Heart Rate Variability as an Index of Sympathovagal Interaction After Acute Myocardial Infarction

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By analysis of spectral components of heart rate variability, sympathovagal interaction was assessed in patients after acute myocardial infarction (AMI). At 2 weeks after AMI (n = 70), the low-frequency component was significantly greater (69 ± 2 vs 53 ± 3 normalized units [NU], p <0.05) and the high-frequency component was significantly smaller (17 ± 1 vs 35 ± 3 NU) than in 26 age-matched control subjects. This difference was likely to reflect an alteration of sympathovagal regulatory outflows with a predominance of sympathetic activity. At 6 (n = 33) and 12 (n = 29) months after AMI, a progressive decrease in the low- (62 ± 2 and 54 ± 3 NU) and an increase in the high-frequency (23 ± 2 and 30 ± 2 NU) spectral components was observed, which suggested a normalization of sympathovagal interaction. An increase in sympathetic efferent activity induced by tilt did not further modify the low-frequency spectral component (78 ± 3 vs 74 ± 3 NU) in a subgroup of 24 patients at 2 weeks after AMI. Instead, 1 year after AMI, this maneuver was accompanied by an increase in the low-frequency component (77 ± 3 vs 53 ± 3 NU, p <0.05) of a magnitude similar to the one observed in control subjects (78 ± 3 vs 53 ± 3 NU). These data indicate that the sympathetic predominance that is detectable 2 weeks after AMI is followed by recovery of vagal tone and a normalization of sympathovagal interaction, not only during resting conditions, but also in response to a sympathetic stimulus.

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Experimental observations[1–5] indicate that acute myocardial ischemia can be accompanied by signs of either sympathetic or parasympathetic hyperactivity. In the clinical setting, a major problem is to find appropriate indexes to detect changes in the neural outflows directed to the cardiovascular system. Signs of autonomic imbalance were found[6] in most patients with acute myocardial infarction (AMI). Little information, however, is available as to the persistence of altered sympathetic and parasympathetic activities after AMI, that is, when patients are discharged from the hospital and are considered free of abnormal neural mechanisms. It has been reported[7] that patients after AMI can have a reduced reflex bradycardia during vagal stimulations, a finding that has been interpreted as a consequence of decreased parasympathetic function. On the other hand, no study has addressed the question of changes in sympathetic activity.

Recently, attention has been focused not only on the responses of heart rate, but on its variability, which can be expressed by standard deviation[8] or variance analysis.[9–11] In a large cooperative study,[8] it was found that a reduced heart rate variability was a significant predictor of mortality in patients after AMI. We suggested[11] that power spectral analysis of RR variability can provide adequate information on sympathovagal interaction. We applied this noninvasive approach to the study of heart rate variability in patients at 2 weeks, 6 and 12 months after AMI. Results indicate that signs of efferent sympathetic activation seem to prevail 2 weeks after AMI, whereas after 6 and 12 months there is a normalization of the indexes that can be considered as markers of sympathovagal interaction.[11]

Methods

Patients: We studied 70 patients discharged from the coronary care unit of our hospital with the diagnosis of AMI, which was based on clinical, electrocardio-

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TABLE I Heart Rate Variability in Control Subjects and Patients After Acute Myocardial Infarction

	Arterial Pressure				Low-Frequency Component		High-Frequency Component		
	Systolic (mm Hg)	Diastolic (mm Hg)	RR Interval (ms)	RR Variance (ms^2)	Normalized Power	Frequency (Hz Eq)	Normalized Power	Frequency (Hz Eq)	LF/HF Ratio
Control subjects (n = 26)	120 ± 3	78 ± 2	907 ± 26	1,222 ± 188	53 ± 3	0.09 ± 0.01	35 ± 3	0.28 ± 0.01	2 ± 0.3
Myocardial infarction					*	*	*		*
2 weeks (n = 70)	121 ± 3	80 ± 2	865 ± 18	1,113 ± 100	69 ± 2	0.06 ± 0.01	17 ± 1	0.29 ± 0.01	8 ± 1.1
6 months (n = 33)	127 ± 4	82 ± 2	882 ± 26	1,151 ± 132	62 ± 2	0.07 ± 0.01	23 ± 2	0.26 ± 0.01	4 ± 0.6
					*		*		*
12 months (n = 29)	128 ± 4	88 ± 3	874 ± 23	1,237 ± 182	54 ± 3	0.09 ± 0.01	30 ± 2	0.27 ± 0.01	3 ± 0.7

*Significantly different contrast ($p < 0.05$).
LF = low-frequency component; HF = high-frequency component.

graphic and enzymatic criteria (CK MB determination). Criteria for inclusion in this study were (1) under 70 years of age; (2) low frequency of ventricular arrhythmias on Holter monitoring performed 12 to 14 days after admission to the coronary care unit; (3) absence of concomitant alterations known to be capable of inducing peripheral neuropathies (such as alcoholism or diabetes). The group included 63 men and 7 women whose mean age was 54 ± 2 years (range 33 to 68). Of these 70 patients, 37 had had an inferior and 33 an anterior AMI. Myocardial infarction without Q waves was present in 16 of the 70 patients. The therapeutic regimens at the time of the study are shown in Figure 1.

Study protocol: All subjects were carefully instructed about the study and all gave their informed consent. In the first phase of the study, electrocardiogram recordings were obtained only 2 weeks after AMI. An additional group of patients was also studied at 6 and 12 months after the acute episode. Data were grouped together at 2 weeks after AMI for all patients, but they were obtained in only 33 and 29 subjects at 6 and 12 months, respectively.

Studies were performed between 9:30 A.M. and 12:30 P.M. Subjects were placed on an electrically driven tilt table connected to a conventional electrocardiographic amplifier and FM tape recorder. After 15 to 30 minutes for stabilization, the electrocardiogram was continuously recorded for 30 minutes.

We also assessed the effects of sympathetic stimulation in a subgroup of patients at 2 weeks (n = 24) and 1 year (n = 19) after myocardial infarction. After the resting period, the electrocardiogram was additionally recorded for 20 minutes after the subjects had been passively moved to an upright 90° position.[11] In all patients the arterial blood pressure was measured using a conventional sphygmomanometer.

Data analysis: Off-line analysis was performed on a PDP 11/24 minicomputer. Electrocardiographic data were played back from the FM tape and digitized at

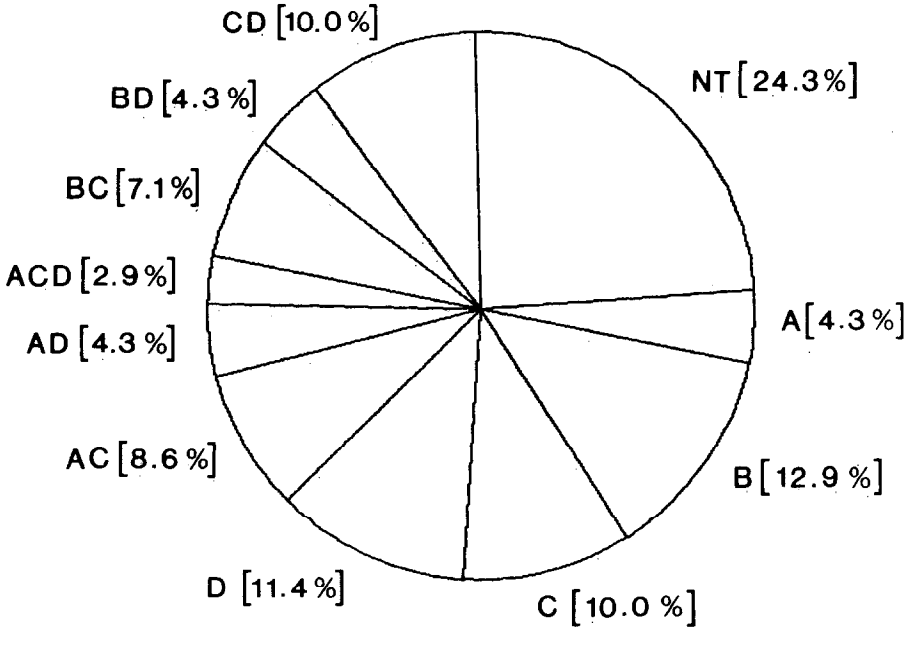

FIGURE 1. Schematic representation of drug treatment in the 70 study patients. A = digoxin; B = β-blocking drugs; C = calcium blocking drugs or angiotensin-converting enzyme inhibitors; D = nitrates; NT = no treatment.

300 samples/s. The software used for data acquisition and analysis has been previously described.[11,12]

Stationary sections of data of appropriate length were selected for analysis at rest and during tilting. The computer program first calculates the interval tachogram. From sections of tachogram of 256 or 512 interval values, simple statistics (mean and variance) of the data are computed. The computer program[11] automatically calculates the autoregressive coefficients necessary to define the power spectral density estimate and prints out the power and frequency of every spectral component, as schematically represented in Figure 2. Each spectral component is presented in absolute units, as well as in normalized form (normalized units [NU]), by dividing it by the total power minus the direct current component, if present. Only components >5% of the total power were considered significant.

Statistics: Data are presented as mean ± standard error. The Student *t* test was used to determine the significance of the differences between rest and tilt. Analysis of variance with Scheffé test was used to assess the differences between groups. Differences were considered significant when a p value of ≤0.05 was observed.[13]

Results

Analysis of RR variance: As illustrated in Table I, RR variance was slightly but not significantly decreased 2 weeks after AMI, in comparison to both control subjects and to what was observed at 6 and 12 months after the acute episode. In addition, no differences were observed when patients at 2 weeks after AMI were separated according to the localization of the infarction. RR variance was 955 ± 138 ms^2 in patients with an anterior and 1,254 ± 140 ms^2 in patients with an inferior AMI. Age was similar in both groups (52 ± 2 vs 54 ± 1 years, respectively).

RR variance was significantly reduced (323 ± 68 ms^2) in 9 patients who had signs and symptoms of heart

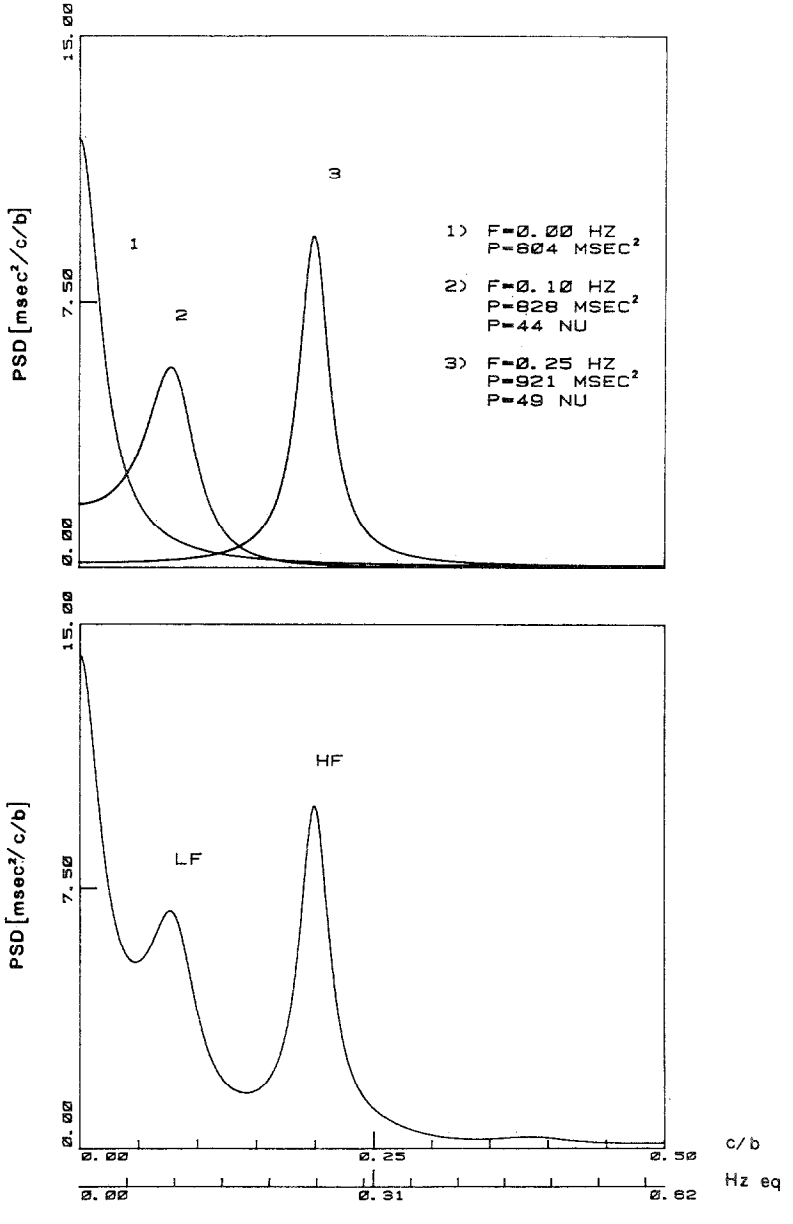

FIGURE 2. Automatic determination of spectral components (*top*) together with their center frequency and associated power. Each spectral component is presented in absolute units as well as in normalized form, by dividing it by the total power less the direct current component. The autospectrum is computed and plotted in the lower part of the panel. F = frequency in Hz Eq; LF = low-frequency spectral component; HF = high-frequency spectral component; P = power in absolute and normalized units. In this and in Figure 4 the power spectral density (PSD) units should be multiplied by 10^3.

TABLE II Effects of Tilt on Heart Rate Variability in Control Subjects and in Patients After Acute Myocardial Infarction

	Arterial Pressure				Low-Frequency Component		High-Frequency Component		
	Systolic (mm Hg)	Diastolic (mm Hg)	RR Interval (ms)	RR Variance (ms^2)	Normalized Power	Frequency (Hz Eq)	Normalized Power	Frequency (Hz Eq)	LF/HF Ratio
Control subjects (n = 26)									
Rest	120 ± 3	78 ± 2	907 ± 26	1,222 ± 188	53 ± 3	0.09 ± 0.01	35 ± 3	0.28 ± 0.01	2 ± 0.3
Tilt	115 ± 3	76 ± 2	745 ± 22	1,197 ± 185	78 ± 3	0.08 ± 0.01	14 ± 2	0.30 ± 0.02	14 ± 3.3
Myocardial infarction 2 weeks (n = 24)									
Rest	120 ± 3	80 ± 1	907 ± 35	883 ± 133	74 ± 3	0.06 ± 0.01	19 ± 3	0.28 ± 0.01	9 ± 2.2
Tilt	114 ± 3	80 ± 2	786 ± 32	679 ± 169	78 ± 3	0.05 ± 0.01	13 ± 2	0.29 ± 0.01	13 ± 2.3
Myocardial infarction 12 months (n = 19)									
Rest	131 ± 4	86 ± 3	862 ± 28	1,081 ± 162	53 ± 3	0.09 ± 0.01	28 ± 2	0.27 ± 0.01	3 ± 0.9
Tilt	133 ± 5	87 ± 3	777 ± 28	959 ± 145	77 ± 3	0.08 ± 0.01	11 ± 2	0.25 ± 0.01	14 ± 3.3

*Significantly different contrast ($p < 0.05$).

failure at the time of the study. In addition, it was also markedly reduced (231 ± 63 ms^2) in 3 patients who were not included in this study because they died suddenly during the first 3 months of observation.

When patients at 2 weeks after AMI were divided according to treatment, RR variance was slightly greater in patients taking no cardiovascular active drugs or nitrates alone in comparison to those taking digitalis, β-blocking drugs and vasodilator drugs alone or in combination.

Analysis of spectral components in control subjects: In 26 age-matched subjects, the spectral analysis revealed 2 major components (Fig. 2). According to our previous study,[11] they have been defined as a low- (0.10 Hz Eq) and a high-frequency (0.25 Hz Eq) component. The normalized area of the low-frequency component was greater (53 ± 3 NU) than the high-frequency component (35 ± 3 NU), with an average low- to high-frequency ratio of 2 ± 0.3. It is important to note that only about 85% of total variability is represented by the sum of low- and high-frequency components, since smaller components could also be present in each individual subject.

During tilt (Fig. 3, Table II), RR variability was represented by predominant low-frequency component (78 ± 3 NU) and smaller high-frequency component

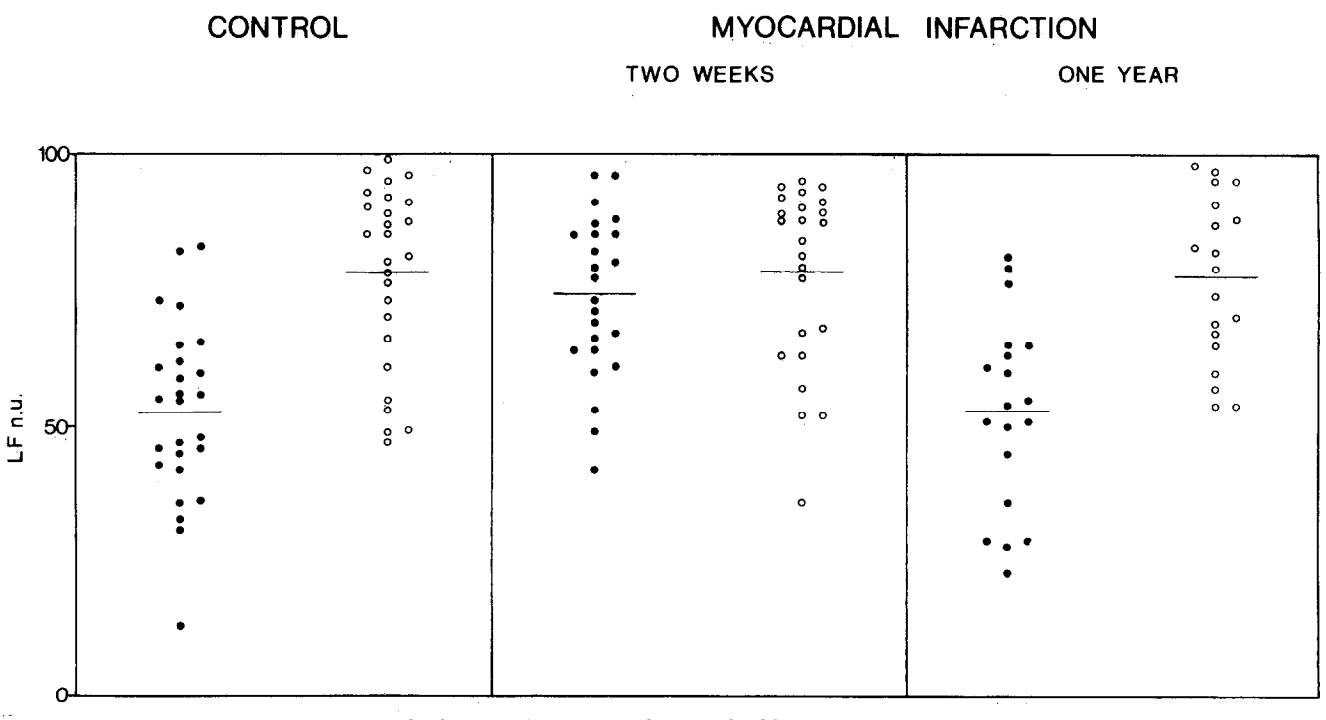

FIGURE 3. Effects of tilt on low-frequency (LF) spectral component in control subjects and in patients at 2 weeks and 1 year after AMI. Individual values and means are presented for resting conditions and tilt.

(14 ± 2 NU). As a result, there was a marked increase in their ratio (14 ± 3).

Analysis of spectral components in patients after myocardial infarction: The low-frequency spectral component of heart rate variability was significantly increased in all patients at 2 weeks after AMI (Fig. 4 and Table I) during resting conditions. This pattern was also evident when we compared the spectral components in the 29 patients in whom heart rate variability was determined in all 3 recording sessions (2 weeks, 6 and 12 months after AMI). In addition, the low-frequency component in patients at 2 weeks after AMI was significantly greater than that of control subjects during resting conditions (69 ± 2 vs 53 ± 3 NU, respectively). Conversely, there was a significant reduction in the high-frequency component. As a result, in patients 2 weeks after AMI, low- to high-frequency ratio was greater (8 ± 1) than at 6 and 12 months (4 ± 1 and 3 ± 1) as well as in control subjects (2 ± 0.3).

The changes in spectral components were not influenced by the site of the infarction. Indeed, patients with an anterior myocardial infarction displayed an increase in low-frequency component and in the low- to high-frequency ratio similar to that observed in patients with an inferior localization.

Effects of tilt on spectral components: As demonstrated in Figure 3 and Table II, in control subjects, tilt determined a significant increase in the low-frequency component (from 53 ± 3 to 78 ± 3 NU) and low- to high-frequency ratio (from 2 ± 0.3 to 14 ± 3). These changes occurred together with a simultaneous and significant reduction in RR interval and in the high-frequency component. No change in RR variance was observed during tilt.

In 24 patients at 2 weeks after AMI tilt did not modify the predominant low-frequency component (Fig. 3 and Table II). A small but not significant reduction was observed in the RR variance and high-frequency component, whereas the RR interval was markedly reduced.

In patients 1 year after AMI, tilt produced a marked increase in the low-frequency component (from 53 ± 3 to 77 ± 3 NU) and in the low- to high-frequency ratio (from 3 ± 1 to 14 ± 3), which had a magnitude similar to that observed in control subjects (Table II).

Discussion

This study analyzes the beat by beat oscillations of cardiac cycle in patients who had had an AMI, according to the hypothesis that changes in sympathetic and vagal efferent activities might be reflected by cardiac beat to beat oscillations.

Power spectral analysis of RR variability as an index of sympathovagal interaction: Cardiac rhythm can be considered the result of a complex interaction between sympathetic and vagal efferent impulse activities and sinus node pacemaker properties. Several approaches have been proposed to evaluate the contribution of either neural regulatory outflows[14] to heart rate variability. It is now generally accepted[15,16] that peak to peak variation of heart period can be used as an index of parasympathetic activity. More recently, we suggested that spectral analysis of heart rate variability could also provide information on changes in the sympathetic activity to the heart and, therefore, on the interaction between sympathetic and parasympathetic regulatory activities.[11] The low-frequency component has been proved to be a likely index of sympathetic activity:[11] it corresponds to the Mayer waves and can be altered by interventions that increase functionally or block pharmacologically the sympathetic drive to the heart. The high-frequency component is known to be synchronous with respiration and has been considered as a quantitative evaluation of respiratory arrhythmia.[10] Because it disappears after atropine,[10] it could represent a clinically useful index of vagal activity: accordingly, low- to high-frequency ratio could be a convenient index of such interaction.[11]

In the present study, by using an autoregressive algorithm, we could not only improve the statistical

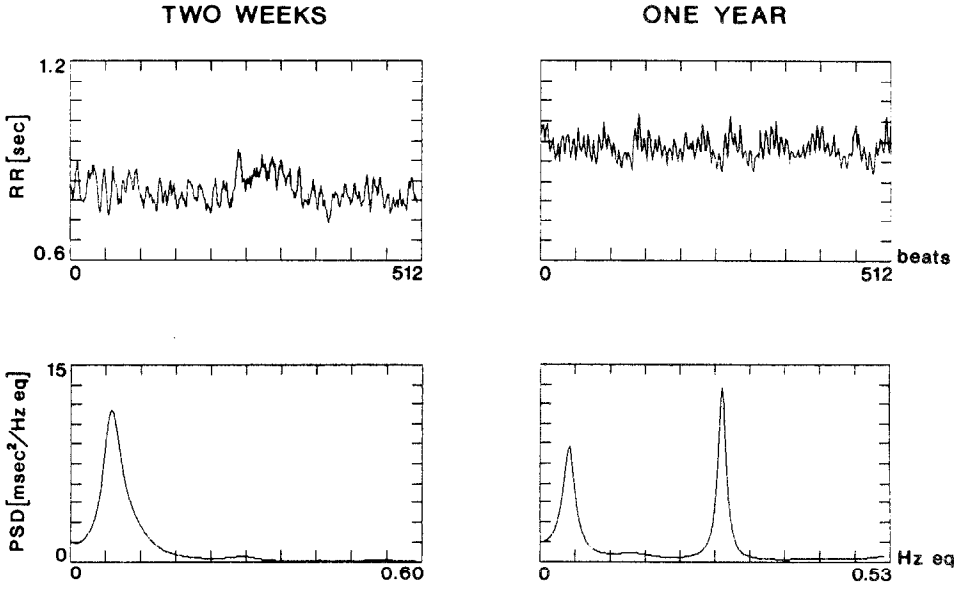

FIGURE 4. RR interval series, that is, tachogram (*top*) and autospectra (*bottom*) in 1 patient after AMI. At 2 weeks after the acute episode, there is a predominant low-frequency component. At 1 year, 2 clearly separated low- and high-frequency components are present.

consistency of the data, compared with previous approaches based on the fast Fourier transform, but we also automatically computed the number and power of each spectral component.[11] Our analysis was restricted to periods of steady-state condition, such as rest or stable response to passive orthostatism, in which the cardiac rhythm was free of arrhythmias. Moreover, to facilitate comparisons, the relative power of spectral components was expressed in normalized units.

Analysis of RR variance: The analysis of RR variance or of standard deviation provides important information on neural control of heart rate.[15,16] However, there might be some limitation[9,17] on the use of only this methodology to characterize RR variability fully. Indeed, we did not find a significant difference in RR variance between patients and control subjects during resting conditions and in response to tilt.

RR variance, instead, was influenced by drug regimens and was reduced in patients who developed signs and symptoms of heart failure after AMI. In addition, we measured a very low RR variance in 3 patients who died from cardiac disease, thus confirming the recent report by Kleiger et al[8] who demonstrated a significant association between decreased heart rate variability and increased mortality after AMI.

Autonomic changes after acute myocardial infarction: Signs of sympathetic activation have been frequently reported in patients during AMI.[6,18,19] Our data suggest that signs of sympathetic hyperactivity are still detectable in patients at 2 weeks after AMI independently of the localization of infarction and of the drug regimen. Conversely, there was a reduction in the high-frequency component, which suggests diminished parasympathetic activity.[9-11] These alterations present at rest were unmodified by tilt: a finding that suggested that the abnormal sympathovagal balance was capable of blunting the expression of a further sympathetic activation.

An impaired parasympathetic regulation of heart rate has been previously reported in patients with heart failure[20] and after AMI[7] by the analysis of heart rate response to different maneuvers. In the present study, in addition, we have detected a sign of sympathetic predominance in conditions in which it was unsuspected. At 6 and 12 months after AMI, the reduction in the low-frequency component and low- to high-frequency ratio, together with the increase in high-frequency component, suggested a normalization of the sympathovagal balance during resting conditions and in response to a sympathetic stimulation. These findings were independent of the clinical localization of the infarction.

As to the mechanisms that might have contributed to determine the alteration in sympathovagal balance, an increased sympathetic efferent tone could reflect a prevailing excitatory sympathetic reflex[1,3,5] elicited by sustained activation of sympathetic cardiac afferent fibers[21-23] as a result of an abnormal mechanical or chemical stimulus located in the heart.[23-25] In addition, sympathetic activation may reflect a reduction of baroreceptor mechanisms, which has been suggested to occur after AMI,[20] or may be the result of a change in what is generally referred to as "central command"[23] with a consequent increase in the sympathetic discharge.[26]

Our technique does not distinguish between changes in efferent neural activities or target function responsiveness. Therefore, the present study, which is based on the spectral analysis of heart rate variability, could not provide any insight into the exact mechanisms responsible for the observed autonomic changes or into the factors that contribute to the restoration of a normal sympathovagal balance.

On the other hand, the interaction between abnormal neural regulatory events[27-29] and arrhythmias[30-33] appears as a major pathophysiologic determinant for sudden cardiac death in the early period after AMI.

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