Heart Rate Variability Analysis of Patients With Idiopathic Left Ventricular Outflow Tract Tachycardia

— Role of Triggered Activity —

Eimei Shimoike, MD; Norihiro Ueda, MD; Toru Maruyama, MD; Yoshikazu Kaji, MD; Shozo Kanaya, MD*; Takehiko Fujino, MD*; Yoshiyuki Niho, MD

There have been several reports with respect to idiopathic ventricular tachycardias (VTs) originating from the left ventricular outflow tract (LVOT). A previous report suggested that triggered activity plays a partial role in idiopathic LVOT tachycardia from the electrophysiological as well as the electropharmacological viewpoint. However, the exact role of triggered activity in this type of VT remains unknown. In the present study the relationship of the frequency of premature ventricular contractions (PVCs) and heart rate was examined and heart rate variability (HRV) was analyzed in 2 cases of LVOT tachycardia using 24-h Holter electrocardiographic (ECG) monitoring. The relation between the PVCs frequency and heart rate showed a persistently positive correlation, indicating frequent PVCs as heart rate increased. In HRV analysis, NN50 (%), a time-domain variable of parasympathetic activity, showed no change prior to ventricular arrhythmias. In frequency-domain analysis of HRV, the high frequency (HF) component tended to fall prior to repetitive PVCs and VTs. The ratio of the low frequency to high frequency (LF/HF) components increased prior to single PVCs, repetitive PVCs and VTs. Sympathetic predominance predisposes the genesis of these kinds of arrhythmias originating from the LVOT and it is suggested that triggered activity plays an important role in LVOT tachycardia, at least in its initiation. (Jpn Circ J 1999; 63: 629–635)

Key Words: Heart rate variability; Left ventricular outflow tract; Triggered activity; Ventricular tachycardia

Methods

Two cases of sustained LVOT tachycardia reported previously1 were enrolled in this study. Briefly, in the first case, the 59-year-old male patient’s 12-lead ECG showed ventricular bigeminy. Echocardiogram, scintigraphy using 201Tl and 123I-labeled metaiodobenzylguanidine (MIBG) and cardiac catheterization failed to disclose any structural heart disease. The LVOT tachycardia was sensitive to intravenous bolus injection of adenosine triphosphate (0.29 mg/kg) and slow infusion of verapamil (0.10 mg/kg) and occurred immediately after exercise. QRS morphology during the VT showed an inferior axis and monophasic R wave pattern in all the precordial leads (Fig 1A). In the electrophysiological study, VT was induced spontaneously during isoproterenol infusion (2–8 mg/min) and the site of origin was aortomitral continuity just beneath the left coronary cusp of the aortic valve.

The second patient, a 64-year-old male, felt general fatigue and palpitations when sustained VT occurred. The results of physical findings, conventional ECG, echocardiogram and 201Tl scintigraphy were normal. Carotid sinus massage was effective in terminating the VT, which was induced by exercise. During the electrophysiological study, LVOT tachycardia was induced by high right atrial rapid pacing under isoproterenol infusion (2–8 mg/min). QRS morphology during the VT showed an inferior axis and monophasic R wave pattern in all the precordial leads (Fig 1A). In the electrophysiological study, VT was induced spontaneously during isoproterenol infusion (2–8 mg/min) and the site of origin was aortomitral continuity just beneath the left coronary cusp of the aortic valve.

The second patient, a 64-year-old male, felt general fatigue and palpitations when sustained VT occurred. The results of physical findings, conventional ECG, echocardiogram and 201Tl scintigraphy were normal. Carotid sinus massage was effective in terminating the VT, which was induced by exercise. During the electrophysiological study, LVOT tachycardia was induced by high right atrial rapid pacing under isoproterenol infusion (2–8 mg/min). QRS morphology during the VT showed an inferior axis and monophasic R wave pattern in all the precordial leads (Fig 1A). In the electrophysiological study, VT was induced spontaneously during isoproterenol infusion (2–8 mg/min) and the site of origin was aortomitral continuity just beneath the left coronary cusp of the aortic valve.

Holter Recordings

A 2-channel, 24-h Holter ECG recording (SM 29, Fukuda Denshi, Tokyo, Japan) was obtained 2 and 5 times from the case 1 and case 2, respectively. Antiarrhythmic agents, including atenolol or propranolol, were adminis-
tered to relief the symptoms of palpitation during baseline Holter recording. The averaged PVC frequency per minute for each hour was obtained automatically and plotted as a function of maximal HR in the corresponding time interval. The PVCs recorded were checked visually throughout by cardiologists who were unaware of the study protocol. The regression line and correlation coefficient were obtained.

Prior to the HRV analysis, VT was defined as 5 or more repetitive monomorphic PVCs. Sustained VT was defined as the VT lasting >30s. Episodes of VT, repetitive PVCs and isolated PVC were included in the analyses if they met all of the following criteria: (1) a satisfactory stable recording and (2) complete sinus rhythm for 60 min before any arrhythmic events. Twelve isolated PVCs (5 from patient 1 and 7 from patient 2), 13 episodes of 2–4 repetitive PVCs (6 from patient 1 and 7 from patient 2), and 10 events of VTs (8 nonsustained and 2 sustained; 6 events from patient 1 and 4 from patient 2) were thus selected for the analyses.

Time- and frequency-domain measures were analyzed from 60, 30, 25, 20, 15, 10 and 5 min before the onset of the

Fig 1. (A) Twelve-lead ECG recording of ventricular tachycardia (VT) observed spontaneously under isoproterenol infusion during the electrophysiological study in case 1. The QRS complex morphology shows an inferior-axis and left bundle branch block pattern. (B) Twelve-lead ECG recording of VT induced by burst pacing from the high right atrium under isoproterenol infusion in case 2. The QRS complex morphology shows an inferior-axis and left bundle branch block pattern (Reproduced with permission: Shimoike E, et al. J Cardiovasc Electrophysiol 1998; 9: 196–202).

Fig 2. Correlation between frequency of premature ventricular contractions (PVCs) per minute in each hour and maximal heart rate in the corresponding time interval in patient 1 (A) and patient 2 (B). In both patients, there was a positive correlation between PVC frequency and heart rate. The regression line in (A) is Y=0.176X–11.6 (r=0.72, p<0.01) and in (B), Y=0.110X–10.1 (r=0.90, p<0.01), where X and Y represent respectively maximal heart rate and PVC frequency per minute in each hour.
arrhythmia for 256 s. The Holter ECG recording was scanned with a Holter ECG analyzer (SCM 280, Fukuda Denshi) to determine the NN interval with visual verification. The NN interval was sampled at an 8-ms interval and digitalized data were transmitted to a personal computer (PC-9821, NEC, Tokyo, Japan) for analyzing time- and frequency-domain measures of HRV. From the time series of the NN intervals of normal QRS complexes, NN50 (%) was defined as percentage of NN intervals showing differences between adjacent normal NN intervals that was >50 ms computed over the selected time interval. With the fast Fourier transform method, 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 automatically.

Statistical Analysis
In the analyses of HRV, data are presented as mean ± SE and analyzed by Student’s t-test for paired observations. Regression analyses were performed to evaluate the relationship between maximal HR and the number of PVCs. P values of 0.05 or less were considered statistically significant.

Results
In both patients, ventricular arrhythmias occurred mainly during the daytime, and the QRS morphology of the isolated and repetitive PVCs and VT was the same. The rate of VT was 120 beats/min in case 1 and 180 beats/min in case 2. The longest duration of VT was about 1 min in case 1 and 2.5 min in case 2.

Relationship Between PVCs Frequency and Heart Rate
In these 2 patients, there was a distinct positive correlation between PVC frequency and maximal HR, and the relationship between PVC frequency and HR was statistically significant (r=0.72 and 0.90, p<0.01). The minimum HR causing PVCs was 84 and 92 beats/min for case 1 and case 2, respectively (Fig 2).

HRV Before PVCs
The mean NN interval and NN50 (%) prior to the single PVCs did not change significantly. Although the magnitude of the HF and LF power did not change significantly, the LF/HF significantly (p<0.05) increased 5 min before the onset of isolated PVCs compared with 10 min before (Fig 3).

The mean NN interval 5 min before the onset of repetitive PVCs was significantly shorter than that of 60 (p<0.05), 30 (p<0.01), and 25 (p<0.05) min before the onset. The NN50 (%) did not change significantly during this period. LF power did not show significant changes before the onset of repetitive PVCs. HF power tended to decrease progressively toward the development of repetitive PVCs, although it was not significant. Consequently, the LF/HF ratio increased 5 min before the onset of repeti-
tive PVCs (p<0.05) compared with any given point of time except for 20 min before the onset (Fig 4).

**HRV Before VT**

The mean NN interval and NN50 (%) did not change significantly. Although these were not significant, LF power tended to increase 5 min before the onset of VTs compared with 10 min before the onset, whereas HF power showed a tendency to progressively decrease toward the onset of VTs. Consequently, the LF/HF ratio increased 5 min before the onset of VTs (p<0.05) compared with 10 min before VTs (Fig 5).

**Discussion**

The major findings of the present study were: (1) there was a distinct positive correlation between the PVCs frequency and the maximal HR, and (2) time- and frequency-domain analyses of HRV revealed sympathetic predominance prior to the occurrence of single or repetitive PVCs and the development of VTs. These noninvasive findings imply that triggered activity caused by delayed afterdepolarization under sympathetic predominance plays an important role in initiating idiopathic LVOT tachycardia.

**Previously Postulated Mechanism of LVOT Tachycardia**

In our previous report of these 2 cases, electrophysiological and electropharmacological characteristics supported the hypothesis that triggered activity based on the delayed afterdepolarization plays a key role in the initiation of idiopathic LVOT tachycardia. In brief, the duration and the rate of the induced LVOT tachycardia was proportional whereas the coupling interval of the first beat of LVOT tachycardia was inversely proportional to the rapid high atrial or ventricular stimulation rate. These electrophysiological findings indicate overdrive acceleration rather than overdrive suppression as a causative mechanism of LVOT tachycardia. In the electropharmacological examinations, adenosine and verapamil suppressed and isoproterenol induced LVOT tachycardia in these patients, which suggests that the triggered activity based on the delayed afterdepolarization has a role in initiating tachycardia. The noninvasive characteristics of LVOT tachycardia recognized in the present study are compatible with these findings.

**PVCs Frequency and Heart Rate**

The relationship between the PVCs frequency and the HR preceding the PVCs has been reported to present important informations in the genesis of ventricular arrhythmias. Winkle was the first to analyze this kind of relationship using Holter ECG monitoring. Thereafter, Ito et al clarified the particular relation between the PVCs frequency and HR as indirect evidence for delayed afterdepolarization leading to triggered arrhythmia? They designated a positive correlation to cases showing more frequent PVCs at higher HR. Furthermore, they found such PVCs

---

**Fig 4.** Changes in mean NN interval, and time- and frequency-domain measures 60, 30, 25, 20, 15, 10 and 5 min prior to the onset of repetitive PVCs <5 beats. Data are mean±SE. Format and abbreviations as in Fig 1. *p<0.05 and **p<0.01 vs 5 min prior to the onset.
were sensitive to oral diltiazem or atenolol administered for 4 weeks or more. In the basic electrophysiology study, the amplitude and coupling interval of delayed afterdepolarization is dependent on the rate and duration of the preceding electrical stimuli and is sensitive to Ca antagonists and $\beta$-adrenoceptor antagonists. They hypothesized that the clinically observable triggered arrhythmias showed electrophysiological and electropharmacological features similar to the basic triggered firing phenomenon. Actually, overdrive acceleration and the results of the treatment with Ca antagonists and $\beta$-adrenoceptor antagonists implies that triggered arrhythmias exist in the clinical setting. In the present patients, who showed overdrive acceleration and verapamil sensitivity in the electrophysiological as well as the electropharmacological studies, a positive correlation between the PVCs frequency and HR during Holter monitoring provided evidence for triggered activity as a cause of idiopathic LVOT tachycardia.

**HRV Prior to Arrhythmic Events**

Spectral analysis of HRV can independently evaluate the sympathovagal drive to the heart. In the present study, the HF component of the spectral HRV and the time-domain variable calculated for the 24-h period were used as a measure of vagal activity, whereas the LF/HF ratio was considered as an index of the sympathovagal balance.9-11 There are several reports with respect to the HRV before the onset of idiopathic VT12-17 Fei et al showed that the LF/HF ratio was significantly increased prior to the idiopathic VT and that the reduced HF component was proportional to the frequency of PVCs in these patients. Therefore, they concluded that a significant increase in the LF/HF ratio based on a decrease in vagal activity rather than an enhanced sympathetic activity was closely associated with the initiation of the idiopathic VT. However, the morphology of idiopathic VT in their cases was right bundle branch block (RBBB) pattern in 15 patients and left bundle branch block (LBBB) pattern in 8 patients. In this light, the foci of the idiopathic VT were not homogeneous in their study. Lermann et al emphasized the differences in HRV prior to the isolated PVCs, couplets, and 3 or more repetitive PVCs originating from RVOT.15 In their study, the mean NN interval shortened preceding couplets and 3 or more repetitive PVCs, but this was not the case in the isolated PVCs. That is, an increase in sympathetic activity rather than a decrease in vagal activity predisposed the onset of this kind of repetitive PVCs.

Recently, Yoshida et al reported that the LF/HF increased preceding VT with LBBB and inferior axis, and concluded that activation of sympathetic tone plays an important role in the occurrence of VT originating from RVOT. The role of sympathovagal balance in the initiation of idiopathic VT originating from RVOT, using time-domain as well as frequency-domain analysis, has been emphasized by Hayashi et al. They drew a conclusion similar to that of Lermann et al that sympathetic predominance was related more closely to the repetition of PVCs or maintenance of VT than to the genesis of isolated PVCs.

Fig 5. Changes in mean NN interval, and time- and frequency-domain measures 60, 30, 25, 20, 15, 10 and 5 min prior to the onset of VT. Data are mean±SE. Format and abbreviations as in Fig 1. *p<0.05 vs 5 min prior to the onset.
In contrast to the ventricular arrhythmias with their site of origin in RVOT,\(^7\) the LF/HF increased not only prior to repetitive PVCs and VTs, but also just before the onset of isolated PVCs from LVOT. The changes of the HF in LVOT tachycardia were similar to those seen in RVOT tachycardias (ie, HF did not show any consistent trends toward the onset in case of isolated PVCs), but the gradual decrease in HF power was noted in cases of repetitive PVCs and VTs. But in contrast to the cases of isolated PVCs from RVOT, the LF tended to increase just before the onset of isolated PVCs, such as repetitive PVCs or VTs, and consequently, the LF/HF ratio increased significantly just prior to the onset of isolated PVCs from LVOT. These results suggest that sympathetic acceleration plays an important role in the initiation of not only repetitive PVCs or VTs, but also isolated PVCs originating in LVOT, even with the administration of β-blocking agents such as atenolol or propranolol.

Study Limitations

The present study contains a few limitations. First, the duration of Holter ECG recordings chosen for computation of HRV affect the result of HRV analysis. We assessed HRV at a 256-s interval for 60 min. The length of the sampling period during which HRV was estimated seems to be critical in terms of time resolution. HRV with 5-min sampling is reported to be useful in evaluating 24-h HRV.\(^{18}\) Fei et al analyzed HRV at 2-min intervals over a 60-min period before the onset of idiopathic VT.\(^{13}\) Therefore, our sampling methodology of 256-s interval for analysis of acute changes in HRV before the arrhythmic events seems similar to that reported in the literature. Second, autonomic balance could be influenced by the presence of various arrhythmias. VT per se was reported to elicit an increase in sympathetic nervous activity.\(^{15}\) Frequent PVCs also have a notable impact on spectral HRV.\(^{20}\) Therefore, this kind of study of the computation of HRV prior to the arrhythmias was potentially limited by the methodologic difficulties. Zuanetti et al however, showed that the presence or suppression of ventricular arrhythmias did not modify vagal activity determined by NN\(_50\) over 24h.\(^{21}\) Moreover, we carefully analyzed only the period that did not contain any PVCs for 60 min before the arrhythmic events.

The final limitation of this study is the limited number of patients treated with antiarrhythmic agents, including β-blocking agents, which interfere with cardiac autonomic tone and hence HRV analyses.\(^{21,22}\) Cook et al reported that atenolol increased the tonic vagal activity based on the HRV analyses applied to normal volunteers.\(^{22}\) If this was the case in the present investigation, sympathetic acceleration would be evident immediately prior to the development of repetitive PVCs and VTs with their site of origin in LVOT when the patients were treated with atenolol or propranolol. We realize that further accumulation of patients with LVOT tachycardia is required to obtain more insight into the genesis of this kind of rare and newly categorized idiopathic VT.

Conclusion

The Holter ECG monitoring of 2 patients with idiopathic LVOT tachycardia showed a positive correlation between PVCs frequency and maximal HR and sympathetic predominance in time- and frequency-domain analyses of HRV prior to the occurrence of single or repetitive PVCs and the development of VTs (ie, a decrease in mean NN interval and HF amplitude, and an increase in LF/HF). This line of evidence suggests that sympathetic predominance predisposes the genesis of LVOT tachycardia and it suggests that triggered activity plays an important role in this kind of arrhythmia, at least in its initiation.

Acknowledgments

We thank Ms Reiko Masaki for her expert technical assistance of Holter monitoring and echocardiographic recording, Mr John Martin for his critical reading of the manuscript and Ms Kaori Horikoshi for her preparing the manuscript.

References

19. Smith ML, Ellenbogen KA, Beighol LA, Eckberg DL: Sympathetic...
neural responses to induced ventricular tachycardia. *J Am Coll Cardiol* 1991; **18**: 1015–1024

