

Sympathovagal Balance Prior to Onset of Repetitive Monomorphic Idiopathic Ventricular Tachycardia

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ZIMMERMANN, M.: Sympathovagal Balance Prior to Onset of Repetitive Monomorphic Idiopathic Ventricular Tachycardia. *Repetitive monomorphic idiopathic (RMI) ventricular tachycardia (VT) occurs typically in patients without structural heart disease, originates in most cases from the right ventricular outflow tract, and can often be induced by exercise or isoproterenol. This study analyzed the dynamic changes in autonomic tone immediately before the spontaneous onset of RMIVT using frequency-domain heart rate variability (HRV) indices. We analyzed the ambulatory electrocardiographic recordings from 6 men and 8 women (mean age: 43 ± 18 years; mean number of VT runs per day: 134 ± 213 ; mean VT rate: 194 ± 40 bpm; median VT run length: 4 cycles) with RMIVT. A total of 36 clusters of nonsustained episodes of RMIVT preceded by ≥ 1 hour of sinus rhythm without VT were analyzed (25 minutes before the onset of RMIVT divided into five 5-minute periods; 8 minutes before onset of RMIVT divided into eight 1-minute periods). During 25 minutes preceding the onset of VT, the mean RR interval decreased from 767 ± 118 to 723 ± 105 ms ($P = 0.015$) and the low-frequency (LF)/high-frequency (HF) ratio increased from 2.24 ± 0.79 to 2.49 ± 1.0 ($P = 0.03$). During the 8 minutes before VT onset, the mean RR interval decreased from 745 ± 118 to 718 ± 102 ms ($P = 0.001$) and the LF components increased from 205 ± 72 to 253 ± 113 ms ($P = 0.014$). No change in HF components was observed during the 25 or 8 minutes periods preceding the RMIVT onset. The changes in HRV indices suggest a strong time-dependent primary activation of sympathetic tone prior to the occurrence of RMIVT. Withdrawal of vagal tone does not appear essential to the initiation of RMIVT clusters. (PACE 2005; 28:S1-S5)*

autonomic tone, idiopathic ventricular tachycardia, heart rate variability

Introduction

Repetitive monomorphic idiopathic (RMI) ventricular tachycardia (VT), initially described by Gallavardin,¹ is characterized by frequent monomorphic single premature ventricular complexes (PVCs), couplets, and runs of nonsustained VT with normal intervening sinus-originated complexes.²⁻⁵ This form of idiopathic VT occurs in clusters, at rest or after exercise, and has been attributed to cAMP-mediated triggered activity.⁶ Most frequently, RMIVT arises from the right ventricular outflow tract and can be induced by isoproterenol infusion.⁷ However, there is controversy regarding the exact role of the autonomic nervous system in the initiation of RMIVT. Some data suggest that sympathetic activation alone is predominantly responsible for the initiation of RMIVT, while others suggest that vagal withdrawal plays the predominant role.⁸⁻¹⁰ The goals of this study were (a) to assess the dynamic changes in sympathovagal balance prior to the onset of RMIVT using frequency-domain heart rate variability (HRV) indices, and (b) to evaluate the time-course of these

variations during the 25 minutes or 8 minutes preceding clusters of VT runs.

Methods

Twenty-four-hour ambulatory electrocardiograms (ECG) from 6 men and 8 women (mean age: 43 ± 18 years) with RMIVT were recorded and analyzed. All but two patients had a structurally normal heart based on history, physical examination, resting 12-lead ECG, exercise stress testing, and echocardiography. One patient had hypertensive heart disease with mild left ventricular hypertrophy and one patient had coronary artery disease. The mean duration of symptoms was 3.6 ± 1.9 years, and the mean number of drug trials was 1.3 ± 0.6 per patient. The mean VT rate was 194 ± 40 bpm, and in all cases the arrhythmia originated from the right ventricular outflow tract with a left bundle branch block pattern and right-axis deviation.

Ambulatory ECG recordings were analyzed if the following criteria were met: (1) predominant sinus rhythm in the drug-free state ($\leq 30\%$ PVCs/24 hour); (2) monomorphic PVCs and VT runs present in clusters; (3) ≥ 1 hour of sinus rhythm with only single PVCs or couplets prior to clusters of RMIVT.

All 24-hour ambulatory ECG recordings were performed using a two-channel bipolar recorder (Recorder 8500, Marquette Electronics Inc,

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Milwaukee, WI) and analyzed using the MARS 8000 Workstation and software (Marquette). All tapes were converted to the digitized format and reviewed by an expert. VT was defined as ≥ 3 consecutive monomorphic PVCs at a rate > 100 bpm. All clusters of VT runs were manually identified, labeled, and printed on paper (30 s/line at 25 mm/s). Ectopic complexes were excluded from the HRV analysis. The following periods were analyzed: (a) total 24-hour ECG recording (24 hour); (b) 1 hour preceding the onset of VT clusters (1 hour); (c) 25 minutes preceding the onset of VT clusters divided into five 5-minute periods; (d) 8 minutes preceding the onset of VT clusters divided into eight 1-minute periods.

The following time-domain HRV indices were analyzed: (a) mean RR interval (mean NN, in ms), standard deviation of NN intervals (SDNN, in ms), standard deviation of 5 minutes means of NN intervals (SDANN, in ms), root mean square of differences between successive NN intervals (rMSSD, in ms), and proportion of adjacent NN intervals differing more than 50 ms (pNN50, in %) for the 24-hour period of recording and for the hour preceding VT runs.

HRV in the frequency-domain (Fast Fourier transform) was analyzed over the 24-hour period of recording, for 1 hour preceding the onset of VT clusters, for the five 5-minute and the eight 1-minute periods before onset of VT clusters. The following indices were calculated: low-frequency (LF) components, from 0.04 to 0.15 Hz, high-frequency (HF) components, from 0.15 to 0.40 Hz, and the LF/HF ratio. The LF and HF oscillatory components were analyzed both in absolute (ms^2) and normalized units (NU) according to the following formula:

$$\text{Power(NU)} = 100 \times \frac{\text{power}(\text{ms}^2)}{\text{total power}(\text{ms}^2) - \text{power VLF}(\text{ms}^2)},$$

where "power" indicates the power of LF or HF. The log transformation of LF and HF values was performed before statistical analysis. The LF/HF ratio was considered as an index of the sympathovagal balance. LF was considered to represent mainly sympathetic activity and HF was used as an indicator of parasympathetic activity.

Statistical Analysis

Data are presented as mean \pm SEM for HRV parameters, and as mean \pm SD for ambulatory ECG data. Comparisons of data obtained at different time intervals were performed using repeated measures analysis of variance or unpaired Student's *t*-test, as appropriate. The statistical significance of

differences between mean values was tested with a paired *t*-test, as appropriate. A *P* value < 0.05 was considered statistically significant.

Results

Ambulatory ECG

During the 24-hour period of recording, the mean sinus rate was 75 ± 7 bpm (range: 51 ± 11 bpm to 139 ± 26 bpm), the mean number of isolated PVCs was $12,049 \pm 10,987$, the mean number of ventricular couplets was $779 \pm 1,185$, and the mean number of VT runs was 134 ± 213 . The mean VT rate was 194 ± 40 bpm and the mean VT run length 16 ± 27 beats (median = 4). Prior to the occurrence of VT runs, a long-short phenomenon was observed in 4/14 cases (29%) and acceleration of the baseline sinus rate was prominent in 5/14 cases (36%).

Time-Domain HRV Indices

The mean RR interval over the 1-hour period preceding VT clusters was not significantly different from the mean RR interval during the 24-hour period (753 ± 107 vs 806 ± 75 ms, *P* = 0.09). The SDNN and SDANN values were significantly shorter during the 1-hour period preceding VT clusters compared to the 24-hour period (101 ± 40 vs 150 ± 36 ms for SDNN, *P* = 0.0002; 66 ± 40 vs 126 ± 38 ms for SDANN, *P* = 0.0001). No differences were observed for rMSSD and pNN50 values.

Frequency-Domain HRV Parameters

A significant decrease in RR interval was observed during the 25 minutes preceding the onset of VT runs. There was also a significant increase in the LF/HF ratio prior to the onset of VT runs (*P* = 0.03), whereas LF and HF values did not vary significantly before the onset of VT clusters (Table I, Fig. 1). Likewise, a significant decrease in RR interval was observed during the 8 minutes preceding the onset of VT runs together with a significant increase in LFNU values (*P* = 0.014). No significant changes were observed in HF values prior to the onset of VT clusters (Table II, Fig. 2).

Discussion

Our observations suggest a strong relationship between the occurrence of RMIVT and sympathetic activation with little or no influence of parasympathetic withdrawal. The impact of exercise, emotions, and isoproterenol infusion on the occurrence of RMIVT has been well documented,⁶ and a positive linear correlation has been demonstrated between the mean preceding heart rate and

Table I.
Frequency-Domain HRV Parameters

Parameter	24 hour	1 hour	25 min	20 min	15 min	10 min	5 min	P
Mean RR (ms)	806 ± 75	753 ± 107	767 ± 118	760 ± 122	752 ± 121	719 ± 166	723 ± 105	0.015*
LF (ms)	30 ± 10	36 ± 16	37 ± 21	36 ± 20	38 ± 18	38 ± 18	38 ± 21	0.91
LF-NU (ms)	210 ± 52	209 ± 49	207 ± 52	206 ± 67	209 ± 53	211 ± 56	231 ± 72	0.089
ln LF	1.45 ± 0.16	1.50 ± 0.22	1.49 ± 0.27	1.47 ± 0.28	1.49 ± 0.29	1.51 ± 0.25	1.50 ± 0.29	0.82
ln LF-NU	2.30 ± 0.15	2.30 ± 0.12	2.30 ± 0.10	2.29 ± 0.13	2.30 ± 0.10	2.30 ± 0.11	2.33 ± 0.15	0.26
HF (ms)	14 ± 5	15 ± 7	18 ± 10	17 ± 9	16 ± 8	15 ± 6	15 ± 8	0.17
HF-NU (ms)	99 ± 30	90 ± 37	102 ± 34	105 ± 47	108 ± 61	95 ± 41	101 ± 51	0.60
ln HF	1.12 ± 0.15	1.10 ± 0.26	1.17 ± 0.24	1.16 ± 0.25	1.16 ± 0.21	1.15 ± 0.19	1.10 ± 0.27	0.28
ln HF-NU	1.97 ± 0.15	1.94 ± 0.27	1.98 ± 0.14	1.98 ± 0.17	1.98 ± 0.19	1.94 ± 0.17	1.94 ± 0.27	0.42
LF/HF	2.21 ± 0.6 ± 121	2.37 ± 0.7	2.24 ± 0.8	2.21 ± 0.8	2.24 ± 0.8	2.49 ± 0.9	2.49 ± 1.0	0.03*

Time = time-interval before the onset of VT; ms = milliseconds; min = minutes; LF = low-frequency components; HF = high-frequency components; ln = natural logarithm; NU = normalized units; statistical analysis using repeated measures ANOVA. Values are expressed as mean ± SD.

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VT run length.⁴ Lerman et al. have suggested that RMIVT is due to cAMP-mediated triggered activity with a transient increase in sympathetic tone preceding nonsustained VT.^{6,7} The increase in LF/HF

ratio observed during the 8 minutes preceding the onset of RMIVT is consistent with sympathetic activation occurring shortly before the onset of VT.^{9,12} Variation in the LF/HF ratio is an index of

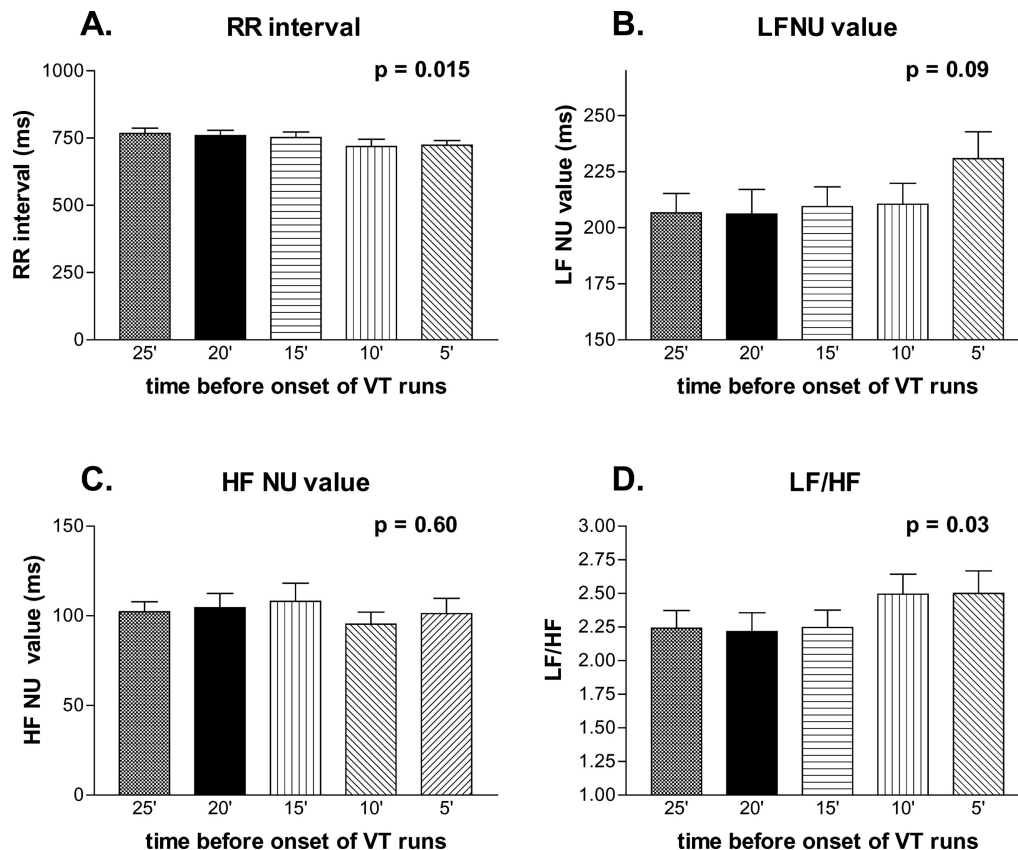


Figure 1 Frequency-domain HRV parameters during the 25 minutes preceding the onset of ventricular tachycardia (VT) clusters in RMIVT. (A) RR intervals; (B) LFNU value; (C) HFNU value; and (D) LF/HF ratio. See text for details.

Table II.
Frequency-Domain HRV Parameters

Parameter	8 min	7 min	6 min	5 min	4 min	3 min	2 min	1 min	P
Mean RR (ms)	745 ± 118	743 ± 116	740 ± 114	735 ± 111	731 ± 108	727 ± 107	724 ± 101	718 ± 102	0.0001*
LF (ms)	40 ± 22	42 ± 23	41 ± 24	40 ± 26	42 ± 27	40 ± 23	40 ± 23	41 ± 24	0.99
LF-NU (ms)	205 ± 72	207 ± 56	220 ± 69	223 ± 74	226 ± 77	229 ± 74	230 ± 85	253 ± 113	0.014*
ln LF	1.53 ± 0.27	1.55 ± 0.27	1.52 ± 0.29	1.50 ± 0.33	1.52 ± 0.31	1.51 ± 0.31	1.51 ± 0.31	1.52 ± 0.31	0.93
ln LF-NU	2.28 ± 0.14	2.30 ± 0.11	2.32 ± 0.12	2.32 ± 0.14	2.33 ± 0.14	2.33 ± 0.14	2.33 ± 0.16	2.37 ± 0.15	0.03*
HF (ms)	17 ± 8	17 ± 8	16 ± 7	15 ± 7	17 ± 8	17 ± 10	17 ± 9	17 ± 9	0.52
HF-NU (ms)	100 ± 52	93 ± 36	99 ± 46	105 ± 56	105 ± 53	107 ± 49	110 ± 62	118 ± 79	0.17
ln HF	1.19 ± 0.21	1.19 ± 0.22	1.15 ± 0.20	1.14 ± 0.21	1.16 ± 0.34	1.16 ± 0.26	1.17 ± 0.26	1.15 ± 0.26	0.74
ln HF-NU	1.94 ± 0.21	1.93 ± 0.15	1.95 ± 0.18	1.96 ± 0.22	1.96 ± 0.22	1.98 ± 0.20	1.99 ± 0.20	2.0 ± 0.23	0.49
LF/HF	2.39 ± 1.0	2.44 ± 0.8	2.50 ± 1.0	2.56 ± 1.2	2.60 ± 1.3	2.47 ± 1.1	2.40 ± 0.9	2.61 ± 1.0	0.67

Time = time-interval before the onset of VT; ms = milliseconds; min = minutes; LF = low-frequency components; HF = high-frequency components; ln = natural logarithm; NU = normalized units; statistical analysis using repeated measures ANOVA. Values are expressed as mean ± SD.

the sympathovagal balance, which does not allow a distinction between pure adrenergic stimulation and parasympathetic withdrawal. This, together with the use of different periods of analysis and different patient populations by other authors, may account for the conflicting results published in the literature regarding variations in the LF/HF ratio prior to the onset of nonsustained VT.^{8,13} The only consistent finding appears to be the presence of an increase in heart rate during the few minutes,^{4,6,8,9,14} or for only a few beats,⁷ before the onset of runs of RMIVT. Abnormal cardiac sympathetic innervation has been described in patients with VT in absence of structural heart disease,¹⁵ but a relationship between regional sympathetic denervation and the results of the present study is not established.

The absence of changes in HF components in the present study argues against significant changes in parasympathetic tone before the onset of RMIVT clusters. An absence of change in HF has also been demonstrated by Lerman et al. using time-domain HRV parameters (rMSSD) on the 15 RR intervals preceding VT.⁶ Although the validity of time-domain analysis over such short periods of time appears questionable, their data also suggest an absence of parasympathetic withdrawal prior to RMIVT. The absence of variation in HF components has also been demonstrated with frequency-domain HRV parameters,¹² although the results have been conflicting.^{9,14} Gill et al. have suggested that parasympathetic activity may have a stabilizing effect on the myocardium. However, that study was limited to the analysis of the number of PVCs on an hourly basis and did not concentrate on periods of time preceding the onset of VT runs.¹⁰ The absence of vagal withdrawal suggests that RMIVT is purely adrenergically mediated, even if VT runs may occur at rest under apparently sedentary conditions.

A trend toward adrenergic predominance prior to the onset of VT has been demonstrated in several other clinical situations, including acute myocardial infarction,¹⁷ in patients with implantable cardioverter-defibrillators^{18,19} and in patients with coronary artery disease and non-sustained or sustained VT.^{13,20} An abnormal response to increased sympathetic activity (decline of LF oscillations in the setting of increasing heart rate) has also been reported in patients with sustained VT associated with structural heart disease.²¹

In conclusion, the changes in frequency-domain HRV indices observed in the present study suggest a strong, time-dependent, primary activation of sympathetic tone before the occurrence of RMIVT, while withdrawal of vagal tone did not appear essential for the development of VT clusters.

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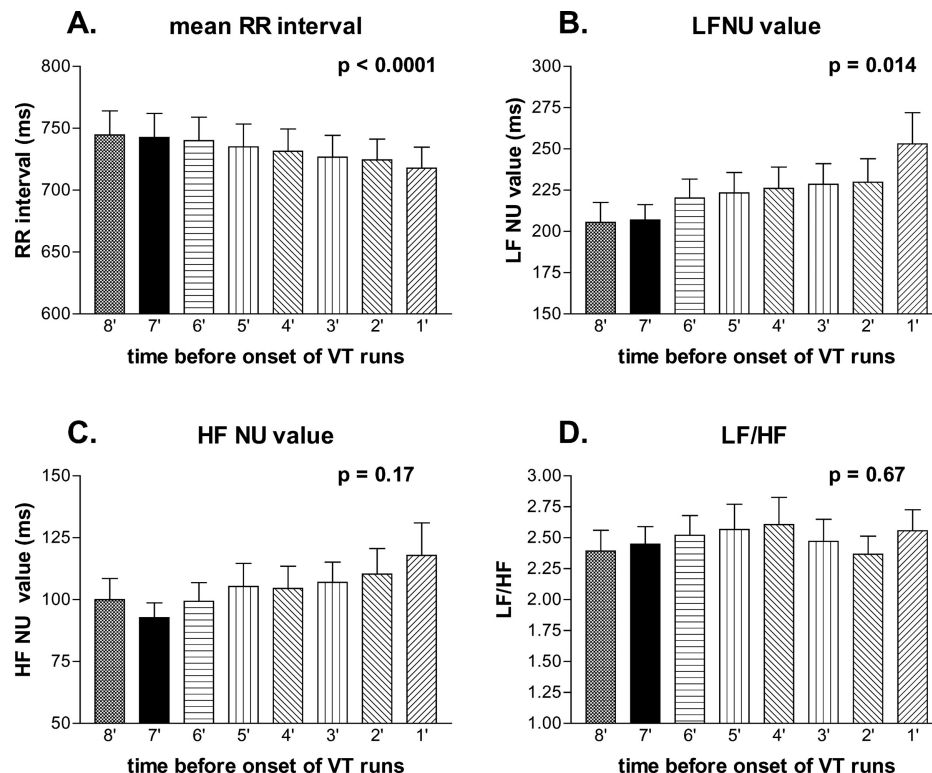


Figure 2 Frequency-domain HRV parameters during the 8 minutes preceding the onset of ventricular tachycardia (VT) clusters in RMIVT. (A) RR intervals; (B) LFNU value; (C) HFNU value; (D) LF/HF ratio. See text for details.

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Queries

- Q1** Author: Please provide the corresponding foot note for the symbol “*” in Tables I and II.
- Q2** Author: Please note that Ref. 18 is not given in the list. Kindly check.
- Q3** Author: Please note that Refs. 11 and 16 are not cited in the text.