

Dynamics of low-frequency R-R interval oscillations preceding spontaneous ventricular tachycardia

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Background Increased sympathetic activity is believed to be an important trigger of sustained ventricular tachyarrhythmias (VT) and is believed to be responsible for the increased heart rate that we and others have reported before the onset of spontaneous VT. However, in the patients reported herein, heart rate variability (HRV) indexes that reflect sympathetic activity unexpectedly declined, whereas heart rate increased. To explain this apparent paradoxical behavior, we tested the hypothesis that baseline levels of HRV determine its reaction to short-term autonomic perturbations before the onset of VT.

Methods and Results Holter electrocardiograms from 47 patients (ejection fraction $36\% \pm 15\%$) with recorded VT were analyzed. Frequency domain HRV indexes (low-frequency power [LFP] 0.04 to 0.15 Hz, high-frequency power [HFP] 0.15 to 0.4 Hz, and total power [TP] 0.01 to 0.4 Hz) were studied in 5-minute intervals and over a period of 24 hours. Patients were divided into those with a decrease in LFP in the 2-hour period before VT (group A, $n = 32$) and those with an increase or no change (group B, $n = 15$). The data were logarithmically transformed. Heart rate increased 15 minutes before the onset of VT compared with the 24-hour mean in both groups (group A: 80.3 ± 15.4 to 86.1 ± 20.0 beats/min, $P = .005$; group B: 80.6 ± 13.5 to 86.7 ± 14.0 beats/min, $P = .017$). Group A had higher TP, LFP, and LFP/HFP 2 hours before VT, and these variables decreased 15 minutes before the onset of VT (TP from 7.31 ± 1.28 to 6.88 ± 1.35 , LFP from 6.09 ± 1.28 to 5.38 ± 1.33 , LFP/HFP from 1.33 ± 0.89 to 0.96 ± 0.80 , $P < .001$ for all 3 variables). HFP also decreased 15 minutes before VT compared with 2 hours (from 4.78 ± 1.05 to 4.49 ± 1.24 , $P = .028$). In group B, which had lower baseline TP, LFP, and LFP/HFP at 2 hours before VT, these variables increased 15 minutes before the event (TP from 6.41 ± 1.41 to 6.86 ± 1.42 , $P = .004$; LFP from 4.59 ± 1.51 to 4.95 ± 0.62 , $P < .001$; LFP/HFP from 0.22 ± 1.22 to 0.52 ± 1.38 , $P = .10$), whereas HFP did not change significantly (4.40 ± 0.94 and 4.53 ± 1.01 , $P = .50$).

Conclusions An increase in heart rate and a drop in the low-frequency oscillations of R-R intervals before the onset of VT occurred in patients with higher baseline level of oscillatory activity. These changes suggest a dissociation between the average and rhythmic modulation of R-R intervals. A decline of the low-frequency oscillations in the setting of increasing heart rate could reflect an abnormal response to increased sympathetic activity in most of the patients from the studied group. The different behaviors of the HRV indexes before the onset of VT in the 2 groups suggest that change in the dynamics of R-R intervals, rather than the direction of change, facilitates arrhythmogenesis. (*Am Heart J* 2000;139:126-33.)

Changes in the autonomic tone play an important role in arrhythmogenesis. An increase in heart rate has been observed preceding the onset of ventricular tachyarrhythmias (VT) in the majority of patients in whom spontaneous initiation has been recorded, which suggests ele-

vated sympathetic and/or diminished parasympathetic activity.¹⁻⁶ Circadian distributions of VT demonstrated 2 peaks: 1 in the morning and 1 in the late afternoon that coincide with the peaks of plasma catecholamine levels.⁷ Catecholamines exert potentially proarrhythmic electrophysiologic effects on myocardial tissue, whereas vagal stimulation reduces ventricular vulnerability.^{8,9} However, the results of heart rate variability (HRV) analysis of the changes that precede VT in human beings have been inconsistent. Several investigations demonstrated an increase in the indexes of sympathetic activity preceding VT, whereas others failed to find significant changes.¹⁰⁻¹⁴ Contrary to the expectations, recent studies in relatively large groups of patients demonstrated a decrease in the HRV indexes of sympathetic activity before VT.^{6,15} In particular, a decrease in the absolute low-frequency power (LFP), LFP/high-frequency (HFP) ratio, and normalized LFP was observed

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before the spontaneous onset of VT.⁶ Valkama et al¹² found that in multivariate analysis, the LFP was the strongest predictor of the occurrence of sustained VT. It is noteworthy that there were no significant changes in HFP, which suggests that the cause for the selective drop in LFP is not a mere increase in heart rate but some shift in rhythmic modulation of R-R intervals that might be related to arrhythmogenesis. A similar loss of LFP without changes in the other frequency elements was observed in patients with congestive heart failure and a high muscular sympathetic nerve activity.^{16,17} Similar short-term decreases in LFP occurred in patients with severe congestive heart failure during tilt-table testing, which suggests that chronically high and further rising sympathetic activity loses its characteristic rhythmic modulation.¹⁸ Thus there is some evidence demonstrating selective loss of the low-frequency R-R interval oscillations in the context of abnormally high sympathetic activity. However, the short-term selective drops in LFP preceding VT have not been studied.

The purpose of this investigation was to define the circumstances during which the magnitude of the slow oscillations of R-R intervals decline before the onset of sustained ventricular arrhythmias. The baseline level of HRV affects its response to parasympathetic activity.¹⁹⁻²¹ Similar relations were described between resting vasomotor activity and its changes during mental stress.²² Therefore we hypothesized that baseline levels of HRV determine its reaction to the short-term autonomic perturbations before the onset of VT.

Methods

Patients

The patients for this study were identified by the presence of spontaneous sustained (≥ 30 seconds in duration, rate > 100 beats/min) monomorphic ventricular tachycardia (VT) recorded on a 24-hour Holter electrocardiogram. The patients were selected from among those recruited for the Electrophysiologic Study Versus Electrocardiographic Monitoring (ESVEM) trial, which has been described in detail.²³⁻²⁶ Patients considered for this clinical trial had a history of cardiac arrest, documented ventricular fibrillation, sustained ventricular tachycardia, or syncope. Patients with recent myocardial infarction, the long QT syndrome, hypertrophic cardiomyopathy, or arrhythmias caused by transient or reversible disorders were excluded. Enrolled patients had at least 10 premature ventricular complexes per hour and inducible sustained VT.²³

Analysis of recordings

Baseline Holter electrocardiograms (1646 tapes) were obtained in 868 of the 2103 patients screened for the trial.²⁴ The tapes were analyzed and verified as described previously.²³ Recordings from 59 patients demonstrated VT as defined above. Recordings with atrial fibrillation ($n = 6$) were excluded from this series. Among the remaining 53 electrocardiograms, 47 recordings that contained at least 2 hours of data preceding the onset of VT were selected, and 1 (longest)

episode of VT per patient was analyzed. Electrocardiographic data were digitized at 400 Hz, and the QRS complexes were classified with the use of a commercial scanning system and custom software (Burdick, Inc, Milton, Wis) and verified by a cardiologist. The R-R intervals between normal QRS complexes were extracted, and a regularly spaced time series was sampled at 2 Hz with the use of a boxcar low-pass filter.²⁷ Gaps in the time series resulting from noise or ectopic beats were filled in with linear splines, which can cause a small reduction in HFP but do not affect other components of the power spectrum.²⁸ We assessed the impact of including segments with varying amounts of ectopic activity by repeating the analyses with intervals with $> 50\%$, $> 75\%$, or 85% of normal beats.

Time and frequency domain analysis of R-R intervals was performed in 5-minute intervals and over the entire 24-hour period.

Time domain analysis. Mean and standard deviation of normal R-R intervals, the square root of the mean of the squared differences between adjacent normal R-R intervals (r-MSSD), and percentage of differences between adjacent normal R-R intervals that are > 50 ms (pNN50) were estimated.²⁰

Frequency domain analysis. After subtracting the mean from the time series, power spectral analysis was performed with fast Fourier transform and a Hanning window. Zero padding was applied to increase the outcome frequency resolution, and the resulting power spectrum was corrected for the filtering and windowing.²⁹ Power was integrated in the following frequency ranges: HFP 0.15 to 0.4 Hz; LFP 0.04 to 0.15 Hz; and very low-frequency power (VLFP) 0.0033 to 0.04 Hz; LFP/HFP was also calculated. The ultra low-frequency component (ULFP), 0 to 0.0033 Hz, and the 24-hour total power (TP), 0 to 0.4 Hz, were determined in the entire recording for comparison with previously published HRV estimates.³⁰ TP and VLFP calculated in the entire 24-hour period and TP and VLFP calculated in 5-minute windows have different frequency resolutions and, because of nonstationary character of the signal, different magnitudes. TP in the 24-hour window includes ULFP with a cycle length > 5 minutes, which cannot be determined in 5-minute windows. To highlight these differences, we separated TP and VLFP calculated over the entire 24-hour period from TP/5 (range 0.01 to 0.4 Hz) and VLFP/5 (range 0.1 to 0.04 Hz) calculated in 5-minute windows. We did not use the normalized LFP and HFP because they provide essentially the same information as the ratio LFP/HFP.³¹

Patient classification

Our previous studies showed that the changes in heart rate and the HRV signal occur during 2 hours before the onset of VT and reach maximum 15 minutes before the event.⁶ Therefore patients in this study were divided into those who had a decrease in LFP between 2 hours and 15 minutes before VT (group A: 32 [68%] patients) and those with an increase or no changes in LFP (group B: 15 [32%] patients).

Electrocardiographic tapes were recorded at least 5 half lives after the discontinuation of antiarrhythmic drugs. β -Blockers were continued in 5 patients from group A for reasons other than antiarrhythmic control (Table I). Inclusion or exclusion of these patients from analysis did not change the trends in R-R variability or the statistical significance of the results.

Statistical analysis

The Shapiro-Wilks W test of normality was used to assess distribution of the data. Because of substantial deviation

Table I. Clinical characteristics of the patients

	Group A	Group B	P value*	Overall
No. of patients	32 (68%)†	15 (32%)	—	47
Age (y)	63.8 ± 11.8	64.9 ± 7.8	.86	64.1 ± 10.7
Men	26 (81%)	14 (93%)	.25	40 (85%)
Ischemic heart disease	26 (81%)	13 (87%)	.64	39 (83%)
Previous MI	26 (81%)	12 (80%)	.92	38 (81%)
Years since last MI	5.6 ± 5.9	6.9 ± 9.0	.92	6.1 ± 7.1
SAS class 3 or 4	7 (22%)	5 (33%)	.41	12 (26%)
Ejection fraction	38.6% ± 15.2%	32.3% ± 15.0%	.25	36.2% ± 15.1%
Presenting arrhythmia				
VF	3 (9%)	2 (13%)	.69	5 (11%)
VT	29 (91%)	13 (87%)	—	42 (89%)
PVC/h on Holter	380 ± 485	355 ± 382	.57	372 ± 459
Ca-blockers	4 (17%)	1 (10%)	.61	5 (15%)
Digitalis	6 (25%)	2 (20%)	.75	8 (24%)
β-Blockers	5 (15.6%)	0	.18	5 (10.6%)
Duration of VTi (s)	671 ± 1472	999 ± 1534	.13	775 ± 1483
(median)	(93)	(352)		(159)
Mean cycle length of VTi (ms)	364 ± 83	388 ± 97	.75	371 ± 87
(median)	(354)	(335)		(352)
No. of VT runs	6.1 ± 15.1	56.1 ± 147.9	.57	20 ± 81
(median)	(2)	(1)		(1)

MI, Myocardial infarction; PVC, premature ventricular complexes; β-Blocker, β-adrenergic receptor blocking drug; SAS, Symptomatic Activity Scale; VT, ventricular tachycardia; VTi, index VT; VF, ventricular fibrillation.

*P indicates significance of the differences between group A and group B.

†Percentages are in parentheses except where indicated and reflect missing data for some variables.

from normal distribution, nonparametric Friedman analysis of variance (ANOVA) was applied to test the significance of changes in each variable over time. The 2 groups of patients were compared with the use of Kruskal-Wallis ANOVA. Statistical significance did not change when skewed variables were reanalyzed with logarithmically transformed data to normalize distribution. ANOVA for repeated measurements was applied to test the significance of temporal changes in the transformed variables preceding VT. Results are expressed as mean ± SD of the logarithmically transformed data unless otherwise indicated. Differences at $P < .05$ were considered significant.

Results

Clinical characteristics

The clinical characteristics of the 47 patients are shown in Table I. The mean age was 64 ± 11 years; 85% ($n = 40$) of patients were men. All had structural heart disease; the underlying cause was ischemic in 83%. The mean ejection fraction was $36\% \pm 15\%$. No clinical characteristic could distinguish groups A and B. Circadian distribution of the index VT was not significantly different between the groups ($P = .22$). The mean start time of arrhythmia was 9 AM and 11 AM in group A and group B, respectively. During the day (6 AM to 11 PM), VT tended to occur more often in group A than in group B (75% and 53%, respectively). There were no significant differences between groups with respect to premature ventricular complex frequency over a period of 24 hours (Table I), and repeating the

HRV analyses by use of intervals with >50%, >75%, or 85% of normal beats did not change the results.

Twenty-four-hour measures of heart rate and R-R interval variability

The 24-hour average heart rate was 80.3 ± 14.6 beats/min (median 78.0, 95% confidence limits 76.3 to 84.4 beats/min). The frequency domain measures of R-R interval variability were severely depressed: TP 8.88 ± 1.22 natural log (ln) ms^2 ; ULFP 8.66 ± 1.25 ln ms^2 ; VLFP 6.53 ± 1.34 ln ms^2 ; LFP 5.50 ± 1.58 ln ms^2 ; HFP 4.53 ± 1.24 ln ms^2 ; LFP/HFP 0.91 ± 1.11 ln ms^2 (Table II).

The average heart rates were not different between groups A and B (80.3 ± 15.4 vs 80.6 ± 13.5 beats/min, $P = .98$), whereas all the spectral indexes were higher in group A than in group B. Group A had higher average values of TP/5, LFP, and LFP/HFP ratios (TP/5 7.28 ± 0.88 ms^2/Hz ; LFP 5.88 ± 1.0 ms^2/Hz ; LFP/HFP 1.21 ± 0.76 ms^2/Hz) than group B (TP/5 6.62 ± 1.38 ms^2/Hz , $P = .06$; LFP 4.80 ± 1.72 ms^2/Hz , $P = .009$; LFP/HFP 0.48 ± 1.34 , $P = .019$). In group A patients, HRV variables decreased significantly 15 minutes before VT (TP/5 6.88 ± 1.35 ms^2/Hz , $P = .009$; LFP 5.38 ± 1.33 ms^2/Hz , $P = .0004$; LFP/HFP 0.96 ± 0.80 , $P = .004$). In group B patients, in contrast, HRV variables did not change significantly or tended to increase before VT (TP/5 6.86 ± 1.42 ms^2/Hz , $P = .4$; LFP 4.95 ± 0.62 ms^2/Hz , $P = .4$; LFP/HFP 0.52 ± 1.38 , $P = .8$).

Table II. Heart rate and heart rate variability in all 47 patients

Variable	Normal value*	Data over various time periods calculated in 5-min windows			P value†
		Entire recording	2 h pre-VT	15 min pre-VT	
Time domain					
Mean R-R	817 ± 103	772 ± 145	797 ± 175	730 ± 146	.0002
r-MSSD	27 ± 12	27.9 ± 15.1	31.8 ± 20.8	31.1 ± 20.7	.40
pNN50	9 ± 7	4.47 ± 5.01	5.05 ± 6.17	5.27 ± 5.96	.99
Frequency domain (expressed as ln)					
TP	9.83 ± 0.51	8.88 ± 1.22			
TP/5		7.07 ± 1.09	7.06 ± 1.37	6.92 ± 1.33	.62
ULFP		8.66 ± 1.25			
VLFP	7.35 ± 0.53	6.53 ± 1.34			
VLFP/5		6.51 ± 1.57	6.39 ± 1.66	6.31 ± 1.66	.88
LFP	6.45 ± 0.68	5.50 ± 1.58	5.67 ± 1.49	5.33 ± 1.34	.020
HFP	5.05 ± 0.83	4.53 ± 1.24	4.67 ± 1.03	4.50 ± 1.17	.13
LFP/HFP	1.41 ± 0.51	0.91 ± 1.11	1.02 ± 1.10	0.86 ± 0.95	.076

*Normal values for healthy, middle-aged persons were obtained from reference 30.

†P value indicates significance of differences in the 15 minutes before VT vs the value in the 2 hours preceding VT onset.

Changes in heart rate and R-R interval variability preceding ventricular tachycardia

In the overall group, heart rate increased during 15 minutes before the onset of VT compared with the 24-hour average (85.3 ± 18.2 vs 80.4 ± 17.3 beats/min, $P = .0008$), whereas LFP and LFP/HFP decreased (LFP [ln] 5.33 ± 1.34 vs 5.50 ± 1.58 , $P = .005$; LFP/HFP [ln] 0.86 ± 0.95 vs 0.91 ± 1.11 , $P = .031$). The magnitude of increase in heart rate between 120 and 15 minutes before the onset of VT was similar in group A (from 77.8 ± 17.2 to 86.1 ± 20.0 beats/min, $P < .001$) and group B (from 78.9 ± 16.6 to 86.7 ± 14.0 beats/min, $P < .001$), and in both groups heart rate 15 minutes before the onset of VT was significantly higher than the 24-hour average ($P = .005$ and $P = .017$, respectively) (Figure 1).

Group A had higher TP/5, LFP, and LFP/HFP 2 hours before VT, and these variables decreased 15 minutes before the onset of VT (TP/5 from 7.31 ± 1.28 to 6.88 ± 1.35 , LFP from 6.09 ± 1.28 to 5.38 ± 1.33 , LFP/HFP from 1.33 ± 0.89 to 0.96 ± 0.80 ; $P < .001$ for all 3 variables). HFP also decreased 15 minutes before VT compared with 2 hours (from 4.78 ± 1.05 to 4.49 ± 1.24 , $P = .028$) (Figure 2).

In group B, which had lower baseline TP/5, LFP, and LFP/HFP at 2 hours before VT, these variables increased 15 minutes before the event (TP/5 from 6.41 ± 1.41 to 6.86 ± 1.42 , $P = .004$; LFP from 4.59 ± 1.51 to 4.95 ± 0.62 , $P < .001$; LFP/HFP from 0.22 ± 1.22 to 0.52 ± 1.38 , $P = .10$), whereas HFP did not change significantly (4.40 ± 0.94 and 4.53 ± 1.01 , $P = .50$).

Discussion

Comparison with previous studies

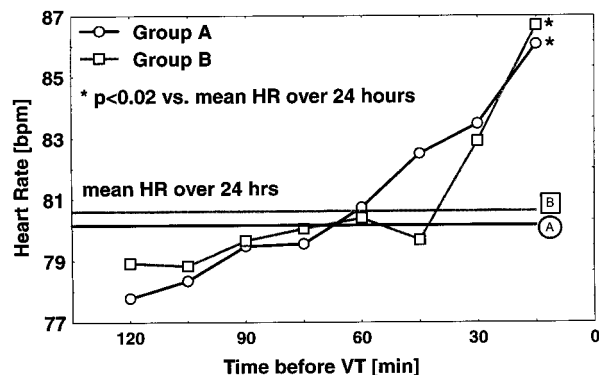
The major finding of this study was the observation that the low frequency, beat-to-beat oscillations of R-R

intervals paradoxically decreased before the onset of ventricular tachycardia in patients with a high baseline level of oscillatory activity. The average heart rate and its increase preceding VT were not different between the patients with a decline in LFP (68% of patients) and the rest of the group. Therefore the drop in LFP cannot be directly linked to a rise in heart rate before the onset of arrhythmia.

A traditional paradigm associates an increase in the sympathetic activity with an increase in the sympathetically modulated low-frequency oscillations of R-R intervals. In normal individuals, conditions that enhance sympathetic tone, including tilt-table testing and exercise, usually produce an increase in LFP.³² However, in patients with congestive heart failure and chronically enhanced sympathetic activity, a further increase in sympathetic tone during head-up tilting causes a paradoxical drop in LFP.¹⁸ Moreover, LFP is reduced in patients with advanced congestive heart failure and high levels of circulating catecholamines.¹⁶ Direct microneurographic measurements of muscular sympathetic nervous activity verify the relation between high muscular sympathetic activity and the loss of the low-frequency oscillations of R-R intervals.^{16,17} In agreement with our findings, previous investigations reported that the changes in LFP were associated with relatively small changes in HFP.^{16,17} Thus the decline of LFP observed in this study is consistent with the previous observations of this phenomenon in patients with abnormally high chronic levels of sympathetic tone.

Direct microneurographic measurements to confirm changes in sympathetic activity or analysis of circulating catecholamines were not obtained in the ESVM trial. The R-R interval variability indexes provide only inferential evidence regarding the changes in autonomic tone, and the accuracy of this analysis depends

Figure 1



Changes in heart rate in 2 hours preceding sustained VT.

on a variety of factors.³¹ Therefore the increase in sympathetic activity cannot be definitively proved with our results. However, we consider the changes in sympathetic activity as the most probable cause of the selective drop in LFP because of the following facts:

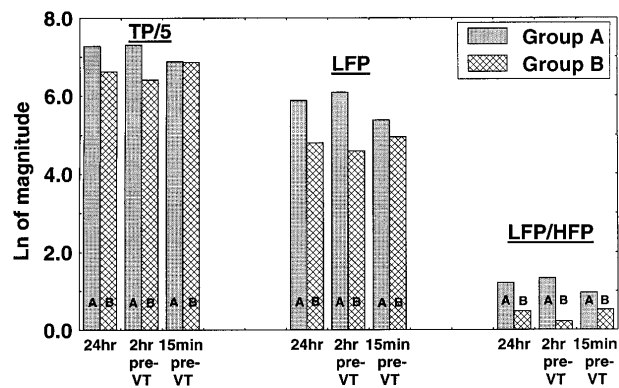
(1) Heart rate increased before the onset of arrhythmia in the majority of patients in this study and in several previous studies, which suggests a rise in sympathetic activity.^{1,2} The sympathetic predominance preceding VT could also result from withdrawal of parasympathetic activity or combined increase in sympathetic activity and a decrease in vagal tone. Although the fall in LFP/HFP observed in this study does not indicate a decrease in vagal activity, the absolute HFP decreased, and therefore the possibility of parasympathetic withdrawal cannot be excluded.

(2) Patients participating in this study had poor left ventricular function, which is usually associated with chronically high levels of circulating catecholamines and enhanced frequency of discharge in the sympathetic nerves.^{16,18,33}

(3) No clinical or heart rate characteristic distinguished patients with a pre-VT decrease in LFP from the rest of the group. However, those with a drop in LFP had significantly higher 24-hour and 2-hour levels of LFP, VLFP/5, TP/5, and LFP/HFP. Thus the patients with high baseline levels of the low-frequency oscillatory activity lost it immediately before the arrhythmia when the heart rate and, presumably, sympathetic activity increased.

Although the number of patients was higher than in previous studies, the failure to detect significant differences between clinical characteristics of the subgroups still could have resulted from a β -error. The proportion of patients with SAS class 3 or 4 was slightly higher and left ventricular ejection fraction tended to be lower in group B (Table I). Other authors have noted a correla-

Figure 2



Natural logarithms of TP/5, LFP, and LFP/HFP are depicted for patient groups A and B. Over entire recording, values for all 3 variables were higher in group A than in group B. During 2 hours before VT, these differences became greater as values in group A increased, whereas those in group B decreased. In 15 minutes before VT onset, values (with previous 2 hours used as baseline) decreased in group A but increased in group B.

tion between HRV variables and the degree of physiologic impairment in diverse patient groups including those with CHF,^{16,33,34} aortic valve disease,³⁵ idiopathic dilated cardiomyopathy,³⁶ and hypertrophic cardiomyopathy.³⁷ Therefore lower average HRV values in group B could have resulted from greater impairment of cardiac function. Blunted HRV responses to autonomic perturbations were observed in patients with moderate congestive heart failure.¹⁸ Thus despite similarity of clinical characteristics, greater impairment of cardiac function in group B patients could be at least partially responsible for the differences in HRV trends preceding the onset of VT.

The differences between the groups could have resulted from different treatments, in particular, β -blocker therapy in some patients from group A. However, exclusion of these patients from the analysis did not change the observed trends or statistical significance of the results. The observed pattern of changes in LFP could be related to circadian variations in the frequency of ventricular tachyarrhythmias and HRV.^{38,39} In this group, the frequency of VT increased during the day compared with night, and the incidence of VT was higher during the daytime in patients with higher average LFP and LFP/HFP. This finding is consistent with the theory about the role of diurnal increase in sympathetic activity in arrhythmogenesis. However, as a rule, LFP increases or does not change in patients with congestive heart failure or cardiac arrest during the day and probably does not account for the drop in LFP preceding VT.³⁹⁻⁴¹

Probable mechanisms of decline in slow oscillations of R-R intervals preceding VT

Despite wide popularity of spectral HRV indexes as indicators of cardiovascular autonomic control, the relations between tonic (average) and rhythmic components of autonomic modulation are not well understood.^{19,20} The 2 facets of the autonomic activity exhibit concordant responses to moderate stimulation in controlled conditions including moderate physical exercises, awakening, and head-up tilt.^{32,42-44} However, the facets of autonomic activity can become dissociated at extreme levels of autonomic stimulation. Discordant rhythmic and tonic parasympathetic reactions were observed in a study of vagal nerve stimulation.⁴⁵ Goldberger et al²¹ reported an inverse relation between the baseline HRV and its ability to increase in response to stimulation of parasympathetic activity. Similar relations were observed between resting levels of vasomotor activity and its reaction to mental stress.²² Direct stimulation of the sympathetic nerves at frequencies above 0.5 Hz did not affect the HRV indexes of sympathetic tone.⁴⁶

Huikuri et al¹⁰ described an inverse correlation between the length of VT episode and the total HRV power before the event: The frequency components of HRV were lower before the onset of sustained VT compared with nonsustained ventricular runs.¹⁰ In agreement with this finding, patients from group B in our study had lower HRV, whereas index VT in this group tended to be longer (Table I). Zimmermann et al¹ also noted a correlation between the duration of arrhythmic episodes and the level of sympathetic stimulation as reflected by heart rate 3 minutes before the event. These findings suggest that sympathetic activity is higher, whereas rhythmic modulation of HRV indexes is reduced before the onset of sustained VT.

The differences in baseline autonomic tone, as was recently stressed by Goldberger et al,²¹ might elucidate the discrepant results of HRV analysis preceding VT in different populations.¹⁰⁻¹⁵ Our results were obtained in a relatively large, homogeneous group of patients with severely impaired cardiac function (left ventricular ejection fraction $36\% \pm 15\%$) and frequent arrhythmias, which are often associated with enhanced sympathetic tone. Moreover, unlike previous studies, this investigation targeted only sustained VT, which is, presumably, preceded by larger increment of sympathetic activity compared with nonsustained ventricular runs. These characteristics of our patient population could have affected the results of this study. Nevertheless, the findings of an increase in heart rate and predominant drop in LFP in patients with relatively preserved HRV before the onset of VT are consistent with the trends in these variables that were reported by other investigators.^{10,12,15}

Several uncontrolled factors, including changes in activity, posture, and respiration frequency, can obscure analysis of HRV in ambulatory recordings. This pre-

cludes mechanistic interpretation of the observed changes in HRV as a result of selective increase in sympathetic activity before the onset of VT. Furthermore, it is likely that a number of other factors participate in arrhythmogenesis. However, as a rule, changes in activity or posture cause an increase in LFP, and changes in respiration frequency primarily affect HFP. On the contrary, we observed a pattern of increasing heart rate, dropping LFP, and relatively small changes in HFP as manifested by a decrease in LFP/HFP, which cannot be a mere result of changes in activity or respiration per se. Moreover, similar patterns were observed in previous investigations of VT in different patient populations.^{10,12,15} Therefore we believe that the observed changes represent important autonomic perturbations that are related to the initiation of arrhythmias.

Limitations

The patients in this study were a highly selected population,^{23,26} and our findings cannot be applied to all patients with VTs. The subjects whose initial arrhythmias were fatal and those with hemodynamically unstable arrhythmias that required continuous suppression could not participate in the study. The fact that a sustained arrhythmia occurred during Holter monitoring favored patients with frequent arrhythmic events. However, the changes in heart rate and R-R interval variability were not related to the number of arrhythmic events that a patient had. The patients made up approximately 10% of the patients screened for the ESSEM trial, and clinical characteristics did not differentiate the patients with spontaneous arrhythmias. This suggests that the major results of the current investigation are valid for other patients with recurrent ventricular tachycardia as well.

The changes in heart rate preceding VT violate the assumption of stationarity of the signal and might obscure the results of spectral analysis.²⁰ However, the increase in heart rate was modest (4.9 beats/min), which suggests that the changes in heart rate did not have a significant impact on the HRV estimates. Application of the Hanning window before spectral analysis also reduced the effects of nonstationarities and discontinuities on the results.

Regression artifact may introduce a significant confounding effect on the results of studies that do not have a control group. Regression to the mean was estimated as $P_{rm} = 100 * (1-r)$, where P_{rm} is the percentage of regression to the mean and r is a correlation between the HRV values at 2 hours and 15 minutes before VT.⁴⁷ Because the correlation between the values at 2 hours and 15 minutes before VT was high (LFP 0.85, LFP/HFP 0.71), P_{rm} could account, in the worst case, for two thirds of the HRV changes in group A. Thus regression artifact could obscure the magnitude of changes in HRV, but it could not be the sole source for pronounced changes in LFP and LFP/HFP preceding the onset of VT in group A.

Conclusions

An increase in heart rate and a drop in the low-frequency oscillations of R-R intervals before the onset of VT occurred in patients with higher baseline levels of oscillatory activity. These changes suggest a dissociation between the average and rhythmic modulation of R-R intervals in most of the patients from the studied group. The different behaviors of the HRV indexes before the onset of VT in the 2 groups suggest that change in the dynamics of R-R intervals rather than the direction of change facilitates arrhythmogenesis.

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