</sup> Dissection of this fat pad results in vagal denervation of the AV node,<sup>8</sup> and stimulation at this site results in negative dromotropic effects without perturbing the rate of the sinus node.<sup>9,10</sup> Thus, the posterior fat pad provides selective innervation to the AV node but not the sinus node. Accordingly, the authors hypothesized that ablation in the posterior septum would not interrupt vagal efferents to the sinus node, and that heart rate changes after ablation of the slow pathway are due to short-term changes in autonomic tone. To this end, the HRV was used to study sequential changes in parasympathetic tone after ablation, and the determinants of autonomic dysfunction were identified.

## Patients and Methods

### Patient Population

The study population consisted of 30 patients (24 women, age  $47 \pm 15$  years) who underwent ablation of AV nodal reentrant tachycardia (AVNRT) between 1995 and 1996. During this era, all patients who underwent catheter ablation at The New York Hospital-Cornell University Medical Center institution were recommended to have a follow-up electrophysiological study 1 day after

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the procedure, and the electrophysiological studies were recorded on a Holter monitor tape and were available for retrospective analysis. All patients gave informed consent for the procedure. Antiarrhythmic and AV node blocking medications were discontinued for at least 5 half-lives prior to ablation and measurements of HRV. Structural heart disease was present in eight patients, including valve disease ( $n = 4$ ), dilated cardiomyopathy ( $n = 2$ ), left ventricular hypertrophy ( $n = 1$ ), and coronary vasospasm ( $n = 1$ ). Another patient had a left lateral accessory pathway that was ablated during the same procedure.

### Electrophysiological Study and RF Ablation

Patients were sedated with intravenous midazolam and morphine, anesthetized locally with 0.25% bupivacaine, and up to four diagnostic catheters were positioned in the heart to record the high RA, the His-bundle electrogram, the right ventricle, and the CS. The stimulation protocol consisted of incremental atrial and ventricular pacing and the introduction of up to double atrial and single ventricular premature stimuli to induce AVNRT. If tachycardia was not inducible, isoproterenol was infused in doses ranging from 0.5 to 4 mg/min, and programmed stimulation was repeated, which was required in 20 patients. All patients had the typical slow-fast form of AVNRT.

RF ablation was performed with a 4-mm tip deflectable thermistor catheter (EPT Blazer, Boston Scientific, Natick, MA, USA) using a target temperature of 60° and maximum power of 50 W. The slow pathway was targeted for ablation guided by an anatomic approach just anterior to the ostium of the CS. RF energy was applied during AVNRT or sinus rhythm, observing for termination of AVNRT and/or junctional rhythm. If these endpoints were

met, RF energy was delivered for up to 60 seconds. If these endpoints were not observed within 15 seconds, the RF application was terminated and the catheter was repositioned anteriorly in the annulus. All ablations were performed in the mid- or posterior septum.

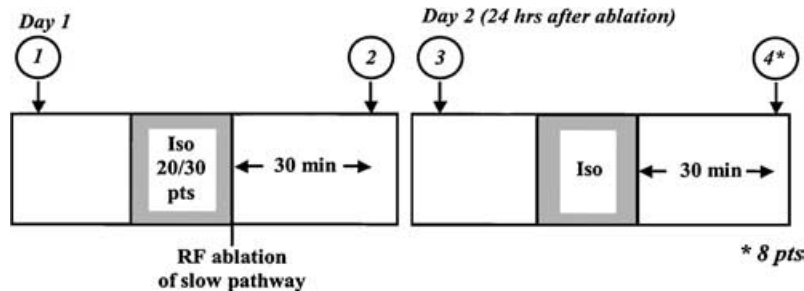
Successful RF ablation was defined as elimination of inducible AVNRT and induction of no more than one AV nodal echo beat during programmed stimulation. Thirty minutes after the last ablation, programmed stimulation was repeated in the baseline state and during isoproterenol infusion to confirm the success of the procedure.

### Follow-Up Study

All patients in this series returned for follow-up electrophysiological studies 1 day after ablation. The protocol for sedation and programmed stimulation was identical to that during the initial study with two catheters positioned to record from the His bundle and the RA/right ventricle. During the follow-up study, patients underwent programmed stimulation during the baseline autonomic state and during infusion of isoproterenol.

### HRV

Five-minute recordings of sinus rhythm were obtained at the following predefined times during the electrophysiological studies (Fig. 1). In phase 1 (control phase), data were collected at two intervals: (1a) prior to sedation and insertion of venous sheaths, and (1b) after sedation and insertion of catheters in the heart. In phase 2 (the immediate postablation state), data was collected 30 minutes after the last successful ablation, prior to restimulation. For patients who received isoproterenol prior to ablation, the infusion was discontinued  $\geq 30$  minutes before this recording. Phase 3



**Figure 1.** Study design for recording heart rate variability. In all patients, 5-minute recordings of sinus rhythm were obtained in three phases. Phase 1 was the control phase, before programmed stimulation and ablation. Phase 2 was the postablation state, 30 minutes after the last ablation. Phase 3 was during the follow-up study 1 day after ablation. In phases 1 and 3, recordings were obtained before and after sedation and catheter insertion. In eight patients, phase 4 was recorded 30 minutes after the infusion of isoproterenol was terminated during the follow-up study. Iso = isoproterenol.

consisted of two intervals during the follow-up study 1 day after ablation: 3a, prior to sedation and insertion of venous sheaths; and 3b, after sedation and insertion of catheters in the heart.

To examine the effects of isoproterenol on HRV, sinus rhythm recordings were also analyzed in eight patients who received isoproterenol during the follow-up electrophysiological study. Although all patients in the study received isoproterenol during the follow-up study, only these eight patients had Holter monitor recordings 30 minutes after the infusion was terminated. This allowed determination of the effects of isoproterenol independent of acute RF ablation.

The Holter tapes were scanned and digitized at 128 Hz using a Holter analysis system (series 8000, Marquette, Milwaukee, WI, USA). Direct visual confirmation of beat types was performed manually by one of the authors (SMM). After scanning, a 5-minute segment was transferred to a personal computer-based system for further analysis. RR intervals before and after ectopic atrial and ventricular beats were removed for analysis.<sup>11</sup> Scans were excluded from analysis if ectopic beats accounted for >5% of the RR intervals. Ectopy was 1.1% in the samples used for analysis with a range of 0 to 4.6%.

Time-domain measures of HRV were computed using custom software. These included the standard deviation of RR intervals (SD), root mean square difference in RR intervals (RMSD), and percentage of successive RR intervals that differ by  $\geq 50$  ms (pNN50). Frequency-domain measures of HRV were computed with the FFTW fast Fourier transform C library (fftw.org). Power in the high frequency (HF) (0.15–0.40 Hz) and low frequency (LF) (0.04–0.15 Hz) domains were calculated (units  $\text{ms}^2$ ).

### Statistical Analysis

Data are expressed as mean  $\pm$  SD. Statistical analyses of frequency-domain measures of HRV were performed on the logarithmic transformation ( $\log_{10} \text{ms}^2$ ). ANOVA with post hoc comparisons using the Scheffe's test was performed to evaluate for intrasubject changes in HRV after ablation, and a two-factor ANOVA was used to determine the independent effects of ablation and isoproterenol infusion on changes in HRV. The two-tailed paired *t*-test was used to compare measures of HRV before and after sedation, and the correlation was tested with the Pearson correlation coefficient. Changes in pNN50 were tested with the nonparametric Wilcoxon and Friedman tests, and correlation was tested with the Spearman rank statistic.

Univariate and multivariate regression were used to examine predictors of change in heart

rate and HRV after ablation. Variables entered into these models included age, sex, cumulative duration of RF energy, site of final RF ablation, exposure to isoproterenol before ablation, isoproterenol dose, and baseline values of HRV. A *P* value of  $\leq 0.05$  was used to determine statistical significance and criteria for removing variables from multivariate regression models (Crunch 4.0, Crunch Software Corp., Oakland, CA, USA).

## Results

### Ablation Results

Ablation was acutely successful in all patients. The median number of RF applications was 2 (range 1–20), and the cumulative duration of RF energy application was  $107 \pm 86$  seconds. No patient had inducible AVNRT during the follow-up study.

### HRV

Of a total of 145 recordings, 129 scans were considered acceptable for HRV analysis. Tapes were excluded because of ectopy exceeding 5% of RR intervals ( $n = 11$ ) or for technical limitations in recording ( $n = 5$ ).

Sedation and catheterization during the electrophysiological studies resulted in no significant change in mean RR interval and time-domain measures of the HRV (Table I). There was no significant difference in HF power, but LF power was reduced after sedation and catheter insertion. There were significant correlations in mean RR interval, pNN50, and HF and LF power before and after sedation and catheterization.

HRV before and after ablation was compared using phases 1b and 3b (after sedation and catheter insertion), unless the recordings were inadequate, in which case phases 1a and 3a were used instead.

**Table I.**  
Heart Rate Variability Before and After Sedation and Catheterization

	Before	After	Correlation (R)
Mean RR (ms)	$852 \pm 130$	$864 \pm 151$	0.80 <sup>†</sup>
SD (ms)	$53 \pm 30$	$44 \pm 18$	0.28
RMSD (ms)	$35 \pm 32$	$31 \pm 18$	0.20
pNN50 (%)	$11 \pm 15$	$10 \pm 13$	0.45 <sup>†</sup>
HF power ( $\log_{10} \text{ms}^2$ )	$4.7 \pm 0.6$	$4.6 \pm 0.5$	0.56 <sup>†</sup>
LF power ( $\log_{10} \text{ms}^2$ )	$5.1 \pm 0.4$	$4.8 \pm 0.4^*$	0.45 <sup>†</sup>

\**P* < 0.05 compared to before;

<sup>†</sup>*P* < 0.05 for correlation statistic.

**Table II.**

Heart Rate Variability Before and After Ablation

	Preablation	30 Minutes	24 Hours
Mean RR (ms)	836 ± 164	724 ± 163*	858 ± 126
SD (ms)	40 ± 18	29 ± 17*	42 ± 15
RMSD (ms)	27 ± 16	15 ± 8*	28 ± 17
PNN50 (%)	9 ± 11	2 ± 4*	11 ± 16
HF power (log <sub>10</sub> ms <sup>2</sup> )	4.5 ± 0.6	4.1 ± 0.4*	4.6 ± 0.5
LF power (log <sub>10</sub> ms <sup>2</sup> )	4.7 ± 0.5	4.6 ± 0.4 <sup>†</sup>	4.9 ± 0.4

\*P &lt; 0.05 compared to pre-ablation and 24 hours;

†P &lt; 0.05 compared to 24 hours.

This was necessary for 3 of the 30 patients. Thirty minutes after ablation, there were significant reductions in mean RR interval, all time-domain measures of HRV, and HF power (Table II). These parameters all returned to baseline within 24 hours of ablation.

A significant interaction was present between exposure to isoproterenol and reduction in mean RR interval after ablation, but an interaction with isoproterenol exposure was not demonstrated for measures of the HRV. In patients exposed to isoproterenol during the diagnostic part of the procedure, the mean RR interval decreased by 17% after ablation compared to 4% in those not exposed to isoproterenol.

Univariate regression identified exposure to isoproterenol and duration of RF ablation as significant predictors of a decrease in mean RR interval after ablation. Isoproterenol dose (P = 0.02) and RF duration (P = 0.02) emerged as statistically significant predictors in a multiple regression model (R<sup>2</sup> = 0.45).

To test the hypothesis that exposure to exogenous catecholamines during the diagnostic electrophysiological study influenced HRV, eight patients had measurements of HRV before and after isoproterenol exposure during the follow-up study 1 day after ablation. There was a significant decrease in mean RR interval, even though the isoproterenol infusion was discontinued 30 minutes prior to the recording, and there were trends toward decreased RMSD, pNN50, and HF power (Table III).

### Discussion

This study demonstrates that changes in autonomic tone after RF ablation of the slow AV nodal pathway are transitory and resolve within 1 day of the procedure. The short-term withdrawal

**Table III.**

Heart Rate Variability Before and After Isoproterenol During Follow-up Study

	Baseline	Isoproterenol Washout
Mean RR (ms)	923 ± 175	841 ± 166*
SD (ms)	46 ± 18	47 ± 20
RMSD (ms)	33 ± 16	27 ± 18
PNN50 (%)	14 ± 16	8 ± 13
HF power (log <sub>10</sub> ms <sup>2</sup> )	4.8 ± 0.6	4.6 ± 0.5
LF power (log <sub>10</sub> ms <sup>2</sup> )	4.7 ± 0.5	4.9 ± 0.5

N = 8;

\*P &lt; 0.05 compared to baseline.

of parasympathetic tone, as demonstrated by increased heart rate and decreased RMSD and HF power, is related to procedural variables, including exposure to exogenous catecholamines, rather than direct injury to vagal efferent fibers. This is supported by the normalization of HRV that occurs much too soon to be explained by reinnervation.

Exposure to exogenous catecholamines, administered to induce supraventricular tachycardia, played a major role in changing HRV. This occurred even though isoproterenol infusion was discontinued at least 30 minutes before measuring heart rate and HRV, a time at which isoproterenol is thought no longer to exert an effect. Furthermore, exposure to isoproterenol during follow-up studies, in the absence of ablation, caused a significant increase in heart rate and trends toward decreases in HRV, thus confirming the independent effect of exogenous catecholamines. Another predictor of change in heart rate was duration of RF energy, suggesting that procedural factors other than drug administration contribute to autonomic perturbations after ablation.

### Effects of Ablation on Autonomic Innervation

Early experience with ablation of AVNRT documented autonomic perturbations, like decreased HRV and inappropriate sinus tachycardia that lasted days or weeks after ablation.<sup>2-5,12,13</sup> This suggested that interruption of vagal efferents was extensive and involved fibers destined to innervate the sinus node. However, there is convincing evidence that vagal efferents that course through the inferior fat pad in the posteroseptal space innervate the AV node and surrounding atrial myocardium but not more distant parts of the atria, like the sinus node.<sup>7,8</sup> In contrast, an epicardial fat pad adjacent to the right pulmonary veins and superior vena cava has been shown to contain vagal

fibers that innervate the sinus node,<sup>7,8,14</sup> and a third fat pad between the superior vena cava and the aorta contains more proximal fibers that innervate both structures.<sup>15</sup> Thus, extensive vagal denervation of the atria resulting from ablation in the posteroseptal RA appears unlikely. The results of the present study confirm that widespread injury to parasympathetic fibers does not occur with focal ablation in the mid- and posterior septum.

It is also doubtful that parasympathetic denervation of the AV node occurs with modern ablation techniques in this region. Negative dromotropic effects, like prolongation of the AV nodal Wenckebach cycle length, occur acutely after ablation of the slow pathway and are inconsistent with parasympathetic denervation.<sup>16</sup> After slow pathway ablation, the effects of edrophonium and phenylephrine on AV nodal conduction<sup>17</sup> and the ability to induce a negative dromotropic effect with neural stimulation<sup>18</sup> are preserved. These findings support the conclusion that acute changes in heart rate after posteroseptal ablation are reflexive and not due to anatomic disruption of vagal efferents.

### Clinical Implications and Comparisons with Other Studies

Studies of heart rate and HRV after septal ablation have been conflicting with some investigators documenting striking alterations in autonomic tone<sup>2-5</sup> and others showing no significant changes.<sup>19-21</sup> Most of these studies used ambulatory monitors to measure HRV 1-2 days after ablation,<sup>2-4,19-21</sup> and two studies examined acute changes in heart rate immediately after ablation.<sup>2,5</sup> However, none of these studies used a consistent methodology to examine the time course of heart rate changes during the first 24 hours after ablation, as reported here.

One explanation for these conflicting data relates to the amount of injury inflicted by RF ablation, as reflected by the cumulative duration of RF energy. Most studies that demonstrate changes in autonomic tone  $\geq 1$  day after ablation used a large number of RF lesions. In one study, the mean duration of RF energy was 1,025 seconds for patients with AVNRT,<sup>2</sup> and in another study the mean duration was 3,474 seconds in a combined group of patients with AVNRT and posteroseptal accessory pathways,<sup>4</sup> compared to 107 seconds in this report. In the present study, an association was observed between the duration of RF ablation and decrease in mean RR interval. It is possible that more extensive ablation in the septum might injure vagal ramifications from the fat pad near the pulmonary veins and superior vena cava, sufficient to cause partial denervation of the sinus node.

Another explanation for these discordant results is a shift from fast pathway to slow pathway ablation. Most reports of inappropriate sinus tachycardia after ablation of AVNRT involved fast pathway ablation.<sup>12,13</sup> It is possible that the anteroseptal region is closer to the fat pad between the right pulmonary veins and superior vena cava, and ablation in this location, especially if more extensive, may affect sinus node function. This interpretation is supported by the relatively high incidence of inappropriate sinus tachycardia that has been reported after ablation of para-Hisian accessory pathways.<sup>22</sup> These differences in technique may explain the low incidence of inappropriate sinus tachycardia observed in more recent clinical experience with AVNRT.

### Pharmacokinetics and Pharmacodynamics of Isoproterenol

An unexpected finding was that alterations in heart rate and HRV last for at least 30 minutes after an isoproterenol infusion. Little is known about the pharmacokinetics and pharmacodynamics of isoproterenol. Following intravenous administration of isoproterenol, a biphasic decline in serum levels is observed.<sup>23,24</sup> The initial half-life ranges from 2.5 to 5 minutes and can be attributed to the distribution, uptake metabolism, and elimination of the drug. The initial rapid half-life is followed by a slower elimination phase marked by a 3-7-hour half-life. The isoproterenol related increase in heart rate also declines rapidly after a bolus injection, corresponding to the initial decline in serum levels with a half-life of 10-67 seconds.<sup>23</sup> A continuous infusion might change the pharmacokinetics and pharmacodynamics of isoproterenol. In one patient studied by Conolly et al.,<sup>23</sup> heart rate declined with a half-life of 10 minutes after a 30-minute infusion of isoproterenol. It is possible persistence of adrenergic stimulation by catecholamines following a continuous infusion may have contributed to the autonomic changes observed during isoproterenol recovery.

### Study Limitations

This study did not use a control group of patients undergoing diagnostic electrophysiological studies. Thus, it is difficult to evaluate the relative contributions of programmed stimulation, procedural duration, and catecholamine infusion to the acute changes in HRV. However, Kocovic et al.<sup>2</sup> reported no acute change in HRV in 21 patients who underwent diagnostic electrophysiological studies. Regardless of the stimulus for increased heart rate and parasympathetic withdrawal after posteroseptal ablation, this study suggests that the changes are transitory and resolve within 24 hours.

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