Relationships between Heart Rate Variability, Functional Capacity, and Left Ventricular Function Following Myocardial Infarction: An Evaluation after One Week and Six Months

JOSÉ V. MONMENEU, M.D., FRANCISCO J. CHORRO, M.D., VICENTE BODÍ, M.D., JUAN SANCHIS, M.D., ANGEL LLÁCER, M.D., ROBERTO GARCÍA-CIVERA, M.D., RICARDO RUIZ, M.D., RAFAEL SANJUÁN, M.D., MIGUEL BURGUERA, M.D., VICENTE LÓPEZ-MERINO, M.D.

Cardiology Service, University Clinic Hospital, Valencia, Spain

Summary

Background: Relationships between heart rate (HR) variability and different prognostic markers such as ejection fraction, functional capacity, and patency of the infarct-related artery, as well as the comparison of their time courses are not fully elucidated.

Hypothesis: The aim of study was to assess prospectively the early postinfarction changes in HR variability and its evolution over a period of 6 months; the relationships between HR variability and functional capacity in exercise testing; left ventricular function in cardiac catheterization; status of the infarct-related artery; and the comparison of their time courses.

Methods: In 42 patients with anterior myocardial infarction, a study was made of the early changes in HR variability analyzed by the complex demodulation method, its evolution over a period of 6 months, and the relationships between HR variability and (1) functional capacity in exercise testing, (2) left ventricular function in cardiac catheterization, and (3) status of the infarct-related artery.

Results: At 1 week HR variability parameters correlated directly with functional capacity indicators such as METS, percent change in HR from rest to peak exercise ($\%\Delta\text{HR}$), difference between initial and peak HR (HR range), percent peak

theoretical HR (% peak HR), left ventricular ejection fraction (EF), and, inversely, with end-systolic volume (ESV). Stepwise multiple regression analysis to establish HR variability parameters (recorded at 1 week) as related to functional capacity and left ventricular function at 1 week and 6 months postinfarction established the following variables: (1) At 1 week: standard deviation (SD) of the RR cycles in relation to $\%\Delta\text{HR}$ ($r = 0.60$, $p < 0.0001$), HR range ($r = 0.43$, $p < 0.01$), and EF ($r = 0.79$, $p < 0.0001$). (2) At 6 months, the sole accepted HR variability parameter was the SD in relation to $\%\Delta\text{HR}$ ($r = 0.38$, $p < 0.05$) and HR range ($r = 0.45$, $p < 0.01$). No variability parameter was accepted in relation to METS, % peak HR, or ESV. Relationship between EF or ESV and HR variability parameters was not significant when both were evaluated at 6 months. At that time, there was a significant increase in all HR variability parameters among all surviving patients ($n = 39$), with the exception of the LF/HF ratio and mean RR cycle. The percent increase in HR variability between the first week and 6 months was greater among those patients with the lowest basal EF. No relation was established between HR variability and patency of the infarct-related artery.

Conclusion: The decrease in HR variability observed following myocardial infarction is associated with a diminished functional capacity and an increased alteration of the EF. This does not affect the recovery of HR variability, which was observed in all surviving patients.

Key words: heart rate variability, myocardial infarction, functional capacity, ventricular function

Introduction

The analysis of heart rate (HR) variability represents a non-invasive method for investigating the influence of the autonomous nervous system upon the heart. Heart rate variability

Address for reprints:

José V. Monmeneu
Cardiology Service
Hospital Clínico Universitario
Avda. Blasco Ibañez, 17
46010 Valencia, Spain

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is found to diminish following myocardial infarction (MI) and constitutes a potent predictor of mortality or adverse events independent of other established prognostic indicators.¹⁻⁵ However, after this initial decrease and in the weeks following MI, HR variability increases and reaches nearly fully restored values after 6 to 12 months.⁶⁻⁸ This recovery is attributed to the reversal of ischemia, the washing out of ischemic metabolites, receptor necrosis, or to the adaptation of the receptors to continuing mechanical and chemical stimuli.^{9, 10}

Several studies have reported relationships between HR variability and different parameters such as ejection fraction (EF),^{1, 4, 8, 11-13} duration of exercise testing,¹ Killip class,^{8, 11} or left ventricular end-systolic volume.¹⁴ Likewise, HR variability correlated with the patency of the infarct-related artery,^{13, 15, 16} although controversy persists in this matter.

The present study investigated (1) the early postinfarction changes in HR variability and its evolution over a period of 6 months, using the complex demodulation method;¹⁷ (2) relationship between HR variability and functional capacity in exercise testing; (3) relationship between HR variability and left ventricular function in cardiac catheterization, as well as comparison of their time courses; and (4) relationship between HR variability and status of the infarct-related artery.

Methods

Patients

Forty-two patients (33 men and 9 women) with anterior (from V₁–V₅) Q-wave MI were studied. Patient age ranged between 25 and 82 years (mean 61 ± 10). Inclusion criteria consisted of any two of the following three criteria: ≥0.2 mV ST elevation in at least two precordial leads (V₁–V₅), severe chest pain lasting > 30 min, and a significant increase in serum creatine kinase and its myocardial isoenzyme in the first hours following hospitalization. Patient age, gender, body surface area, cardiovascular risk factors, Killip class, history of previous infarction, and the administration of beta blockers and/or thrombolytic therapy were recorded in all cases (Table I).

TABLE I Clinical characteristics of study group (n = 42)

Mean age (years)	61 ± 11
Age range (years)	25–82
Male gender (%)	33 (79)
Body surface area (m ²)	1.82 ± 0.17
Diabetes mellitus (%)	17 (40)
Systemic hypertension (%)	18 (43)
Smokers (%)	26 (62)
High cholesterol levels (%)	13 (31)
Killip class I (%)	31 (74)
Thrombolytic therapy (%)	33 (79)
Beta blockers (%)	8 (19)
Previous infarction (%)	4 (9)

Exercise Testing

Symptom-limited treadmill exercise testing was performed in all cases prior to hospital discharge, using the Bruce protocol. In addition to the presence of angor or ischemia, the parameters evaluated were METS, percent peak theoretical HR reached (% peak HR), difference between the initial and peak HR recorded during exercise testing (HR range), and percent change in HR from rest to peak exercise (%ΔHR). Maximal exercise testing was repeated 6 months post MI to evaluate the time course of the above parameters.

Left Ventriculography

Left ventriculography was performed using a 6F pigtail catheter. Forty ml of contrast were injected at an injection speed of 12 ml/s in the 30° right anterior oblique projection. Software of an x-ray digital imaging system (Integris HM 3000, Philips, Eindhoven, The Netherlands) was used for global and regional left ventricular analysis. Calibration was obtained by catheter diameter. Endocardial end-diastolic and end-systolic contours were automatically traced from a normal sinus beat, and left ventricular volumes (end-diastolic and end-systolic) as well as EF were determined. The values of left ventricular volumes were normalized by the body surface area. Infarct size was estimated by quantitatively assessing left ventricular function. Centerline chord motion analysis was used according to Sheehan *et al.*¹⁸ With this technique, endocardial motion is measured along 100 chords constructed perpendicular to a centerline drawn midway between the end-diastolic and end-systolic contours. Motion at each chord is normalized by the end-diastolic perimeter length to yield a shortening fraction. This value is then converted into units of standard deviation (SD) from the normal mean motion of each chord, as derived from a normal reference population. Normal motion was considered to be between 1 and – 1 SD from reference. Abnormal wall motion extent was defined as the number of chords displaying hypokinetic motion (< – 1 SD) expressed as a percentage of the total number of chords analyzed.

The procedure was performed in all cases prior to hospital discharge and was repeated 6 months later in 31 of 39 surviving patients (79%).

Coronary Angiography

Coronary angiography was performed by the Judkins technique. Multiple injections were given in the right and left oblique view, including cranial and caudal angulations. The infarct-related artery was identified by analysis of acute electrocardiographic (ECG) changes, regional wall motion abnormalities in the left ventriculogram, and coronary angiogram. Flow in the infarct-related artery was graded according to the Thrombolysis in Myocardial Infarction (TIMI) criteria. Quantitative coronary analysis was performed using the automatic edge method included in the software of the Integris HM 3000 system (Philips). The end-diastolic frames showing the narrowest stenotic diameter were selected for analysis. Stenosis percentage and minimum lumen diameter were calculated.

As with left ventriculography, the procedure was repeated in 31 patients at 6 months post infarction.

Heart Rate Variability Analysis

All patients underwent 24-h Holter ECG monitoring between Days 6 and 8 post infarction, using a double-channel Tracker 90m. The recordings were read and analyzed using a Pathfinder III Mk 2 cardioanalyzer (Reynolds Medical Ltd., Hertford, U.K.).

Information concerning the duration of the RR cycles and the characterization of aberrations or extrasystoles was stored in a PC 486DX2 microcomputer (IBM, Madrid, Spain) in individual files for each patient investigated. Based on the time series of the successive RR cycles, an analysis of HR variability was made by dividing the time series into consecutive 7.5-min segments. Heart rate variability analysis was performed by means of the fast Fourier transform (FFT) and its inverse.¹⁷ This procedure was used to create a specific pass-band filter for the time series, thus allowing us a separate reconstruction of the component oscillations of the original signal. The oscil-

lations obtained were high frequency (HF) (0.15–0.40 Hz), low frequency (LF) (0.04–0.15 Hz), and very low frequency (VLF) (<0.04 Hz) (Figs. 1 and 2). From each oscillation we obtained the corresponding amplitude and mean and instantaneous frequency (in ms and Hz, respectively). The validity of the procedure was verified by reconstructing the original from the demodulated signal and calculating the correlation coefficient (>0.98). In carrying out the analysis, we took into account the existence of extrasystoles or system detection failures (i.e., indicated by the analyzer, defined by the operator, or visually identified), which were excluded from the study.

The main HR variability parameters were obtained from the 192 segments of 7.5 min into which the 24 hours of the day are divided. We then recorded the mean RR cycle values (in ms) and their SD; amplitude (in ms) and frequency (in Hz) of the HF, LF, and VLF oscillations; and the ratio between the LF and HF oscillations amplitudes (LF/HF). In turn, for each individual we calculated the averages corresponding to the global 24 hours, for the 8 consecutive diurnal hours that comprise the highest HR, as well as the four consecutive nocturnal hours during which HR is lowest.

FIG. 1 Graphic representation of the RR series analyzed employing the complex demodulation method (CDM), with its respective resulting very low (VLF), low (LF), and high frequency (HF) oscillations. The ordinate axis represents the variations, with scales between + 250 and - 250 ms. The abscissa represents time elapsed. By means of the CDM we observe the changes in RR cycle and the VLF, LF, and HF oscillations along the time segment analyzed. From each oscillation we obtained the corresponding amplitude and mean and instantaneous frequency (in ms and Hz, respectively). (A): 7.5 min segment obtained at 1 week post infarction in a male patient with left ventricular ejection fraction < 40%. (B): The same patient at 6 months post infarction. In this case a reduced mean amplitude for all oscillations at 1 week (VLF = 8.1, LF = 5.3, and HF = 2.1 ms) and a generalized increase at 6 months post infarction (VLF = 29.7, LF = 8.7, and HF = 6.8 ms) can be observed.

FIG. 2 (A): 7.5 min segment obtained at 1 week post infarction in a female patient with left ventricular ejection fraction > 40%. (B): The same patient at 6 months post infarction. In this case, few variations in the mean amplitude of the oscillations are observed between 1 week (VLF = 35.9, LF = 25.4, and HF = 9.4 ms) and 6 months post infarction (VLF = 32.3, LF = 29.0, and HF = 8.6 ms).

TABLE II Comparison of the global 24-h heart rate variability parameters at 1 week and 6 months after myocardial infarction

Variable	1 Week	6 Months	p Value
RR cycle (ms)	843 ± 114	874 ± 123	NS
SD (ms)	33 ± 17	45 ± 19	<0.0001
Amplitude VLF (ms)	22 ± 11	30 ± 12	<0.0001
Amplitude LF (ms)	11 ± 6	14 ± 6	<0.0001
Amplitude HF (ms)	6 ± 3	8 ± 4	<0.0001
LF/HF ratio	1.86 ± 0.55	1.84 ± 0.41	NS

Abbreviations: ms = milliseconds, NS = not significant, p = probability; SD = standard deviation of RR intervals, VLF = very low frequency, LF = low frequency, HF = high frequency.

To evaluate the time course of HR variability parameters, a new 24-h ECG recording was made 6 months after MI in all surviving patients, using the same analytical procedure as before.

Statistical Analysis

The values obtained are expressed as mean ± SD. The paired Student's *t*-test was applied both to evaluate the diurnal and nocturnal HR variability differences and to study the time course of HR variability between 1 week and 6 months post infarction. Relationships between variables were evaluated by simple linear and multiple stepwise regression analysis. A *p* value of <0.05 was considered to be statistically significant.

The calculations were made with the Statistical Package for Social Sciences (SPSS) 6.1 (SPSS Inc., Chicago, Ill., USA).

Results

Time Course of Recovery of Heart Rate Variability

During the 6-month follow-up period, there were three cardiac deaths (7.1%). At 6 months post infarction, a significant increase with respect to 1 week was observed in the SD and in the amplitudes of the HF, LF, and VLF oscillations (Table II). In contrast, and although the mean RR cycle was lengthened and the LF/HF ratio presented a slight decrease, the differences failed to reach statistical significance.

The differences between the diurnal and nocturnal hours were significant at both 1 week and 6 months regarding the mean RR cycle, HF amplitude, and VLF mean frequency (see Tables III and IV). The SD and LF oscillations exhibited significant diurnal/nocturnal differences 6 months after MI, but not at 1 week.

Relationship between Heart Rate Variability and Age

Patient age correlated significantly and inversely with HR variability parameters (mean 24 h values) recorded 1 week after MI: RR ($r = -0.58$); SD ($r = -0.75$); amplitude (in ms) of VLF ($r = -0.72$), LF ($r = -0.71$) and HF ($r = -0.74$) ($p < 0.0001$ in

TABLE III Diurnal and nocturnal heart rate variability parameters at 1 week post infarction

Variable	Day	Night	p Value
RR cycle (ms)	826 ± 123	919 ± 149	<0.0001
SD (ms)	35 ± 17	35 ± 16	NS
Amplitude VLF (ms)	24 ± 12	23 ± 10	NS
Amplitude LF (ms)	11 ± 6	11 ± 6	NS
Amplitude HF (ms)	5 ± 3	7 ± 5	0.001
Frequency VLF (Hz)	0.0138	0.0155	0.001
Frequency LF (Hz)	0.0695	0.0691	NS
Frequency HF (Hz)	0.265	0.269	NS
LF/HF ratio	2.04 ± 0.63	1.71 ± 0.48	<0.01

Abbreviations: Hz = Hertz. Other abbreviations as in Table II.

all cases). In contrast, no differences were recorded in LF/HF ratio as a function of patient age. At 6 months post infarction, the above relations persisted, with similar significance levels.

Relationship between Heart Rate Variability and Functional Capacity

In the first week post infarction, a significant correlation was observed between the METS reached and RR ($r = 0.52$, $p = 0.001$), SD ($r = 0.40$, $p = 0.01$), and amplitude (in ms) of VLF ($r = 0.39$, $p = 0.01$), LF ($r = 0.39$, $p = 0.01$), and HF ($r = 0.39$, $p = 0.01$). The percent change in HR from rest to peak exercise (%ΔHR) correlated directly and significantly with RR ($r = 0.58$, $p < 0.0001$); SD ($r = 0.60$, $p < 0.0001$); and amplitude (in ms) of VLF ($r = 0.61$, $p < 0.0001$), LF ($r = 0.56$, $p < 0.0001$), and HF ($r = 0.48$, $p = 0.003$). The HR range reached during exercise testing (HR range) in turn correlated significantly with RR ($r = 0.34$, $p = 0.04$); SD ($r = 0.43$, $p = 0.009$); and amplitude (in ms) of VLF ($r = 0.43$, $p = 0.008$) and LF ($r = 0.38$, $p = 0.02$). Statistical significance was not reached in the case of HF amplitudes, however. Finally, percent peak theoretical HR reached (% peak HR) only correlated with RR ($r = -0.35$, $p = 0.03$) and HF amplitude (ms) ($r = -0.34$, $p = 0.04$). These correlations persisted when analyzing the relationship between HR vari-

TABLE IV Diurnal and nocturnal heart rate variability parameters at 6 months post infarction

Variable	Day	Night	p Value
RR cycle (ms)	792 ± 117	963 ± 140	<0.0001
SD (ms)	41 ± 18	49 ± 20	0.001
Amplitude VLF (ms)	28 ± 12	31 ± 12	NS
Amplitude LF (ms)	13 ± 7	17 ± 8	0.001
Amplitude HF (ms)	7 ± 4	10 ± 6	<0.0001
Frequency VLF (Hz)	0.0136	0.0174	<0.0001
Frequency LF (Hz)	0.0761	0.0728	<0.01
Frequency HF (Hz)	0.259	0.249	<0.05
LF/HF ratio	1.88 ± 0.48	1.76 ± 0.50	NS

Abbreviations as in Tables II and III.

ability in the first week post infarction and functional capacity at 6 months. In contrast, the significant relationship between HR variability and functional capacity was lost when both were analyzed 6 months after MI. The HR variability parameters did not correlate with the presence of angor or ischemia in exercise testing at 1 week and 6 months post infarction.

Stepwise regression analysis accepted the following independent parameters (Table V), taking as dependent variables the parameters obtained in the exercise testing in the first week post infarction: SD in relation to $\% \Delta \text{HR}$ and to HR range; no HR variability parameters were accepted as being related to $\% \text{peak HR}$. At 6 months, the independent variables were found to be SD in relation to $\% \Delta \text{HR}$ and HR range. No HR variability parameters were established as being related to METS or $\% \text{peak HR}$.

Relationship between Heart Rate Variability and Left Ventricular Function

In the first week post infarction, left ventricular EF was found to correlate positively with RR ($r = 0.47$, $p = 0.002$); SD ($r = 0.46$, $p = 0.003$); amplitude (in ms) of both VLF ($r = 0.51$, $p = 0.001$) and LF ($r = 0.41$, $p = 0.009$); and LF/HF ratio ($r = 0.39$, $p = 0.01$). Left ventricular end-systolic volume exhibited an inverse and significant correlation with SD ($r = -0.34$, $p = 0.03$), amplitude (in ms) of VLF ($r = -0.36$, $p = 0.02$), LF/HF ratio ($r = -0.41$, $p = 0.009$).

As in the case of the functional parameters derived from exercise testing, the correlations between HR variability at 1 week post infarction and EF and end-systolic volume evaluated at 6 months were found to persist. In contrast, however, the relationship between HR variability and hemodynamic findings showed no correlation when both were evaluated 6 months post MI.

The abnormal wall motion extent (AWME) correlated slightly with the different HR variability parameters, statistical significance only being observed for VLF amplitude ($r = -0.31$, $p = 0.05$).

Stepwise multiple regression analysis accepted SD (ms) as the HR variability parameter related to left ventricular EF

TABLE V Equations derived from the stepwise multiple regression analysis to establish the heart rate variability parameters (recorded prior to hospital discharge) accepted as related to functional capacity and left ventricular function parameters, both at 1 week and 6 months post infarction

Dep. variable	Equation	r	p Value
1 Week			
METS	$Y = 0.09 \cdot \text{AGE} + 11.6$	0.40	<0.05
$\% \Delta \text{HR}$	$Y = 1.23 \cdot \text{SD} + 32$	0.60	<0.0001
HR range	$Y = 0.53 \cdot \text{SD} + 37.8$	0.43	<0.01
$\% \text{peak HR}$	$Y = 0.42 \cdot \text{AGE} + 58$	0.39	<0.05
EF	$Y = 0.26 \cdot \text{SD} - 0.46 \cdot \text{AWME} + 69$	0.79	<0.0001
ESV	$Y = 0.80 \cdot \text{AWME} + 13$	0.66	<0.0001
6 Months			
METS	$Y = 0.06 \cdot \text{EF} - 0.12 \cdot \text{AGE} + 12.4$	0.70	0.0001
$\% \Delta \text{HR}$	$Y = 0.74 \cdot \text{SD} + 59$	0.38	<0.05
HR range	$Y = 0.55 \cdot \text{SD} + 45$	0.45	<0.01
EF	$Y = -0.54 \cdot \text{AWME} + 84$	0.75	<0.0001
ESV	$Y = 0.71 \cdot \text{AWME} + 18$	0.53	<0.005

Abbreviations: $\% \Delta \text{HR}$ = percent change in heart rate from rest to peak exercise, HR range = difference between the initial and peak heart rate recorded during exercise testing, $\% \text{peak HR}$ = percent peak theoretical heart rate reached, EF = left ventricular ejection fraction, ESV = left ventricular end-systolic volume, AWME = number of chords displaying hypokinetic motion ($< -1 \text{ SD}$) expressed as a percentage of the total number of chords analyzed (see text). Other abbreviations as in Table II.

obtained at 1 week post infarction (Table V). No HR variability parameters were established as being related to left ventricular end-systolic volume, at either 1 week or 6 months post infarction.

On dividing the population as a function of left ventricular EF obtained at 1 week post infarction (< 40 vs. $\geq 40\%$), greater increases in all HR variability parameters were observed among patients with the lowest EF, who in turn exhibited the lowest HR variability basal values (Table VI). Statistical sig-

TABLE VI Basal values of the heart rate variability parameters, and the increments observed between the first week and 6 months post infarction, in patient subgroups with basal ejection fraction < 40 or $\geq 40\%$

Variable	Basal values (1 week post infarction)			Δ between 1 week and 6 months (%)		
	EF $< 40\%$ (n = 8)	EF $\geq 40\%$ (n = 34)	p Value	EF $< 40\%$ (n = 5)	EF $\geq 40\%$ (n = 26)	p Value
RR cycle (ms)	735 $\pm$ 125	875 $\pm$ 106	<0.01	3 $\pm$ 21	5 $\pm$ 17	NS
SD (ms)	19 $\pm$ 7	38 $\pm$ 15	<0.01	83 $\pm$ 40	39 $\pm$ 28	<0.05
Amplitude VLF (ms)	13 $\pm$ 5	25 $\pm$ 9	<0.01	85 $\pm$ 45	37 $\pm$ 27	<0.01
Amplitude LF (ms)	6 $\pm$ 3	12 $\pm$ 6	<0.01	120 $\pm$ 88	42 $\pm$ 43	<0.01
Amplitude HF (ms)	4 $\pm$ 1	7 $\pm$ 4	NS	100 $\pm$ 118	53 $\pm$ 63	NS
LF/HF ratio	1.5 $\pm$ 0.4	2 $\pm$ 0.5	<0.01	0.2 $\pm$ 0.8	0.08 $\pm$ 0.5	NS

Abbreviations: EF = left ventricular ejection fraction, Δ = percent change in the values recorded at 1 week and 6 months post infarction. Other abbreviations as in Table II.

nificance was reached for the increases in SD ($p = 0.01$) and the amplitudes of both VLF ($p = 0.008$) and LF ($p = 0.009$) (Figs. 1 and 2).

Relationship between Heart Rate Variability and Infarction Artery Status

It should be pointed out that no significant relationships were observed between the severity of the stenosis in the infarct-related artery (minimal luminal diameter, percent stenosis, TIMI flow) and the presence of multivessel disease and the HR variability parameters investigated. On dividing the study group into patients with total occlusion of the infarct-related artery at 1 week ($n = 8$) and those in whom the artery was found to be patent ($n = 34$), we likewise observed no significant differences in any of the HR variability parameters at 1 week post infarction. No analysis was made at 6 months because, during this period, coronary revascularization procedures had been adopted in nine patients.

Discussion

Time Course

There has been a recent increase in interest over the analysis of HR variability as a method for risk stratification following MI. In this sense, HR variability is known to decrease as soon as a few hours after onset of the symptoms,^{6, 8, 19} followed by gradual recovery after a few weeks^{6, 20} and up to 6–12 months.⁷ However, HR variability does not usually return fully to normal values. Our results, based on the complex demodulation model,¹⁷ are in agreement with those reported by other authors, based on the time domain^{1, 2, 4, 13, 14} or on the frequency domain methods,^{12, 13, 21} and reflect the existence of a highly significant increase in most of the HR variability parameters recorded at 6 months post infarction with respect to the same parameters determined in the first week. Obtaining similar results by using a different methodology for analyzing HR variability supports previous observations.

Based on a single 24-h recording, we separately analyzed the periods of diurnal activity, nocturnal rest, and the differences between the two periods, at both 1 week and 6 months post infarction. Thus, in absolute terms, both the diurnal and nocturnal values were found to increase in the ECG study made 6 months after MI. Likewise, the differences between the diurnal and nocturnal values were statistically significant for a greater number of HR variability parameters when recorded at 6 months postinfarction than when determined before hospital discharge. This suggests that the diurnal and nocturnal differences in HR variability are possibly attenuated in the early postinfarction stages, followed by gradual recovery over the following weeks. Our findings moreover agree with the hypothesis of a diminished circadian rhythm after acute MI.²²

On the other hand, analysis of the LF/HF ratio revealed a predominant sympathetic tone during the daytime hours that was more patent in the first week after MI than at 6 months, despite the fact that in this period the absolute values of all HR

variability parameters (including those attributed to the influence of the autonomous nervous system) were seen to increase. These findings coincide with those reported elsewhere.²³ The fact that no significant differences in LF/HF ratio, measured in the first week and at 6 months post infarction, were observed in our patients may be attributable to a combination of factors such as the different physical activities of the patients during the recordings made at 1 week (in hospital) or at 6 months post infarction (on an outpatient basis), which may have influenced the sympathovagal balance; an insufficiently prolonged follow-up period; a reduced sample size; or factors related to the method employed to analyze HR variability.

Heart Rate Variability and Age

As in healthy subjects, patients exhibited an inverse relationship between HR variability and age. According to Kleiger *et al.*,¹ age exerts a less marked influence on HR variability after MI than in normal subjects. This is probably attributable to the observation that other factors such as infarct size are more relevant in deciding autonomous balance. Nevertheless, the proportion of patients with markedly diminished HR variability parameters following MI is greater among the elderly, and the utility of HR variability in predicting sudden death decreases with advancing age.²⁴ On the other hand, the incidence of arrhythmia-induced sudden death appears to be more frequent among younger patients.²⁵ Inasmuch as the causes underlying these findings have not been clarified, they will continue to be of relevance in the HR variability-based rating of patient risk.²⁵ Thus, as suggested by Odemuyiwa,²⁴ the fit of risk stratification may be improved by defining the normal postinfarction HR variability values corrected for patient age, or by employing different variables to predict events in the different patient age groups.

Regarding the LF/HF ratio, no differences were observed among our patients in terms of age. This agrees with the observations reported by Pagani.²⁶ These findings suggest that age is characterized by the establishment of a new equilibrium between the two components of the autonomous nervous system, rather than by alterations in sympathetic activity only.

Heart Rate Variability and Functional Capacity

We have verified significant but weak correlations between most of the functional capacity parameters in exercise testing and HR variability in the first week post infarction. These findings agree with those reported by Kleiger *et al.*,¹ who observed a direct and discretely significant correlation between the SD of the RR intervals and the duration (in min) of exercise testing ($r = 0.15$, $p = 0.0007$). On the other hand, HR variability parameters recorded 6 months after acute MI no longer correlated with any of the functional capacity parameters investigated. In this sense, a generalized and significant increase was recorded in all HR variability parameters between 1 week and 6 months post infarction, whereas none of the functional capacity indicators exhibited significant improvements. Both the absence of a marked correlation between HR variability and

functional capacity indicators and their different time course could account for the independent prognostic value of HR variability parameters in relation to arrhythmias and mortality, as suggested by Kleiger *et al.*³ and Farrell *et al.*⁴

In turn, in the same way that functional capacity is related to left ventricular function or patient age, HR variability (SD) is related to functional capacity parameters, as reflected by stepwise multiple regression analysis.

Heart Rate Variability and Left Ventricular Function

We have obtained significant correlations between HR variability, analyzed in the first week post infarction, and both left ventricular EF and end-systolic volume. At 6 months, these correlations did not persist. Some authors, for example, Kleiger *et al.*,¹ observed a weak correlation between the SD of the RR intervals and mean EF as determined by radiolabeling techniques ($r = 0.24$, $p = 0.0001$). Casolo *et al.*⁸ also reported a direct correlation between the SD of the RR interval in 24-h recordings carried out 2–3 days post infarction and EF ($r = 0.44$, $p = 0.0001$). In turn, Farrell *et al.*⁴ observed correlations between the HR variability triangular index and EF ($r^2 = 0.091$, $p < 0.0001$), while Odemuyiwa *et al.*¹¹ obtained discretely significant correlations between the triangular index and the EF ($r = 0.3$, $p < 0.001$). In a recent study, Singh *et al.*¹³ reported a discretely significant correlation between the EF and certain HR variability parameters in the time (pNN50) and frequency domains (LF intensity). Dambrink *et al.*¹⁴ found significant correlations between HR variability index ≤ 25 , measured from Holter recordings made prior to hospital discharge, and both end-systolic volume as determined echocardiographically and EF. In this sense, the HR variability index ≤ 25 was found to be an independent predictor of posterior ventricular dilatation.

As in the case of functional capacity parameters, the stepwise multiple regression analysis indicated that the SD of the RR cycles is related to left ventricular EF in addition to its association with abnormal wall motion extent.

In an attempt to clarify the significance of the increase in HR variability between the first week and 6 months post infarction, we observed that patients with lower EF at 1 week (who in turn exhibited the lowest HR variability) tended to show greater HR variability increments at 6 months post infarction. Such observations suggest that an initially diminished HR variability may be partly caused by an impairment in ventricular function, as proposed by Camm and Fei.²⁷ On the other hand, they also indicate that HR variability recovery among survivors of MI is a general phenomenon in all patients, regardless of the deterioration of the basal left ventricular function. These observations seem to be related to the hypothesis that the arrhythmogenic sudden death predictive value of a diminished HR variability should decrease over time from infarction onward.²⁸ This hypothesis seems to find confirmation in a study by Odemuyiwa *et al.*,¹¹ in which diminished HR variability was seen to constitute an independent predictor of sudden death only in the first 6 months post infarction.

Heart Rate Variability and Infarction Artery Status

We analyzed the possible relationship between HR variability and the angiographic parameters relating to patency of the infarct-related artery. According to a number of authors, decreased HR variability may correlate with the angiographic severity of the coronary disease.²⁹ Such a relationship has been reported in patients post infarction,^{13, 15, 16} although other authors such as Nolan *et al.*³⁰ have failed to observe such a relationship in patients with severe uncomplicated coronary pathology. Farrell *et al.*,⁴ in patients post infarction, observed no relationship between HR variability and either the number of diseased coronary vessels or the patency of the infarct-related artery. In the present series, we found no significant correlations between any of the HR variability parameters investigated and the degree of residual coronary stenosis, evaluated 1 week after MI. No analysis was made of the possible relation of coronary patency to HR variability at 6 months, since in this period coronary revascularization procedures were adopted in some patients—a fact that would affect the value of the results obtained.

Study Limitations

Heart rate variability changes daily, and in this sense 48-h recordings have been more informative. The material afforded by 42 patients is limited and precludes the drawing of any prognostic information. Other factors that also affect HR variability were present in variable degrees in the patients studied—a fact that may complicate interpretation of the results obtained. Of the patients studied, 40% were diabetic, and only 19% were treated with beta blockers, while 79% received fibrinolytic therapy that affects HR variability. Despite the fibrinolytic measures, all patients developed Q-wave infarctions; this is due either to the delay in applying fibrinolysis or to the fact that we excluded from the study those patients who, following fibrinolytic treatment, did not develop Q waves. Patients with an ejection fraction of $< 40\%$ were so few that analysis remains inconclusive.

Conclusions

Heart rate variability is low after acute myocardial infarction. This decrease tends to accentuate as secondary functional impairment increases. All of the HR variability parameters studied exhibit a significant increase over the postinfarction months in all surviving patients.

The SD of the RR interval is related to functional capacity at 1 week and 6 months post infarction. The mean RR cycle is related to left ventricular function at 1 week post infarction. The evolutive increment in HR variability at 6 months is greater among patients with initially depressed left ventricular function, as these same individuals also exhibit the lowest basal HR variability values.

No relationship was found between HR variability and the patency of the infarct related artery.

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