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Autonomic Changes Associated With Spontaneous Coronary Spasm in Patients With Variant Angina

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Objectives. **This study sought to investigate whether changes in nervous autonomic tone may have a role in the mechanisms triggering spontaneous coronary spasm in variant angina.**

Background. **Previous studies have suggested that both sympathetic and vagal activation may act as a trigger of epicardial artery spasm in patients with variant angina, but the actual role of autonomic changes in spontaneous coronary spasm remains unknown.**

Methods. **We analyzed the changes in heart rate variability associated with episodes of ST segment elevation detected on Holter monitoring in 23 patients with variant angina (18 men, 5 women; mean [±SD] age 59 ± 12 years). For study purposes, episodes of transmural ischemia lasting ≥3 min and without any ST segment changes in the previous 40 min were selected for analysis. Heart rate variability indexes were calculated at 2-min intervals, at 30, 15, 5 and 1 min before ST elevation and at peak ST segment elevation. Ninety-three of 239 total ischemic episodes (39%) fulfilled the inclusion criteria.**

Results. **The results showed that 1) high frequency (HF) (0.04 to 0.15 Hz), a heart rate variability index specific for vagal activity, decreased in the 2 min preceding ST segment elevation ($p < 0.001$) and returned to basal levels at peak ST segment elevation; 2) heart rate and low frequency (0.04 to 0.15 Hz), which are partially correlated with sympathetic activity, showed a significant increase at peak ST segment elevation ($p < 0.001$ for both); 3) the pattern of the HF reduction before ST segment elevation was consistently confirmed in several subgroups of ischemic episodes, including those of patients with or without coronary stenoses, those of patients with anterior or inferior ST segment elevation, those occurring during daily or nightly hours and silent episodes. There were no significant variations in heart rate variability in control periods selected from Holter tapes of patients and before ST segment elevation induced by balloon inflation in 20 patients undergoing coronary angioplasty.**

Conclusions. **Our data show that changes in autonomic tone are likely to contribute to trigger or predispose to epicardial spasm. In particular, although not excluding an active role for adrenergic mechanisms, our data suggest that a vagal withdrawal may often be a component of the mechanisms leading to spontaneous coronary vasospasm.**

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Prinzmetal's variant angina (1) is due to a primary reduction in myocardial blood flow caused by epicardial coronary spasm (2,3) and is characterized by anginal pain occurring at rest and associated with ST segment elevation on the electrocardiogram (ECG). Coronary spasm has been well characterized both clinically and angiographically (2–6), but despite this characterization, its pathophysiologic substrate is still unknown (7,8), as is the stimulus or stimuli that can trigger the spasm in these patients.

Acute arousal of both adrenergic (9,10) and vagal (11,12) nervous autonomic tone has been suggested to be implicated, but, as opposed to stable angina (13,14), no significant changes in heart rate have been found in the minutes preceding ischemia in variant angina (6,15). Nevertheless, heart rate could not be sensitive enough to identify minor or selective autonomic changes; moreover, simultaneous and parallel variations in the sympathetic and parasympathetic systems could result in a stable heart rate. Several studies have recently demonstrated that analysis of heart rate variability is a simple and reliable tool for assessing the state and variations in the autonomic nervous system (16–18), with relevant prognostic implications for patients with myocardial infarction (19,20) or at risk for sudden death (21).

We therefore investigated whether variations in autonomic tone may play a role in the induction of epicardial spasm in patients with variant angina by assessing the changes of frequency domain indexes of heart rate variability before and during spontaneous ischemic episodes detected on ECG Holter recordings in a group of such patients.

Methods

Patients. Twenty-three patients with a diagnosis of typical variant angina (18 men, 5 women; mean [±SD] age 59 ± 12 years) were included in the study. All patients had anginal pain

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Abbreviations and Acronyms

ANOVA = analysis of variance
ECG = electrocardiogram, electrocardiographic
HF = high frequency
LF = low frequency

occurring at rest, usually lasting only few minutes, highly sensitive to sublingual nitrates and associated with transient ST segment elevation in one or more standard ECG leads. ST segment elevation was located in anterior (or anterolateral) leads in 16 patients (70%) and in inferior (or inferolateral) leads in 7 (30%). All patients had their chest pain and ST segment elevation reproduced by either hyperventilation, ergonovine (intravenous or intracoronary) or intracoronary serotonin administration. In particular, 16 patients underwent provocative tests during coronary angiography, and occlusive epicardial spasm was induced in all 16. Coronary angiography after intracoronary injection of nitroglycerin showed the absence of hemodynamically significant stenoses (defined as a reduction in internal lumen diameter >50%) in 10 patients (43%) and their presence in at least one epicardial vessel in 13 (57%). No patient had a history of myocardial infarction or basal alterations on the ECG that could interfere with ST segment analysis. Furthermore, all patients had normal global and regional left ventricular function on echocardiographic examination.

Holter monitoring. All patients underwent 24-h Holter monitoring using two-channel tape recorders (Oxford Medilog 4500). In each patient the CM_5 lead was always recorded on the first channel, whereas the lead most similar to that of the standard ECG showing the maximal ST segment changes during angina was selected for monitoring on the second channel (CM_3 or CM_2 for anterior and a modified aVF lead for inferior ST segment elevation). All patients were admitted to the hospital and had continuous ECG telemetric monitoring. Holter monitoring was carried out completely off therapy, except for sublingual nitrates, which were allowed to relieve anginal pain. Patients were invited to keep a detailed diary of their activities and symptoms. The recordings were analyzed by two expert cardiologists using the Oxford Medilog Excel 2.0 device. ST segment elevation was considered as significant if it occurred ≥1 mm after 0.08 s from the J point and lasted ≥1 min.

Heart rate variability. For accurate evaluation of the relation between heart rate variability and ST segment changes, only the ischemic episodes fulfilling the following inclusion criteria were selected for analysis: 1) absence of any ST segment or T wave changes, or both, in the 40 min preceding ST elevation; 2) duration of ST segment elevation ≥3 min (to have a reliable measure of heart rate variability at peak ST segment elevation; 3) absence of any significant arrhythmias or artifacts that could alter the measure of heart rate variability. The mean RR interval (in ms) and the standard deviation of

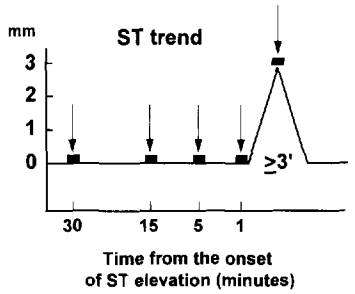

Figure 1. Method used to evaluate changes in heart rate variability associated with episodes of ST segment elevation. Heart rate variability was measured at 2-min intervals (**squares**) at 30, 15, 5 and 1 min before and at peak ST segment elevation. Ischemic episodes included in the analysis were ≥3 min in duration.

RR intervals (in ms) were obtained as time domain measures of heart rate variability. Frequency domain heart rate variability was evaluated in the range of frequencies from 0 to 0.5 Hz by means of fast Fourier transform spectral analysis, with a spectral resolution of 0.0005 Hz, using the Oxford heart rate variability analysis package 7.0, which is provided with the Holter Excel 2.0 Oxford Medilog system. The values of the deviation (i.e., amplitude) of low frequency (LF) (0.04 to 0.15 Hz, in ms) and of high frequency (HF) (0.15 to 0.40 Hz, in ms) and the LF/HF ratio, as an index of sympathovagal balance (17,18,22), were obtained for each of the periods analyzed. The heart rate variability indexes were calculated at 2-min intervals, at 30, 15, 5 and 1 min before onset of ST segment elevation and at peak ST segment elevation (Fig. 1). Heart rate variability analysis was performed for all ischemic episodes and separately for the following subgroups: 1) episodes occurring in patients with and those occurring in patients without hemodynamically significant coronary stenoses; 2) episodes occurring in patients with anterior and those occurring in patients with inferior ST segment elevation; 3) episodes occurring during diurnal (7 AM to 10 PM) or nocturnal (11 PM to 6 AM) hours; 4) episodes associated (symptomatic) or not associated (silent) with angina.

Control periods. Control periods were obtained from the Holter tapes of each patient. To this end we randomly selected, for each tape, three reference time points without any ST segment alteration in the previous 40 min and in the following 10 min, which were considered equivalent to the onset of ischemic episodes. Heart rate variability analysis was performed for 2-min periods, at 30, 15, 5 and 1 min before the reference points, similar to that done for the ischemic episodes. The equivalent of the peak of the ischemic episodes was fixed at 3 min after the reference times. This time was selected because it was nearly equal to one-half of the mean duration of ischemic episodes.

Changes in heart rate variability were also assessed in a second control group of 20 patients (16 men, 4 women; mean [±SD] age 59 ± 9 years) with chronic stable angina and one-vessel disease at coronary angiography who underwent coronary angioplasty and developed ST segment elevation

Table 1. Changes in Heart Rate Variability Indexes Associated With 93 Episodes of ST Segment Elevation in 23 Patients With Variant Angina

	30'B	15'B	5'B	1'B	Peak ST
RR interval (ms)	915 ± 175	904 ± 190	905 ± 168	888 ± 183	184 ± 157†
SD (ms)	44.2 ± 24	46.3 ± 25	43.0 ± 25	46.0 ± 28	62.6 ± 41†
LF (ms)	21.7 ± 14	23.3 ± 19	19.9 ± 13	19.6 ± 13	25.5 ± 17*
HF (ms)	15.2 ± 8	16.8 ± 11	15.5 ± 10	13.3 ± 8‡§	15.4 ± 10
LF/HF	1.70 ± 1.0	1.64 ± 1.3	1.54 ± 1.1	1.69 ± 0.9	1.86 ± 1.1

*$p < 0.05$, †$p < 0.01$ versus all other data points. ‡$p < 0.01$ versus 15 and 5 min before ST segment elevation. §$p < 0.05$ versus 30 min before ST segment elevation and peak ST segment elevation. Data presented are mean value ± SD. 'B = minutes before ST segment elevation; HF = high frequency; LF = low frequency; Peak ST = peak ST elevation; SD = standard deviation of RR intervals.

during balloon inflation. All 20 patients had no history of myocardial infarction and had normal standard ECG results and normal left ventricular function on echocardiography. Coronary angioplasty was performed in the left anterior descending coronary artery in 13 patients, the right coronary artery in 6 and the left circumflex artery in 1. Patients were withdrawn from antiischemic drugs 3 days before the procedure, but aspirin was continued, and sublingual nitrates were administered to relieve chest pain.

Heart rate variability indexes were obtained before and during angioplasty-induced ST segment elevation at the same points and with the same procedure as that described for patients with variant angina. However, heart rate variability during ischemia was measured starting from the onset of ST segment elevation after the first inflation because of the shorter duration of ischemic changes in these patients (90 to 120 s).

Statistical analysis. The changes associated with ischemic episodes of the RR interval were evaluated by analysis of variance (ANOVA) with a repeated measures design. The nonparametric ANOVA Friedman test was applied to evaluate the changes of the other heart rate variability indexes because they all showed a statistical distribution significantly different from the normal one, as assessed by the Kolmogorov-Smirnov test. In case of global statistical significance, either a paired *t* test with Bonferroni correction or an appropriate nonparametric ANOVA Friedman-derived test (23) was applied, as indicated, to assess the changes in heart rate variability in the 2 min immediately preceding ST elevation versus 30, 15 and 5 min before ischemia, or the changes in heart rate variability at peak ST segment elevation versus all other data points. The Fisher exact test and unpaired *t* test were used to compare discrete and continuous variables between subgroups, respectively. The proportions of ischemic episodes with the lowest HF value at the different time points before ischemia were compared by the goodness of fit chi-square test. Results are reported as mean value ± SD, unless otherwise indicated; $p < 0.05$ was considered statistically significant.

Results

On the whole, 239 episodes of ischemic ST segment elevation were detected in the 23 patients during 24-h Holter monitoring, 51 of which (21.3%) were symptomatic. Of the 239 ischemic episodes, 136 (57%) were first excluded because there were ischemic changes in the 40 min preceding their onset and two episodes because their duration was <3 min; another eight episodes (3%) were excluded because there were significant bradyarrhythmias or tachyarrhythmias during ST segment elevation. Therefore, 93 episodes (39%) met the inclusion criteria for the study (mean 4 ± 3.3 episodes/patient, range 1 to 12), 27 of which (29%) were associated with angina. The duration of these episodes was 5.7 ± 3.6 min, and the extent of the ST segment elevation was 2.5 ± 1.3 mm (range 1 to 4).

Heart rate variability. Table 1 summarizes the changes in heart rate variability indexes observed in relation to all 93 episodes included in the study. The RR interval did not change before ST segment elevation, whereas it decreased significantly (i.e., heart rate increased) at peak ST segment elevation, when the standard deviation of RR intervals showed a significant increase (Fig. 2, left). Spectral analysis showed a significant

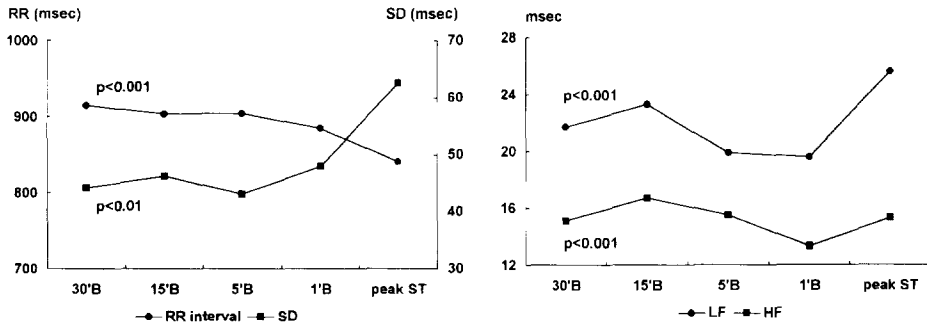

Figure 2. Changes in RR interval and standard deviation (SD) of RR intervals **(left)** and changes in LF and HF amplitude **(right)** associated with 93 episodes of ST segment elevation detected in 23 patients with variant angina. Global statistical significance by ANOVA for repeated measures (RR interval) or ANOVA Friedman test (standard deviation of RR intervals, LF, HF) is shown. See Table 1 for differences among data points. B = before ST segment elevation.

Table 2. Distribution of Ischemic Episodes With Lowest Frequency Value Immediately Before ST Segment Elevation in Individual Patients

Pt No.	No. of Episodes Analyzed	No. (%) of Episodes With Lowest HF Value in 2 min Before ST Elevation
1	2	2 (100)
2	4	2 (50)
3	3	0 (0)
4	11	3 (27)
5	1	0 (0)
6	2	1 (50)
7	3	1 (33)
8	3	3 (100)
9	3	2 (67)
10	5	4 (80)
11	11	5 (45)
12	1	0 (0)
13	5	1 (20)
14	1	0 (0)
15	1	0 (0)
16	5	1 (20)
17	2	1 (50)
18	7	5 (71)
19	2	1 (50)
20	12	6 (50)
21	3	1 (33)
22	5	2 (40)
23	1	0 (0)

HF = high frequency; Pt = patient.

decrease in the HF component in the 2 min preceding the onset of ischemia, with a return to basal levels at peak ST segment elevation, whereas the LF component did not show any significant changes before ischemia, but increased at peak ST segment elevation (Fig. 2, right). There were no significant changes in LF/HF ratio. The analysis of individual episodes showed that the HF component had its lowest value 30 min before ischemia in 21 episodes (23%), 15 min before ischemia in 14 (15%), 5 min before ischemia in 17 (18%) and immediately before ischemia in 41 (44%) episodes (chi-square 19.2, $p < 0.001$). The pattern characterized by HF component decrease immediately before ischemia was found in at least one episode in 17 (74%) patients, whereas it was absent in 6. However, five of these latter patients had only one episode selected for study (Table 2).

Subgroup analysis. The main findings of the episodes detected in subgroups considered for separate analysis are summarized in Table 3, whereas the heart rate variability results are shown in Tables 4 and 5. A reduction in the HF component in the 2 min immediately preceding ST elevation was consistently found in all subgroups (Fig. 3), although the changes did not attain statistical significance in the subgroup of symptomatic episodes.

The analysis of the results also showed some differences among the subgroups of ischemic episodes: 1) a considerable increase at peak ST segment elevation in both the LF component and LF/HF ratio was observed only in the episodes of ST segment elevation that occurred in inferior but not anterior leads; 2) significant changes in the LF component were also found in nocturnal and silent, but not in diurnal and painful episodes; 3) finally, a significant increase in heart rate at peak ST segment elevation was absent only in the group of episodes associated with angina.

Control periods (Table 6). No changes in RR interval and heart rate variability were observed throughout the 69 control periods (3/patient) selected from the Holter recordings of the patients. Similarly, no changes in heart rate variability indexes were associated with angioplasty-induced ST segment elevation, except for a mild reduction in RR interval during ischemia.

Discussion

The most important finding of this study is that in patients with variant angina, a reduction in the HF component indicating a decrease in vagal activity (16–18,22) often occurs in the 2 min immediately preceding the ECG appearance of myocardial ischemia, suggesting either that it is part of the mechanisms that trigger spontaneous coronary spasm or that it is a condition that facilitates or predisposes to the induction of spasm by other vasoconstrictor agents (24–26). The average decrease in HF component before ST segment elevation was

Table 3. Main Characteristics of Episodes of ST Segment Elevation in Subgroups Considered for Analysis

Subgroup	No. of Episodes	No. of Pts	ST Elevation (mm)*	Duration (min)*	No Stenosis/ Stenosis†	Anterior/ Inferior†
No stenosis	50	10	2.4 ± 0.9	5.6 ± 3.0		25/25‡
Stenosis	43	13	2.6 ± 1.8	5.9 ± 4.3		31/12
Anterior	56	16	2.9 ± 1.5§	5.9 ± 4.1	25/31‖	
Inferior	37	7	1.8 ± 0.7	5.5 ± 3.0	25/12	
Day	50	19	2.5 ± 1.5	5.9 ± 1.5	24/26	31/12
Night	43	18	2.4 ± 1.3	5.6 ± 3.7	26/17	23/20
Silent	67	20	2.5 ± 1.5	6.0 ± 4.1	35/32	40/27
Painful	26	12	2.5 ± 1.2	5.1 ± 2.6	15/11	16/10

*Mean value ± SD. †Number of episodes. ‡$p < 0.05$ versus subgroup with stenosis. §$p < 0.01$, ‖$p < 0.05$ versus inferior ST segment elevation. Pts = patients.

Table 4. Heart Rate Variability Index Changes Associated With Ischemic Episodes Detected in Patients With Variant Angina With or Without Significant Coronary Artery Stenoses and With Anterior or Inferior ST Segment Elevation

	30′B	15′B	5′B	1′B	Peak ST
RR interval (ms)					
No stenosis	957 ± 171	957 ± 168	961 ± 155	937 ± 171	888 ± 130‡
Stenosis	865 ± 170	842 ± 196	841 ± 162	826 ± 175	785 ± 169‡
Anterior	891 ± 193	878 ± 215	878 ± 176	864 ± 201	797 ± 168‡
Inferior	950 ± 141	943 ± 134	949 ± 128	919 ± 140	906 ± 114‡
SD (ms)					
No stenosis	41.1 ± 24	45 ± 26	36.7 ± 19	45.2 ± 31	66.7 ± 50†
Stenosis	47.6 ± 23	48.2 ± 22	50.9 ± 30	51.3 ± 29	57.9 ± 30
Anterior	42.8 ± 22	43.5 ± 17	43.2 ± 17	44.1 ± 29	55.7 ± 32†
Inferior	46.1 ± 26	50.9 ± 31.9	43.4 ± 23	53.9 ± 31	73.0 ± 52†
LF (ms)					
No stenosis	18.8 ± 12	19.9 ± 15	16.6 ± 9	16.0 ± 7	26.5 ± 19†
Stenosis	25.1 ± 16	27.1 ± 22	23.8 ± 16	23.8 ± 17	24.4 ± 15
Anterior	20.6 ± 12	20.7 ± 13	21.8 ± 14	20.1 ± 14	21.6 ± 15
Inferior	23.3 ± 16	27.1 ± 25	17.1 ± 11	18.8 ± 11	31.5 ± 19†
HF (ms)					
No stenosis	14.3 ± 80	17.1 ± 12	14.9 ± 10	13.1 ± 9*	15.9 ± 11
Stenosis	16.0 ± 8	16.4 ± 9	16.2 ± 9	13.6 ± 6§‖	14.7 ± 8
Anterior	13.3 ± 6	14.5 ± 9	14.4 ± 8	12.4 ± 7*	17.4 ± 11
Inferior	18.0 ± 11	20.3 ± 12	17.2 ± 11	14.8 ± 9†	17.8 ± 11
LF/HF					
No stenosis	1.61 ± 1.0	1.37 ± 0.7	1.40 ± 0.8	1.62 ± 1.0	1.92 ± 1.3
Stenosis	1.81 ± 1.1	1.96 ± 1.8	1.71 ± 1.3	1.78 ± 0.9	1.79 ± 0.9
Anterior	1.76 ± 1.0	1.67 ± 0.8	1.71 ± 1.1	1.76 ± 1.0	1.71 ± 1.0
Inferior	1.61 ± 1.1	1.61 ± 1.9	1.29 ± 0.9	1.60 ± 0.9	2.1 ± 1.0†

*$p < 0.05$, †$p < 0.01$, ‡$p < 0.001$ versus all other data points. §$p < 0.01$ versus 30, 15 and 5 min before ST segment elevation. ‖$p < 0.05$ versus peak ST segment elevation. Data presented are mean value ± SD. Abbreviations as in Table 1.

consistently confirmed in several subgroups of ischemic episodes, including those occurring in patients with or without coronary stenoses, those occurring in patients with anterior or inferior ST elevation, those detected during diurnal or nocturnal hours and painless and painful episodes, although in this latter group it did not reach statistical significance, most likely because of the low statistical power due to the small number of episodes. Analysis of single episodes showed that the trend of the decrease in HF component before ischemia was substantially patient independent. Indeed, this pattern occurred in at least one episode in 74% of patients, with a proportion varying from 20% to 100%.

Our results differ from those of a previous study (27) in which an increase in both LF and HF components in the minutes preceding ST segment elevation was reported. However, only seven episodes were included in that study, and spectral analysis was performed for longer periods (~4 min), with an unusual range for the HF component (0.22 to 0.32 Hz).

Pathophysiologic mechanisms. Many pathogenetic hypotheses have been proposed to explain the increased susceptibility to coronary spasm of patients with variant angina, but both the basilar mechanisms predisposing to spasm and the stimulus (or stimuli) that can trigger spontaneous spasm in the hyperreactive coronary artery segment remain unknown (28).

Acute variations in nervous autonomic tone have been suggested (9–12) to be implicated in the induction of coronary spasm for many years. Some studies (29–32) have suggested that an arousal in sympathetic activity can be a major determinant of coronary spasm, but others have denied this hypothesis (33,34).

In contrast, the higher incidence of anginal attacks during sleep in most patients (35,36) and the possibility of inducing coronary spasm with cholinergic drugs (37–39) suggested a role for a vagal activation. However, the exogenous administration of vagomimetic substances to provoke spasm (37,38) can result in high, nonphysiologic intracoronary concentrations that may not occur in the clinical setting; furthermore, ischemic episodes occurring in the night could actually be triggered by transient adrenergic predominance or activation (e.g., during rapid eye movement [REM] sleep phases [40]) rather than by vagal activation. Indeed, the possible upregulation of adrenergic vascular receptor during a condition of low sympathetic activity during sleep could facilitate sensitivity to adrenergic-induced vasoconstriction (41). Moreover, vagal stimulation is known to normally induce coronary vasodilation (42,43), an effect that seems to be mainly mediated by the release of endothelium-derived relaxing factor (39), whereas vagotomy can result in coronary artery constriction (43).

As previously stated, the trend toward a decrease in HF before ischemia in our patients suggests that vagal withdrawal, rather than vagal activation, may be a more frequent component involved in the mechanisms leading to spontaneous

Table 5. Heart Rate Variability Index Changes Associated With Ischemic Episodes Detected in Patients With Variant Angina Occurring During Diurnal or Nocturnal Hours and Associated or Not Associated With Anginal Pain

	30′B	15′B	5′B	1′B	Peak ST
RR interval (ms)					
Day	877 ± 201	861 ± 223	861 ± 185	843 ± 202	804 ± 170
Night	958 ± 129	955 ± 124	958 ± 130	936 ± 137	883 ± 130‡
Silent	919 ± 169	919 ± 169	911 ± 166	889 ± 179	831 ± 164‡
Painful	905 ± 194	865 ± 231	893 ± 175	877 ± 187	866 ± 139
SD (ms)					
Day	40.8 ± 20	41.9 ± 20	38.9 ± 18	37.0 ± 17	49.7 ± 32*
Night	48.0 ± 27	51.8 ± 28	48.4 ± 32	60.8 ± 36	77.7 ± 47†
Silent†	45.7 ± 26	49.0 ± 26	43.7 ± 27	50.2 ± 30	62.2 ± 45
Painful	40.1 ± 17	39.8 ± 16	42.3 ± 20	42.4 ± 29	63.6 ± 31
LF (ms)					
Day	20.6 ± 13	21.6 ± 19	19.9 ± 13	17.8 ± 10	22.1 ± 15
Night	23.0 ± 15	25.1 ± 18	19.9 ± 13	21.6 ± 15	29.6 ± 19†
Silent	23.1 ± 15	25.5 ± 21	20.2 ± 14	20.2 ± 14	24.2 ± 16†
Painful	18.1 ± 10	17.6 ± 9	19.1 ± 12	18.1 ± 8	29.2 ± 21
HF (ms)					
Day	14.0 ± 8	15.5 ± 10	15.0 ± 10	11.7 ± 6§‖	13.6 ± 9
Night	16.5 ± 9	18.3 ± 12	16.2 ± 10	15.2 ± 10*	17.4 ± 11
Silent	16.0 ± 9	18.3 ± 12	16.4 ± 10	13.9 ± 9¶#	15.0 ± 9
Painful	12.9 ± 6	12.9 ± 6	13.2 ± 8	11.9 ± 6	16.4 ± 12
LF/HF					
Day	1.74 ± 1.0	1.69 ± 1.7	1.63 ± 1.2	1.71 ± 0.9	1.93 ± 1.4
Night	1.65 ± 1.1	1.58 ± 0.8	1.44 ± 0.9	1.68 ± 1.0	1.77 ± 0.7
Silent	1.73 ± 1.1	1.70 ± 1.5	1.50 ± 1.1	1.70 ± 1.0	1.77 ± 0.9
Painful	1.61 ± 0.8	1.55 ± 0.7	1.65 ± 1.1	1.69 ± 0.7	2.10 ± 1.4

*$p < 0.05$, †$p < 0.01$, ‡$p < 0.001$ versus all other data points. §$p < 0.05$ versus 15 and 5 min before ST segment elevation. ‖$p < 0.05$ versus 30 min before ST segment elevation and peak ST elevation. ¶$p < 0.05$ versus 15 min before ST segment elevation. #$p < 0.05$ versus 30 and 5 min ST segment elevation. Data presented are mean value ± SD. Abbreviations as in Table 1.

coronary spasm in variant angina. During ischemia, however, we observed a simultaneous increase in vagal and sympathetic activity that was indicated, respectively, by the return to basal values at peak ST segment elevation of the HF component and by the significant increase in heart rate (which should actually be decreased after vagal activation). The stimulation of cardiac

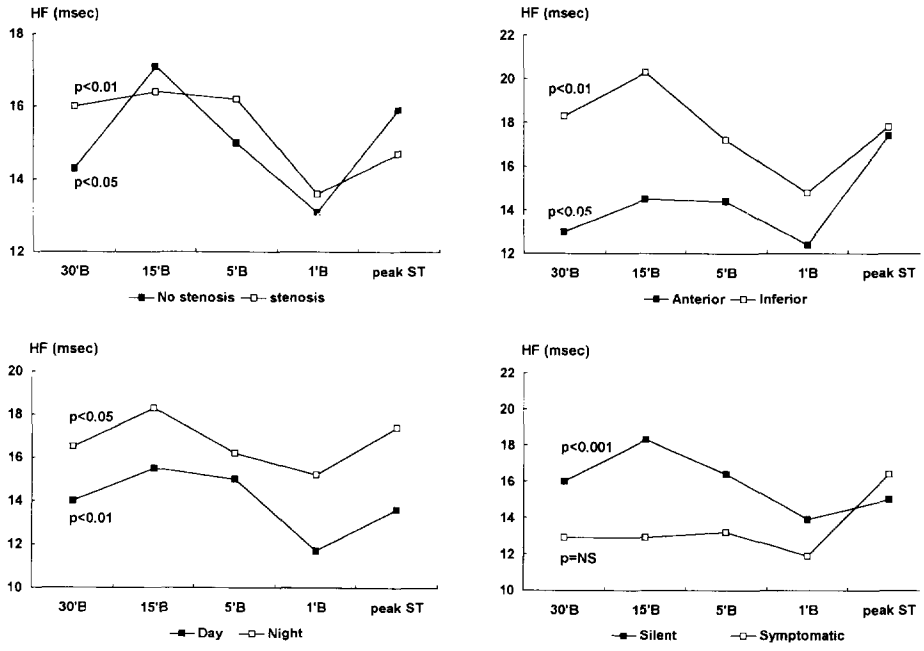

Figure 3. Changes in HF amplitude associated with episodes of ST segment elevation in patients with variant angina with or without significant coronary stenoses at angiography **(top left)**; patients with anterior or inferior ST segment elevation on the standard ECG **(top right)**; occurring during diurnal or nocturnal hours **(bottom left)**; and associated or not associated with angina **(bottom right)**. Global statistical results by nonparametric ANOVA Friedman test are shown. See Tables 4 and 5 for statistical differences among data points. B = before ST segment elevation.

Table 6. Heart Rate Variability Index Changes Associated With Control Periods Obtained in Patients With Variant Angina and in 20 Patients Undergoing Coronary Angioplasty

	Control Periods in Variant Angina (mean ± SD)			Coronary Angioplasty (mean ± SD)		
	30'B	1'B	Peak ST	30'B	1'B	Peak ST
RR interval (ms)	875 ± 189	874 ± 204	880 ± 198	933 ± 260	888 ± 272	838 ± 231*
SD (ms)	42.2 ± 26	45.1 ± 31	42.4 ± 25	44.7 ± 25	43.5 ± 22	47.1 ± 33
LF (ms)	20.3 ± 11	21.8 ± 13	21.3 ± 12	21.4 ± 10	21.4 ± 11	22.4 ± 17
HF (ms)	14.6 ± 11	14.8 ± 11	14.2 ± 9	14.9 ± 9	14.3 ± 11	13.4 ± 7
LF/HF	1.9 ± 1.6	2.0 ± 1.6	2.0 ± 1.9	1.6 ± 0.7	1.9 ± 0.9	1.7 ± 0.8

*$p < 0.01$ versus all other data points. 'B = minutes before onset of ST segment elevation (coronary angioplasty) ot its equivalent (control period in patients with variant angina; see Methods for explanation; other abbreviations as in Table 1.

autonomic system during ischemia was also indicated by the increase in the LF component, which is known to be influenced by both sympathetic and parasympathetic activity (16–18,22).

Although vagal activation at peak ST segment elevation is most likely secondary to mechanoreceptor and chemoreceptor stimulation induced by ischemia (44,45) and can have protective effects on the ischemic myocardium by limiting cardiac work, preventing life-threatening arrhythmias and inducing coronary vasodilation (40), we cannot exclude the possibility that the adrenergic activation observed during ST elevation in our patients could be, at least in part, causally related rather than merely secondary (46,47) to ischemia. Therefore, it would be possible that the combination of a reduced vagal drive to the heart with a following or associated sympathetic activation may be the final mechanism facilitating or contributing to induction of spasm.

Subgroup analysis. The analysis of heart rate variability in subgroups of episodes revealed some intriguing differences, suggesting that autonomic changes may be sharper or at least partially different in some groups than in others. Thus, despite a similar decrease in HF component before ST elevation, a reduction in LF component before ischemia and an increase in both LF component and LF/HF ratio at peak ST segment elevation were observed only in episodes occurring in anterior but not inferior leads. A statistically significant increase in LF component at peak ST segment elevation was similarly observed in nocturnal but not in diurnal episodes and during silent but not symptomatic episodes. Finally, a significant increase in heart rate at peak ST segment elevation was absent only in painful episodes. This finding may suggest a stronger vagal activation at peak ST segment elevation, most likely due to stronger mechanoreceptor stimulation, in this group, although this hypothesis was not supported by the changes in the other heart rate variability indexes. The findings observed in the subgroups, however, should be interpreted cautiously because of the relatively small number of episodes included in the subgroups and the retrospective nature of the analysis.

Limitations of the study. We cannot completely exclude the possibility that, rather than a condition contributing or predisposing to spasm, the decrease in vagal activity preceding ST segment elevation may simply occur in response to an unknown stimulus that independently causes both coronary spasm and vagal inhibition. However, there is no experimental or clinical evidence for the existence of such a stimulus at present.

Furthermore, by means of heart rate variability we were able to adequately investigate only the changes in vagal activity associated with spontaneous ischemia; however, no substantial conclusions can be drawn about the involvement of the adrenergic system in the pathogenesis of coronary spasm from our data because no heart rate variability index was found to be specific enough for selective assessment of sympathetic function.

Conclusions. Our findings suggest that changes in autonomic tone can act as a trigger of spasm or contribute significantly to its induction in patients with variant angina. In particular, although not excluding an active role for the adrenergic system, our data suggest that vagal withdrawal may frequently be a component of the mechanisms that can lead to or predispose to coronary vasospasm. However, heart rate variability did not change before ST elevation in a sizable proportion of ischemic episodes, suggesting that spontaneous epicardial spasm is also frequently provoked by stimuli different from autonomic changes, such as either blood-borne or locally produced vasoconstrictor substances (24–26).

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