Changes in Autonomic Nervous Activity After Catheter Ablation of Right Ventricular Outflow Tract Tachycardia

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Idiopathic right ventricular outflow tract (RVOT) tachycardia is prone to occur when sympathetic nervous activity increases. The effects of catheter ablation on the arrhythmia may be modified by changes in the sympatho-vagal balance induced by the ablation. In 8 patients with RVOT tachycardia, analyses of heart rate variability (HRV) were performed before, early (1–3 days, POST1) and late (7–14 days, POST2) after the ablation. From 24-h ambulatory Holter monitoring, RR intervals of a 2-h period during sleep (00.00–06.00 h) were analyzed. MSSD and pNN50 were increased along with a decrease in the frequency of ventricular arrhythmias at both POST1 and POST2 after successful ablation. In contrast, high frequency power (HF) was increased, and low frequency power (LF) and LF/HF were decreased only at POST2 in the 8 patients. In 4 patients in whom the initial ablation had been unsuccessful, the indices of HRV did not change significantly after the unsuccessful ablation, but after successful ablation they changed as in the other 4 patients. After successful catheter ablation of the RVOT tachycardia, sympathetic nervous activity was decreased and parasympathetic nervous activity was increased along with a decrease in the frequency of ventricular arrhythmias. The presence of ventricular tachyarrhythmia could, therefore, elicit sympathetic predominance and consequently modify arrhythmogenesis. (Jpn Circ J 1999; 63: 697–703)

Key Words: Autonomic nervous activity; Catheter ablation; Heart rate variability; Holter monitoring; Ventricular tachycardia

Methods

Patients

Eight patients (1 male, 7 females; mean [±SD] age 44±14 years, range, 26–60) with symptomatic sustained or nonsustained monomorphic VT originating from the RVOT were enrolled (Table 1). Episodes of VT were defined as sustained if the VT lasted more than 30 s or required termination because of hemodynamic compromise. However, changes in autonomic activity after catheter ablation of RVOT tachycardia remain obscure and may possibly modulate the effect of catheter ablation. Therefore, the purpose of the present study was to elucidate the effects of catheter ablation of RVOT tachycardia on autonomic nervous activity using both time and frequency domain measures of HRV.

Table 1 Patient Characteristics

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Age/Sex</th>
<th>Symptoms</th>
<th>Spontaneous VT/cycle length (ms)</th>
<th>VT induction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>EX</td>
</tr>
<tr>
<td>1</td>
<td>54/F</td>
<td>Dizziness</td>
<td>NS/260</td>
<td>–</td>
</tr>
<tr>
<td>2</td>
<td>27/F</td>
<td>Palpitation</td>
<td>S, NS/280</td>
<td>NS</td>
</tr>
<tr>
<td>3</td>
<td>26/F</td>
<td>Syncope</td>
<td>NS/254</td>
<td>NS</td>
</tr>
<tr>
<td>4</td>
<td>45/F</td>
<td>Dizziness</td>
<td>NS/260</td>
<td>NS</td>
</tr>
<tr>
<td>5</td>
<td>37/F</td>
<td>Palpitation</td>
<td>S, NS/260</td>
<td>S</td>
</tr>
<tr>
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<td>Palpitation</td>
<td>S, NS/375</td>
<td>S</td>
</tr>
<tr>
<td>7</td>
<td>40/F</td>
<td>Syncope</td>
<td>S, NS/354</td>
<td>NE</td>
</tr>
<tr>
<td>8</td>
<td>60/M</td>
<td>Palpitation</td>
<td>NS/240</td>
<td>NS</td>
</tr>
</tbody>
</table>

EX, treadmill exercise test; IP, isoproterenol infusion; NS, non-sustained; PES, programmed electrical stimulation; S, sustained; NE, not examined.
mise, and nonsustained if it lasted from 3 beats to 30 s and terminated spontaneously without hemodynamic compromise. Two patients presented with syncope, 2 with dizziness, and 4 with palpitation only. In these patients, history, physical findings, routine 12-lead electrocardiogram (ECG), exercise test, echocardiogram and thallium myocardial scintigram failed to disclose evidence of organic heart disease.

VT arising from the RVOT was diagnosed if a left bundle branch block pattern with inferior axis was present on 12-lead ECG. Four patients had both sustained and nonsustained VT, and the other 4 patients had repetitive nonsustained VT. The mean cycle length of clinically documented VT was 285±50 ms (range, 240–375). All 8 patients had previously had unsuccessful treatment or were intolerant to 1–3 antiarrhythmic agents including β-blockers. Oral β-blockers were partially effective in suppressing VT, but failed to eliminate VT in all patients. Therefore, they underwent catheter ablation to eliminate the symptomatic VT. All antiarrhythmic drugs were discontinued for at least 5 half-lives before the study.

Electrophysiological Study and Mapping of VT

Each patient gave written informed consent to undergo a diagnostic electrophysiological study and RF-CA. Under local anesthesia, multipolar catheters were introduced transvenously and positioned in the His bundle region and the right ventricular apex. In addition, a steerable quadripolar catheter with 5-mm interelectrode spacing and a large tip (7F; distal electrode length 4 mm) was inserted and positioned for delivery of the RF current. The standard protocol for the induction of VT included extrastimulus technique using 1 to 2 extrastimuli from the right ventricular apex and the outflow tract at 2 basic cycle lengths of 600 and 400 ms, and incremental rapid pacing up to 200 beats/min for 10 beats. When VT was not inducible by electrical stimulation, isoproterenol was infused to increase the sinus rate by 20% and the programmed stimulation was repeated with the same protocol for induction. The site of origin of the VT was mapped using the catheter technique with the steerable ablation catheter. The site of origin was determined as the site of the earliest activation during sustained or nonsustained VT. Because the VT had a left bundle branch block configuration and an inferior axis, and because none of the patients had evidence of structural heart disease, the site of origin of the VT was presumed to be in the right ventricle and detailed left ventricular mapping was not performed; mapping efforts were instead concentrated in the RVOT. Then, pacing was performed during sinus rhythm at a rate similar to the VT rate. The QRS morphology in each of the 12 leads of the ECG was compared with that during sustained or nonsustained VT. Mapping was directed toward identifying the site at which pacing resulted in the closest possible match between the QRS complex during pacing and during VT. Pace-maps were graded on a scale of 0–12, based on the number of leads in which there was a close match between pacing and VT.

Fig 1. Changes in frequency of premature ventricular contractions (left panel), couplets (middle panel), and ventricular tachycardia (right panel) per 24 h before and after the successful catheter ablation of PVOT tachycardia in each patient. Closed square and bars indicate mean value and standard error, respectively. PRE, before catheter ablation; POST1, early (1–3 days) after catheter ablation; POST2, late (7–14 days) after catheter ablation. *p<0.05, **p<0.005, *p<0.01 vs PRE.

Fig 2. Changes in frequency of premature ventricular contractions (left panel), couplets (middle panel), and ventricular tachycardia (right panel) per 24 h before the initial ablation (PRE) and after unsuccessful (ABL1) and successful (ABL2) ablation in 4 patients. Closed square and bars indicate mean value and standard error, respectively. (Abbreviations are as in Fig 1.) *p<0.05, **p<0.005 vs PRE.
Radiofrequency Catheter Ablation

Using a generator (NL-50-IT, Central Industry, Tokyo, Japan) a RF was applied at 500 Hz through the distal, large tip of the steerable catheter and a skin patch on the back during sustained or nonsustained VT for 30 s. Using this method, we considered that RF-CA was effective if sustained VT was terminated or nonsustained VT was eliminated during the session. If VT had been induced by ventricular stimulation before ablation, the ablation was judged to be successful when VT was no longer inducible after the ablation. If VT had been induced by isoproterenol infusion or treadmill exercise test but not by ventricular stimulation before the ablation, the same provocation procedures were repeated 1–2 weeks after the ablation. If VT was not induced by these procedures, the ablation was judged to be successful.

Heart Rate Variability Analysis

HRV was analyzed from ambulatory Holter ECG recordings. All patients underwent 2-channel 24-h ambulatory Holter monitoring before and after the ablation. Postablation monitoring was done 1–3 days (POST1) and also 7–14 days (POST2) after the procedure. In 4 patients in whom the initial ablation (ABL1) had been unsuccessful, Holter recording was also repeated before and after the subsequent successful ablation (ABL2), which was performed 7–14 days after initial attempt. Therefore, in these 4 patients, we regarded the Holter recording before ABL2 (after ABL1) as the data before successful ablation.

RR intervals of a 2-h period during 00.00–06.00h, when ectopic beats were less likely (<5% of total beats), were analyzed on a Holter analyzing system (DMW-9000H, Fukuda Denshi, Tokyo, Japan). In calculating the HRV variables, only normal RR intervals were included with visual verification. Normal RR intervals were sampled at an 8 ms interval and digitized data were transmitted to a personal computer (PC-9801, NEC, Tokyo, Japan) for analyzing the time and frequency domain measures of HRV. Normal RR intervals during a 256-s period were analyzed every 5 min by fast Fourier transformation. Power spectra were quantified by measuring the area in 2 frequency bands: low frequency (LF) power from 0.04 to 0.15 Hz and high frequency (HF) power from 0.15 to 0.40 Hz. The ratio of LF to HF (LF/HF) was calculated as an index of the sympathetic activity.

HF was used as an indicator of the parasympathetic nervous activities. From the time series of RR intervals of normal QRS complexes during the 2 h, pNN50 (%) was defined as the percentage of difference between adjacent RR intervals that differed by more than 50 ms and MSSD (ms) was defined as the root mean square of differences of successive RR intervals.

Statistical Analysis

Results are presented as mean value ± standard error. Serial changes in indices of HRV were analyzed by analysis of variance for repeated measures. Multiple comparisons were made using the Scheffe test. A p value<0.05 was considered significant.
**Results**

**Induction of VT**

The treadmill exercise test induced sustained VT in 2 patients and nonsustained VT in another 4 patients. Nonsustained VT was induced by isoproterenol infusion in 2 patients, and in one of those patients premature ventricular contractions (PVC) increased in frequency during administration of isoproterenol. However, during the electrophysiological study, VT could not be induced by programmed ventricular stimulation in 6 of 7 patients with or without isoproterenol infusion. Only in 1 patient was nonsustained VT induced by programmed ventricular stimulation, but the VT could not be entrained with rapid ventricular pacing (Table 1). All these induced VT and PVC showed an identical QRS morphology to that of the clinical VT in all patients.

**Results of Mapping and RF-CA of VT**

In each patient, the best pace-map was achieved at the RVOT. The pace-map score was 12/12 in 4 patients and 11/12 in the remaining 4 patients. In each patient, the site of the best pace-map was also the site at which the earliest endocardial activation was recorded. Ablation was attempted at the site of the earliest activation (ie, 26±6 ms before the onset of the QRS complex of the VT). The mean number of attempts was 2.9±0.4 and the mean total energy delivered was 2,650±530 J. In all patients, VT was not inducible 10–15 min after the last successful application. In the 4 patients with recurrence of spontaneous or inducible VT during the 1–13 days after ABL1, we attempted the second session (ABL2) at 7–14 days after ABL1. Between ABL1 and ABL2, the total delivered energy (1,930±630 and 1,950±300 J, respectively) and the number of attempts (2.8±1.0 and 3.0±1.0) were not different in these 4 patients. Five of the 8 patients had no episodes of spontaneous VT either 1–3 (POST1) or 7–14 days (POST2) after successful ablation. In the remaining 3 patients, spontaneous nonsustained VT recurred at POST1. In 2 of these 3 patients no VT was seen 7–14 days (POST2) after the ablation. Two episodes of nonsustained VT, which lasted only 3–5 beats, were still documented at POST2 in the third patient. However, even in these 3 patients we judged the ablation to be successful, because VT could not be induced by treadmill exercise or isoproterenol infusion 1–2 weeks after the ablation. The mean maximum creatine kinase (CK) concentration after ablation was 104±21 IU/L (normal range, 55–280). No electrocardiographic or echocardiographic abnormalities were noted after ablation in any of the patients.

**Changes in Frequency of PVC after RF-CA (Figs 1, 2)**

In 24-h ambulatory Holter monitoring, the frequency of PVC decreased significantly from the baseline value at both POST1 and POST2 after the successful ablation. However, the frequency of both couplets and VT decreased significantly only at POST2. In 4 patients in whom the initial ablation had been unsuccessful, only the frequency...
of couples decreased significantly from the baseline value after both the successful and the unsuccessful ablation. The frequency of both total PVC and VT, however, decreased significantly only after the successful ablation in these 4 patients.

*Serial Changes in HRV After the Successful RF-CA (Figs 3, 4)*

Indices of the HRV changed dramatically after the successful ablation. HF power increased significantly (p<0.05) from the baseline value (434±106 to 553±132 ms²), whereas both LF power (662±112 to 476±92 ms², p<0.01) and LF/HF (2.3±0.4 to 1.3±0.3, p<0.05) decreased significantly from the baseline value at POST2 after the successful ablation. However, all these variables did not change significantly at POST1. MSSD increased significantly (p<0.05) at both POST1 (37±4 ms) and POST2 (36±3 ms) from the baseline value (30±3 ms). Similarly, pNN50 increased significantly (p<0.05) at both POST1 (10.9±3.0%, p<0.005) and POST2 (12.2±3.4%, p<0.01) from the baseline value (7.2±2.5%). The mean RR intervals increased significantly only at POST2 (1094±42 ms, p<0.05) from the baseline value (1015±52 ms).

*Changes in HRV in Patients With an Unsuccessful Initial RF-CA (Figs 5, 6)*

The outcome of ablation affected changes in autonomic activity after the ablation procedure. In 4 patients in whom the initial ablation had been unsuccessful, the indices of HRV did not change significantly and only changed after the successful ablation. HF power, MSSD and pNN50 increased significantly from the baseline values (355±102 ms², 34±5 ms and 10.4±3.7%, respectively) to 539±152 ms² (p<0.05), 45±3 ms (p<0.05) and 17.7±4.3% (p<0.01) after the successful ablation. LF power and LF/HF tended to decrease and the mean RR interval tended to increase from the baseline values after the successful ablation, but the difference did not reach significance.

**Discussion**

The major findings of the present study are as follows.

1. After the successful RF-CA of the RVOT tachycardia, decreased sympathetic nervous activity and enhanced parasympathetic nervous activity were demonstrated by analyzing HRV on Holter monitoring.

2. The changes in the autonomic balance were not evident early after the successful ablation or after unsuccessful ablation.

3. The frequency of ventricular arrhythmias appeared to change in parallel with changes in autonomic activity.

**Mechanisms of VT of the RVOT Origin**

Some investigators previously reported that VT originating from the RVOT was induced by exercise and suppressed by β-blockers. In those cases VT appeared repeatedly with a treadmill exercise test or isoproterenol infusion, but not with programmed ventricular stimulation. Therefore, automaticity or triggered activity would be the most feasible explanation of the underlying mechanism in those patients. In the present patients, VT showed a similar response to exercise, isoproterenol and programmed ventricular stimulation, and so we considered the mechanism of VT was the same.

**Autonomic Balance and RVOT Tachycardia**

Increased sympathetic activity, decreased parasympathetic activity or both facilitate the initiation of ventricular tachyarrhythmias. Idiopathic RVOT tachycardia frequently occurs during physical exercise and is repetitively inducible with programmed ventricular stimulation during isoproterenol infusion. Consequently, β-blockade is effective in suppressing VT in these patients. Therefore, increased sympathetic nervous activity could be involved, at least in part, in the initiation of idiopathic RVOT tachycardia as determined in the present study by analyzing the changes in HRV preceding the VT episodes.

The effect of parasympathetic nervous activity on the appearance of HRV is obscure. Experimental and clinical data support the concept of an antiarrhythmic effect of vagal activation on ventricular arrhythmias. In a previous report, carotid sinus massage after administration of edrophonium could repeatedly terminate VT episodes in some selected patients. Another study demonstrated that reflex vagal activation markedly reduced the frequency of PVC. Therefore, increased vagal activity could exert a protective effect against ventricular tachyarrhythmias and elimination of this protective effect would trigger the initiation of VT.

**Effect of RF-CA on HRV**

Analyses of HRV is a well-established tool in the studies of autonomic physiology and has been used clinically in various patient populations. Mean heart rate could be increased and HRV may be decreased as a consequence of enhanced sympathetic tone, decreased parasympathetic tone, or a combination of both. Although certain time domain indices of HRV, such as pNN50 and particularly MSSD, are known 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 the present study, both time domain and frequency domain analyses of HRV were used, and indicated increased parasympathetic tone with decreased sympathetic tone after the successful ablation of the RVOT tachycardia. Recently, Kocovic et al showed that increased heart rate, a decrease in HRV, and attenuation of the parasympathetic component of HRV were seen in patients undergoing atrioventricular (AV) node modification or posteroseptal accessory pathway ablation. They hypothesized that ablation in the anterior, mid, and posterior regions of the low interatrial septum may disrupt the preganglionic or postganglionic parasympathetic fibers in these regions that are destined to innervate the sinus node.

In contrast to these results, increased parasympathetic tone with decreased sympathetic tone was demonstrated after the successful ablation of the RVOT tachycardia in the present study. The mechanism of these changes in the autonomic balance after ablation is obscure. The anatomy of the sympathetic and parasympathetic innervation in the human heart has not been well delineated. In contrast, the cardiac innervation in dogs has been elucidated more clearly. In those studies, the preganglionic or postganglionic parasympathetic fibers destined to innervate the sinus node were not located in the RVOT from which idiopathic VT originates.

Recently, Ito et al have shown the efferent vagal and sympathetic innervation of the right ventricle is not linked to innervation of the sinus node. Assuming that the
sympathetic and parasympathetic innervation of the human and canine heart is similar, ablation of the RVOT will not affect the innervation to the sinus node. In an earlier study by Huikuri et al., an increase in sinus rate was demonstrated during induced VT. They suggested that both vagal withdrawal and sympathetic activation may play a role in the increase in sinus rate during VT. Other experimental and clinical studies have shown an increase in sympathetic nerve activity during programmed ventricular stimulation and induced VT, and even in the presence of PVC. In the present study, increased vagal tone and decreased sympathetic tone were demonstrated after the successful ablation.

Interestingly, in the present study these changes in the autonomic balance were not evident after the unsuccessful ablation. Moreover, a decrease in the frequency of PVC, couplet and VT early and late after the ablation was apparently associated with changes in the autonomic balance. Thus, the decrease in the frequency of ventricular tacharyrhythmias itself may play an important role in changes in the autonomic balance after ablation.

However, the reasons why the autonomic balance was not significantly changed early after the ablation are not fully elucidated. One possible explanation is that the anxiety, pain or other symptoms related to the ablation procedure could cause an increase in sympathetic tone soon (1–3 days) after the ablation. Therefore, an essential effect of ablation of the RVOT tachycardia on the autonomic balance was masked early after the ablation and only became evident late after the ablation.

Methodological Considerations and Study Limitations

There are potential limitations regarding the methodology of HRV for assessing autonomic balance in the presence of ventricular arrhythmias. We noted that there were frequent PVC as well as VT episodes during 24-h recordings in many of the patients in this study, PVC and VT can elicit an increase in sympathetic nervous activity which may subsequently influence the frequency of ventricular arrhythmias. Therefore, we analyzed normal RR intervals of only a 2-h period during sleep (00.00–06.00 h), when ectopic beats are least likely (<5% of total beats), in order to minimize the influence of PVC on HRV. This may be a time of elevated vagal tone and have biased the findings. However, in some of the study patients, average 24-h values of the HRV indices changed in the same way as the 2-h values during sleep after the successful ablation of the RVOT tachycardia. Accordingly, we considered that overall changes in autonomic activity could be evaluated by analysis of the 2-h values of HRV. Secondly, plasma levels of catecholamines were not determined in the present study. Demonstration of a possible role of the sympathetic nervous system will require a study of catecholamine metabolism. Finally, the relation between the frequency of PVC or VT and the value of HRV indices in each patient should be fully evaluated in a larger group of patients.

Although limited for these reasons, the present study sheds light on the relation of autonomic nervous activity to the genesis of ventricular tacharyrhythmias. The presence of ventricular tacharyrhythmias itself affects autonomic nervous activity, which could in turn facilitate the occurrence of ventricular tacharyrhythmias.

References

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