Relationship between baseline sympatho-vagal balance and the autonomic response to cardiac rehabilitation after a first uncomplicated myocardial infarction

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Key words:
Autonomic nervous system; Cardiac rehabilitation; Myocardial infarction.

Background. **After a first uncomplicated myocardial infarction, cardiac rehabilitation increases the parasympathetic tone, in a direction linked to a reduced risk of sudden cardiac death. This change in sympatho-vagal balance may be related to other clinical variables. The aim of this study was to define the factors implicated in determining the autonomic response to cardiovascular rehabilitation after myocardial infarction.**

Methods. **In 55 patients (39-80 years) we evaluated the modulation of the autonomic profile induced by 8 weeks of rehabilitation: we analyzed the changes in pNN50 derived from time-domain analysis (ΔpNN50) and in the low frequency/high frequency (LF/HF) ratio derived from autoregressive power spectral analysis (ΔLF/HF). A control group of 15 patients not undergoing rehabilitation was also studied. Variables considered at 4 weeks postinfarction and related to ΔpNN50 and ΔLF/HF ratio were: age, site of myocardial infarction, previous thrombolysis, ejection fraction, stress test duration, baseline LF/HF ratio.**

Results. **Patients not undergoing rehabilitation did not change their autonomic profile. On the contrary, rehabilitation induced a higher vagal tone (pNN50 from 6.5 – 1.5 to 16.2 – 3.1; LF/HF ratio from 8.3 – 5.2 to 5.1 – 2.9, $p < 0.05$). Eleven patients (20%) had baseline LF/HF ratio exceeding the mean value by 1.5 SD (19.4 – 1.4): in this subgroup, pNN50 was very low. In these patients, rehabilitation increased pNN50 and decreased LF/HF ratio. Indeed, both ΔpNN50 and ΔLF/HF ratio were significantly related to their baseline values ($p < 0.001$), even considering thrombolysis, site of myocardial infarction, age, and β-blocker therapy.**

Conclusions. **After a first uncomplicated myocardial infarction, sympatho-vagal balance may be very disturbed in some patients, despite a preserved ventricular function, good exercise capability and β-blockers. These patients should be encouraged to undergo rehabilitation, since the significant improvement in the parasympathetic tone may protect them against subsequent arrhythmic events.**

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Introduction

It is increasingly recognized that cardiovascular rehabilitation after a myocardial infarction may offer additional protection from morbidity and mortality[1,2]. In recent years, we have provided evidence that a period of rehabilitation with physical training after a first uncomplicated myocardial infarction may modulate the sympatho-vagal balance, shifting it toward a greater parasympathetic tone[3]: an autonomic profile of that kind, similar to what is obtained with β-adrenergic blockers[4] has been linked with a lesser risk of sudden cardiac death[5-7]. We also showed that this potentially favorable autonomic modulation interacted with that offered by β-blockers[8] and could persist in the long term in those patients who maintained a good adherence to the lifestyle and exercise prescriptions[9]. The modulation of the autonomic tone by rehabilitation has also been confirmed in a recent randomized study[10]. In the previous papers, we did not investigate whether the individual autonomic response to cardiac rehabilitation could be predicted by a given baseline clinical or autonomic profile. This issue, that constitutes the aim of the present retrospective analysis, may indeed be useful for risk stratification and patients management, helping the selection of those who need a supervised, hos-

pital-based rehabilitation program with respect to those who can safely undergo self-administered programs after physician s counseling.

Methods

Patients and protocol. Fifty-five patients (48 males and 7 females) were referred to our Center for outpatient rehabilitation after a first uncomplicated myocardial infarction (Group 1). An additional group of 15 patients not undergoing rehabilitation for logistical reasons was taken as a control group (Group 2). The characteristics of the two groups are summarized below. Mean age was 56 – 8 years in Group 1 and 55 – 9 years in Group 2 (mean – 1 SD). Myocardial infarction was anterior in 21 and postero-inferior in 35 of Group 1, and anterior in 4 and postero-inferior in 11 of Group 2. The majority (36/55 - 64% - in Group 1, and 10/15 - 67% - in Group 2) had undergone fibrinolysis. Coronary angiography was available for 21 Group 1 patients (36%, 13 with anterior and 8 with inferior myocardial infarction) and in 6 Group 2 patients. We did not include in the analysis patients with diabetes, severe hypertension, peripheral neuropathy, atrial fibrillation, frequent atrial or ventricular arrhythmias, digitalis treatment. The initial therapy was maintained during the rehabilitation period, and thereafter until the annual follow-up visit (e.g., ACE-inhibitors and β-blockers, administered to many patients, were not withdrawn). Left ventricular ejection fraction and dimensions were assessed by two-dimensional echocardiography at the initial visit. The mean baseline ejection fraction was 56 – 5%. Patients not undergoing rehabilitation had the same schedule of clinical and autonomic evaluation at 1 and 3 months after myocardial infarction[3,8]: they too had a preserved ejection fraction after myocardial infarction (56 – 7%). The ambulatory rehabilitation program consisted of an endurance training of 8 weeks, starting 3-4 weeks (25 – 3 days) after myocardial infarction in all patients[3,8]. Each 1-hour session was repeated 5 days a week, the intensity of the callisthenics and bicycle exercise being increased gradually every week. Educational sessions were performed by the medical and paramedical staff. Exercise capability and the likelihood of residual ischemia were evaluated with maximal bicycle stress test (3 min steps of 25 W each) before and after rehabilitation.

Measurement of heart rate variability. In all patients, heart rate variability was evaluated in a separate session 1) before the initiation of exercise training, 4 weeks after myocardial infarction, 2) 8 weeks later, i.e. 3 months after infarction. The test was performed late in the morning; patients were studied while quietly supine, awake, breathing regularly while following a metronome at 20 acts/min. We chose this breathing rate because it was easier for the patients to follow with respect to slower rates; in fact, this rate has previously been used by Pagani et al.[11] while controlling tidal volume, gas exchange and oxygen saturation, and respiratory alkalosis was never found. After 15 min of adaptation, the recording was started and continued for another 15 min. We assessed heart rate variability with a commercially available recording system and software (Predictor II, Corazonix LdT, Oklahoma City, OK, USA). The ECG signal was digitized at 500 Hz, and QRS complex was recognized by cross correlation with a template chosen by the investigator. Premature beats and the subsequent intervals were automatically discarded, and this detection was also visually checked. In the time domain, variables obtained were: standard deviation of the RR intervals (RRSD), root mean square of the successive RR intervals (MSSD), and percent of RR intervals exceeding the previous RR by > 50 ms (pNN50). All these indexes seem to be related to vagal tone[11]. Frequency-domain analysis was achieved with an autoregressive algorithm, with DC filtering and an Akaike model of 16 to 22. Boundaries of the low frequency (LF) oscillation (0.03-0.15 Hz) and those of the high frequency (HF) oscillation (0.15-0.35 Hz) were chosen by the investigator, their area calculated by the software and converted into normalized units (nu) to better identify the individual spectral component[10,11]. The amount of LF and HF oscillation (in absolute and nu) and the LF/HF ratio were obtained: LF/HF ratio was chosen as the simpler and more accurate index of the sympatho-vagal control of heart rate[10,11]. The autospectra obtained from these short period recordings did not show a very low frequency (VLF) component (0.00 to 0.03 Hz) as do longer, Holter-based recordings. Thus, the analysis was restricted to LF and HF oscillations.

Statistical analysis. Results are expressed as mean value – SD. Differences between patients regarding discrete variables were assessed by χ^2 test. Correlation between continuous variables was obtained by means of linear regression analysis. Differences among continuous variables were analyzed by ANOVA for repeated measurements (within the same group of patients before and after rehabilitation) or by ANOVA (among two groups of patients). *Post-hoc* comparisons were analyzed by Tukey s test. A $p < 0.05$ was considered statistically significant.

Results

Effects of rehabilitation on the autonomic tone. Eight weeks of cardiac rehabilitation induced a significant shift in the sympatho-vagal balance in Group 1, while in Group 2, i.e. in patients not undergoing rehabilitation, there was no change in the various indexes of heart rate variability in the time or frequency domain (Table I).

Age and the autonomic response to rehabilitation. All patients reached a good training effect with rehabilita-

Table I. Effects of rehabilitation on heart rate variability.

	RR (ms)		pNN50 (%)		MSSD (ms)	
	Before	After	Before	After	Before	After
Rehabilitation (n = 55)	803 – 135	903 – 181*	6.5 – 1.6§	16.1 – 1.8*	25.6 – 3.3	34.9 – 7.6*§
No rehabilitation (n = 15)	810 – 211	815 – 178	6.1 – 2.3	6.9 – 2.1	23.3 – 2.1	24.5 – 6.2

	LF (ms^2)		HF (ms^2)		LF (nu)		HF (nu)		LF/HF	
	Before	After	Before	After	Before	After	Before	After	Before	After
Rehabilitation (n = 55)	876 – 125	938 – 166	156 – 88	252 – 101*	73 – 1	67 – 2*§	13 – 1	18 – 2*	8.8 – 1.4	4.9 – 1.3*§
No rehabilitation (n = 15)	825 – 152	839 – 146	132 – 67	150 – 94	75 – 5	73 – 2	12 – 2	13 – 2	9.1 – 1.1	8.1 – 1.2

HF = high frequency; LF = low frequency; MSSD = root mean square of the successive RR intervals; pNN50 = percent of RR intervals exceeding the previous RR by > 50 ms. * $p < 0.05$ vs before rehabilitation; § $p < 0.05$ vs other group.

tion: exercise duration increased from 11 – 1 to 14 – 1 min, the workload from 106 – 19 to 135 – 18 W ($p < 0.01$). A modulation of the sympatho-vagal balance with an increase in the parasympathetic tone was seen in all patients. In the time domain, pNN50 increased from 6.5 – 1.5 to 16.2 – 3.1% ($p < 0.05$). In the frequency domain, LF/HF ratio decreased from 8.3 – 5.2 to 5.1 – 2.9 ($p < 0.05$). These data did confirm previous observations from our laboratory[3,8]. Despite a good overall training effect, there was a slight significant reduction in the training effect with declining age (Fig. 1). However, no age effect was present on the degree of sympatho-vagal modulation by rehabilitation (Table II).

Autonomic response to rehabilitation in anterior and inferior myocardial infarction. Patients with anterior myocardial infarction had a normal, but slightly lower left ventricular function compared to patients with inferior

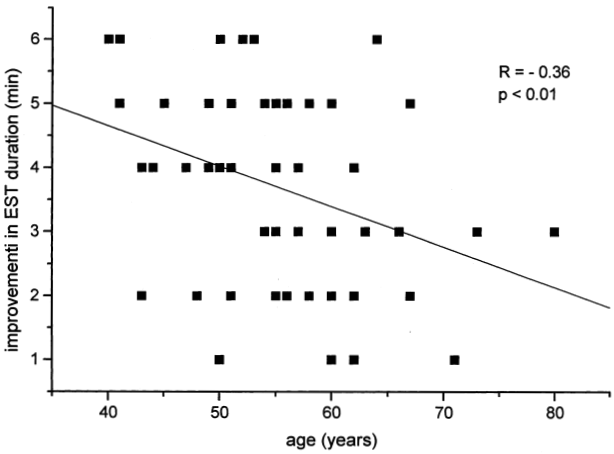

Figure 1. *Relationship between age and training effect, expressed as the increase in exercise stress test (EST) duration. There was a slight but significant reduction in the training effect with increasing age, despite a good overall effect in every age group.*

Table II. Age and heart rate variability.

	RR (ms)		pNN50 (%)		MSSD (ms)	
	Before	After	Before	After	Before	After
< 50 years (n = 13)	801 – 155	925 – 201*	9.1 – 2.2§	21.3 – 1.9*§	33.8 – 4.1§	47.9 – 8.8*§
50-60 years (n = 25)	811 – 240	899 – 188*	6.2 – 2.3	15.5 – 2.1*	23.3 – 2.1	30.5 – 5.2*
> 60 years (n = 17)	798 – 190	885 – 141*	4.1 – 1.9	11.6 – 2.5*	19.9 – 3.9	26.5 – 3.2*

	LF (ms^2)		HF (ms^2)		LF (nu)		HF (nu)		LF/HF	
	Before	After	Before	After	Before	After	Before	After	Before	After
< 50 years (n = 13)	1423 – 135	1496 – 122	527 – 46	704 – 81	73 – 2	68 – 2	13 – 2	18 – 2*	9.4 – 2.1	4.4 – 1.6*
50-60 years (n = 25)	798 – 88	825 – 91	352 – 48	425 – 39	76 – 5	66 – 2*	12 – 2	17 – 2*	8.4 – 0.9	5.6 – 0.7*
> 60 years (n = 17)	426 – 59	416 – 48	174 – 21	234 – 24	71 – 3	64 – 2*	14 – 2	18 – 2*	7.5 – 1.2*	4.7 – 0.7*

Abbreviations as in table I. * $p < 0.05$ vs before rehabilitation; § $p < 0.05$ vs > 60 years.

myocardial infarction (ejection fraction 53 – 7 vs 58 – 6%, $p < 0.05$). However, they had a similar good training effect with rehabilitation: exercise duration increased from 10 – 2 and 11 – 1 min to 14 – 1 and 15 – 2 min, respectively in anterior vs inferior myocardial infarction; and the workload duration increased from 108 – 2 and 109 – 3 W to 138 – 18 and 137 – 19 W, respectively. Moreover, no differences were found between anterior vs inferior myocardial infarction with respect to the autonomic modulation obtained with training (Table III). In this respect, it is noteworthy to remark that no relationship was found between ejection fraction soon after myocardial infarction and the degree of pNN50 or LF/HF ratio modulation.

Autonomic response to rehabilitation in patients with and without thrombolysis. Patients with previous thrombolysis had similar left ventricular function and training effect with rehabilitation compared with patients who did not undergo thrombolysis. Exercise duration increased from 11 – 1 to 15 – 2 min vs 11 – 2 to 14 – 1 min, and the workload increased from 106 – 19 to 136 – 19 W vs 115 – 16 to 142 – 22 W. Similarly, no differences were found between thrombolyzed vs non-thrombolyzed myocardial infarction with respect to autonomic modulation (Table IV).

Baseline sympatho-vagal balance and autonomic response to rehabilitation. Soon after myocardial infarction, the spectral analysis of heart rate variability showed signs of reduced vagal tone and increased sympathetic activation in patients (pNN50 6.5 – 1.5%, LF/HF 8.3 – 5.2.). However, the degree of such an activation was quite different among patients: 11 of them (20%) had baseline LF/HF ratio exceeding the mean LF/HF value by 1.5 SD (LF/HF 16.1 nu: LF/HF 19.4 – 1.4). This high LF/HF ratio coexisted with very low pNN50 (2.1 – 0.5) compared to patients with signs of lesser sympathetic activation (pNN50 10.9 – 2.2, LF/HF 6.1 – 3.2). This subgroup did not differ (χ^2 = NS) from the group of patients with lesser adrenergic activation, that is, lower LF/HF ratio and higher pNN50 with respect

Table III. Site of myocardial infarction and heart rate variability.

	RR (ms)		pNN50 (%)		MSSD (ms)	
	Before	After	Before	After	Before	After
Anterior (n = 16)	797 – 159	902 – 212*	5.9 – 2.1	15.1 – 2.1*	23.2 – 4.1	37.5 – 5.8*
Inferior (n = 39)	809 – 211	904 – 163*	7.1 – 2.3	17.2 – 2.4*	28.1 – 2.3	32.4 – 6.2*

	LF (ms^2)		HF (ms^2)		LF (nu)		HF (nu)		LF/HF	
	Before	After	Before	After	Before	After	Before	After	Before	After
Anterior (n = 16)	767 – 68	851 – 77	283 – 29	379 – 41	73 – 2	63 – 3*	12 – 2	18 – 2*	9.5 – 1.4	4.3 – 2.1*
Inferior (n = 39)	972 – 84	971 – 101	378 – 38	499 – 49	72 – 3	67 – 1*	13 – 1	17 – 2*	7.8 – 0.8	5.5 – 1.7*

Abbreviations as in table I. * $p < 0.05$ vs before rehabilitation.

Table IV. Previous thrombolysis and heart rate variability.

	RR (ms)		pNN50 (%)		MSSD (ms)	
	Before	After	Before	After	Before	After
rt-PA (n = 34)	800 – 129	911 – 187*	7.9 – 1.9	17.2 – 2.5*	27.5 – 3.6	36.0 – 4.8*§
No rt-PA (n = 21)	806 – 197	895 – 203*	5.1 – 2.5	15.1 – 2.1*	23.8 – 2.9	33.9 – 5.3*

	LF (ms^2)		HF (ms^2)		LF (nu)		HF (nu)		LF/HF	
	Before	After	Before	After	Before	After	Before	After	Before	After
rt-PA (n = 34)	951 – 64	932 – 77	350 – 29	479 – 45	72 – 1	64 – 2*	13 – 2	19 – 2*	8.9 – 1.1	4.9 – 1.0*
No rt-PA (n = 21)	788 – 72	890 – 101	311 – 32	439 – 38	76 – 2	68 – 1*	11 – 1	17 – 2*	8.6 – 0.8	5.4 – 0.7*

rt-PA = recombinant tissue-type plasminogen activator. Other abbreviations as in table I. * $p < 0.05$ vs before rehabilitation; § $p < 0.05$ vs other group.

to the site of myocardial infarction (anterior in 44 vs 35%), therapy (β-blockers in 33 and 48%), and previous thrombolysis (70 vs 62%). In these 11 patients, rehabilitation was maximally effective in modulating the autonomic tone, increasing pNN50 to 18.5 – 3.2, and decreasing LF/HF ratio to 5.9 – 3.4 ($p < 0.001$). Rehabilitation modified the sympatho-vagal balance also in patients with less severe autonomic derangement: pNN50 increased from 10.9 – 2.2 to 14.1 – 1.9; LF/HF ratio decreased from 6.1 – 3.2 to 4.8 – 2.6 ($p < 0.05$). In fact, a significant relationship was also found between ΔpNN50 and baseline pNN50% ($r = -0.68$, $p < 0.001$) and between ΔLF/HF and baseline LF/HF ratio ($r = -0.85$, $p < 0.001$) (Fig. 2), that held even considering different subgroups: anterior vs inferior myocardial infarction, and previous thrombolysis. No relationship was found between ΔpNN50 or ΔLF/HF and ejection fraction, or between ΔpNN50 or ΔLF/HF and initial stress test duration or its improvement with training, when a linear regression analysis was performed.

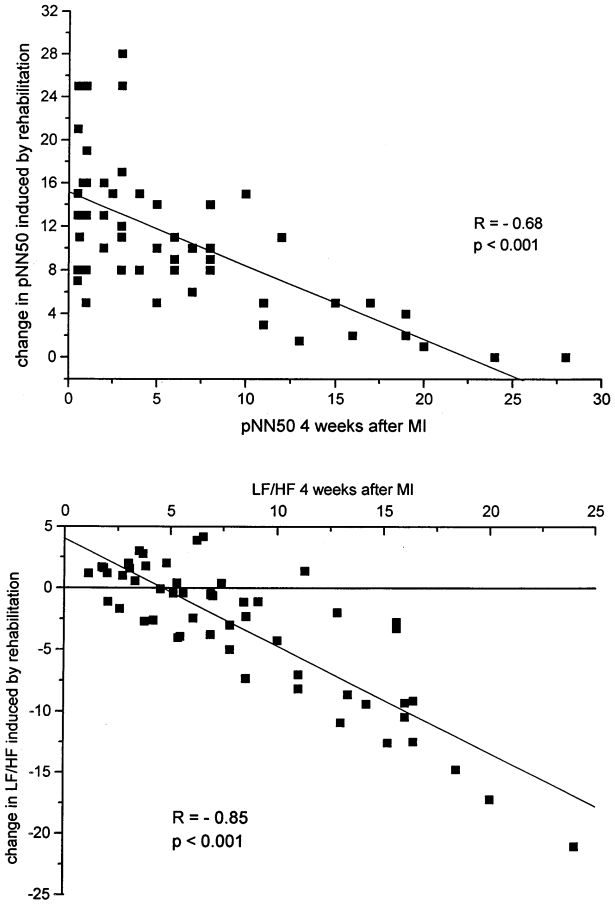

Figure 2. *Relationship between baseline sympatho-vagal balance (expressed as pNN50 in the* upper panel *and LF/HF in the* lower panel*) and the effect of rehabilitation on the sympatho-vagal balance, expressed as the increase in pNN50 in the* upper panel *and the decrease in LF/HF in the* lower panel*. A significant relationship was found in both cases between the initial degree of sympatho-vagal derangement and the amount of autonomic modulation. LF/HF = low frequency/high frequency ratio; MI = myocardial infarction; pNN50 = percent of RR intervals exceeding the previous RR by > 50 ms.*

Discussion

The results of this study are two-fold. First, we confirmed and extended our previous observations that a 2-month period of rehabilitation can induce a significant shift in the sympatho-vagal control of heart rate, increasing the parasympathetic tone and smoothing the adrenergic activation observed soon after a first, uncomplicated myocardial infarction[3,8,9]. Moreover, we investigated the mutual relationship between some clinically relevant variables and such a favorable short-term autonomic response to cardiac rehabilitation. We carried out this analysis with the aim of identifying which subset of patients should follow a formal, hospital-based rehabilitation program with clinical monitoring. In fact, postinfarction patients who have good ventricular function, no arrhythmias, no residual ischemia, are at low risk for further cardiovascular events[12], and frequently are only given standard counseling on the importance of training and lifestyle changes. However, even these subjects are at risk of sudden cardiac death, especially if their autonomic tone and reflexes are abnormal[12,13]. Cardiac rehabilitation significantly reduces mortality also by reducing sudden cardiac death[1]: following various experimental and clinical observations[3,5,6,14,15] it has been suggested that this effect may be the consequence of the powerful autonomic modulation obtained with physical training[3,4,10,15] and possibly of lifestyle changes[9]. Indeed, the overall results of the present study confirm the existing data on the overall positive effect of rehabilitation on cardiovascular autonomic modulation and thus its potentially useful effect in the prevention of sudden death[3,4,10].

Age did not influence the autonomic response: elderly patients, besides having a good training effect, showed a significant blunting of adrenergic activation together with an increase in the parasympathetic tone similar to that observed in younger patients. Thus, patients should not be denied rehabilitation on the basis of age. This concept has recently been confirmed in a large, multicenter study[10].

The site of infarction did not influence the subsequent sympatho-vagal modulation, nor did the patients after anterior myocardial infarction have a different autonomic profile at baseline. In the past, it was postulated that a greater sympathetic activation could follow anterior rather than inferior myocardial infarctions, due to a different pattern of innervation[15], but this hypothesis was not confirmed[16]. In addition, a recent clinical study showed that, in the subacute phase of myocardial infarction, the prevailing autonomic pattern is that of a predominant adrenergic tone like the one we observed, independent of the site of the ischemic event[17].

The fact that a previous fibrinolysis did not have a significant effect on baseline autonomic tone and on its response to rehabilitation was somewhat surprising. Following previous reports of enhanced baroreflex sensitivity in patients with open infarct-related artery[18] we

expected a lesser sympathetic activation in patients who had undergone fibrinolysis, but this was not the case. However, we did have coronary angiography data only for a minority of patients (38%): therefore, often being unaware of the real efficacy of the pharmacological reperfusion procedure, we might have considered together patients with fully open, partially open and close infarct-related arteries. In this respect, our preliminary data on patients who underwent primary coronary angioplasty after anterior myocardial infarction show a better autonomic profile compared to patients with similar infarction treated with standard procedures (Malfatto G. et al., unpublished data).

The only variable that anticipated the amount of the subsequent sympatho-vagal balance modulation was the feature of the sympatho-vagal balance observed soon after myocardial infarction. That is to say, the greater the initial disturbance of the autonomic balance, the better the final rearrangement obtained with rehabilitation. Our observation is in line with several clinical observations indicating that for a given therapy the benefit is more relevant in the more severely compromised patients. We can only speculate about the reasons why sympathetic activity was so high (and the counterbalancing vagal tone so low) in some patients despite a preserved ventricular function, good exercise capability, no residual ischemia and β-blocker therapy. These patients may have a greater sympathetic outflow due to an enhanced central command, being more aroused and stressed by their clinical condition: it is well known that behavioral challenges are powerful activators of the adrenergic nervous system, and that this activation is well reflected by power spectral analysis[19]. Rehabilitation, with its mixture of physical training and behavioral conditioning (counseling, relaxation, stress avoidance) represents probably the more complete clinical intervention for those patients who are severely distressed after myocardial infarction. Unfortunately, when the study began we did not routinely perform a psychological examination and the analysis of heart rate variability during mental stress and we cannot prove our hypothesis.

Some limitations of the study must be emphasized. First, it was a small, retrospective, observational study. Second, we could not perform a multivariate analysis on the variables influencing the autonomic response due to the mixture of continuous (age, ejection fraction, LF/HF ratio, pNN50) and discrete (site of myocardial infarction, occurrence of thrombolysis) initial data. Third, there is not a follow-up validating the predictive power of the initial autonomic profile; on the other hand, in our small low-risk group (good ejection fraction, no residual ischemia, no arrhythmias) one would not have expected serious events to occur in the first year.

Despite these limitations, the present data show that a significant minority of patients (about 20%), after a first and otherwise uneventful myocardial infarction, have signs of exceedingly enhanced sympathetic activation and blunted vagal tone, whose origin should be investigated. Further prospective studies with a more powerful design may provide a better definition of these patients and a better way to screen them. For the moment, since they could be at a higher risk for sudden cardiac death, they should be encouraged to follow a rehabilitation program with physical training and behavioral counseling. The significant improvement in parasympathetic tone may protect them against subsequent arrhythmic events.

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