Original articles

Primary coronary angioplasty and subsequent cardiovascular rehabilitation are linked to a favorable sympathovagal balance after a first anterior myocardial infarction

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Angioplasty, primary; Autonomic nervous system; Cardiac rehabilitation; Myocardial infarction; Power spectral analysis.

Background. **Modulation of the autonomic tone may contribute to the positive clinical effects of reperfusion of the ischemic zone after acute myocardial infarction (AMI). Little information exists about the effects on the sympathovagal balance of the early reopening of the vessel achieved by means of primary coronary angioplasty (PTCA). Even less is known on the autonomic effects of rehabilitation in patients undergoing PTCA.**

Methods. **We performed spectral analysis of the RR interval variability during 15 min of ECG in resting conditions in 51 patients (47 males, 4 females, mean age 55 ± 6 years) 2-3 weeks after a first anterior AMI, and after 8 weeks of rehabilitation with physical training. The ratio between the low- and high-frequency (LF/HF) components of each autospectrum was used to describe the sympathovagal balance. Patients were divided into three groups: group 1 (n = 26, primary PTCA/stenting); group 2 (n = 11, recombinant tissue-type plasminogen activator); group 3 (n = 14, no reperfusion). Treatment was similar in the three groups and was maintained during the whole rehabilitation period.**

Results. **Before rehabilitation, group 1 showed an adrenergic activation that was more blunted than that observed in groups 2 and 3. This activation was maximal in those patients with the shortest delay before the procedure. Cardiovascular rehabilitation modulated the LF/HF ratio in all groups.**

Conclusions. **Early and effective reperfusion of the infarct-related artery is associated with a better sympathovagal tone shortly after AMI; this is followed by the known benefits of cardiovascular rehabilitation on autonomic tone.**

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Introduction

An unwarranted sympathetic activation plays a pivotal role in determining the most dreadful complications of myocardial infarction, namely, sudden cardiac death[1,2] and heart failure through adverse ventricular remodeling[3]. As a consequence, interventions that blunt adrenergic hyperactivity through a modulation of the sympathovagal balance – i.e. drugs such as β-blockers[4] and ACE-inhibitors[5] – lower the risk of sudden cardiac death and left ventricular dilation[6-8]. Non-pharmacological approaches, such as the reopening of the infarct-related artery by thrombolysis[9] or coronary angioplasty (PTCA)[10], and cardiovascular rehabilitation with physical training[11], also afford a significant prognostic improvement: however, it is unclear whether an interference with the cardiac autonomic control contributes to their favorable effects[12-15].

Quite often, patients recovering from myocardial infarction after an interventional procedure do not follow a rehabilitation program; they are hence excluded from the possibility of further improving their prognosis through an extensive secondary prevention approach[16]. In our Center, after myocardial infarction patients are always offered an outpatient cardiac rehabilitation period. We therefore performed this retrospective analysis, with a 2-fold purpose: 1) to evaluate, after myocardial infarction, the effects of primary PTCA on autonomic tone in a selected population of patients, and 2) to analyze whether a period of cardiac rehabilitation could add further changes to their cardiovascular control.

Methods

Patients and protocol. Fifty-one patients (47 males, 4 females, mean age 55 ± 6

years) were referred for outpatient rehabilitation 2 to 3 weeks after a first anterior myocardial infarction (mean 17 ± 3 days). Most (n = 35, 75%) had been treated at our coronary care unit. The patients were divided into three groups depending on the management they received in the acute phase: group 1 (n = 26) underwent primary or facilitated PTCA and stenting with a good TIMI grade flow; group 2 (n = 11) received recombinant tissue-type plasminogen activator (indirect signs of reperfusion were present), and group 3 (n = 14) did not receive reperfusion due to the delay in their arrival to the emergency unit. All patients signed an informed consent for the use of their clinical data; the study was approved by our Ethics Committee. The baseline characteristics of the three groups of patients are summarized in table I: they did not differ with regard to any clinical variable considered. Patients with diabetes, a history of severe arterial hypertension, peripheral neuropathy; atrial fibrillation and/or any ventricular arrhythmia that contraindicated rehabilitation were excluded. Therapy was maintained during the rehabilitation period (e.g. nitrates, ACE-inhibitors, β-blockers, lipid-lowering drugs). The outpatient rehabilitation program consisted, in accordance with national and international recommendations[17], of an endurance training period lasting 8 weeks. Each 1-hour session was repeated 5 days a week, the intensity of the calisthenics and bicycle exercise being increased gradually every week. The target heart rate was 70% of that achieved at the initial stress test, or 70% of the maximal theoretical heart rate (60% in patients receiving β-blockers). Medical and paramedical staff performed the educational sessions. The left ventricular ejection fraction and dimensions were assessed at discharge from the coronary care unit by means of two-dimensional echocardiography. These parameters were again measured after rehabilitation. The exercise capability and the occurrence of residual ischemia were evaluated at bicycle stress test (2-min steps of 25 W each), before rehabilitation in groups 2 and 3, and after rehabilitation in all patients. Group 1 patients did not undergo a stress test during the first month after the procedure due to the likelihood of false-positive results.

Table I. Clinical characteristics of the patients.

	Group 1 (n=26)	Group 2 (n=11)	Group 3 (n=14)
Age (years)	53 ± 9	56 ± 6	56 ± 7
Sex (M/F)	23/3	10/1	13/1
Ejection fraction (%)	47 ± 5	51 ± 5	52 ± 7
Aspirin (%)	100	100	100
β-blockers (%)	71	64	65
Nitrates (%)	67	58	57
ACE-inhibitors (%)	70	63	59
Statins (%)	71	64	67

No differences among variables (ANOVA and χ^2 test); probability of type II error also tested.

Measurement of heart rate variability. In all patients, heart rate variability was evaluated in a separate session a) before the initiation of exercise training, 2-3 weeks after myocardial infarction, and b) 8 weeks later, i.e. about 3 months after the infarction. The test was performed late in the morning; patients were studied while quietly supine, awake and breathing regularly following a metronome set at 20 breaths/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 been previously used by Pagani et al.[18] in order to evaluate the tidal volume, gas exchange and oxygen saturation. In no case did respiratory alkalosis develop. 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 Ltd., Oklahoma City, OK, USA). The ECG signal was digitized at 500 Hz and the QRS complex was identified by cross correlation with a template chosen by the investigator. Premature beats and the subsequent interval were automatically discarded, and this process was also visually checked. Frequency-domain analysis was achieved with an autoregressive algorithm, with DC filtering and a 16 to 22 Akaike model. 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 using the software and converted to normalized units (nu) so as to better identify the individual spectral component[18]. The amount of LF and HF oscillation (in absolute units and nu) and the LF/HF ratio were obtained: the LF/HF ratio was chosen as the simpler and more accurate index of the sympathovagal control of heart rate[18,19]. In contrast to longer, Holter-based recordings, the autospectra obtained from these short period recordings did not show a very LF component (0.00 to 0.03 Hz). Thus, the analysis was restricted to LF and HF oscillations.

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

Results

Baseline autonomic control. Overall, the patients had an increased adrenergic tone, as expressed by a high LF/HF ratio calculated at the time of baseline examination soon after acute myocardial infarction

(AMI) (LF/HF ratio 8.4 ± 1.1). However, a significant attenuation of this sympathetic hyperactivity was observed in patients in whom an effective reperfusion had been achieved (group 1), in comparison with patients in whom no thrombolysis was performed (group 3) (Fig. 1). A somewhat intermediate result was observed in group 2 patients who had undergone recombinant tissue-type plasminogen activator and therefore could be expected to have a variable reperfusion (Fig. 2). In group 1, a relationship was found between the delay in reperfusion (minutes from symptom onset to reperfusion) and the LF/HF ratio. Clearly in contrast with those who had a later reperfusion, patients with a door-to-balloon time < 2 hours had almost no signs of sympathetic hyperactivity at baseline (Figs. 3 and 4). In detail, a positive relationship was found between the time to reperfusion and the LF/HF ratio: the earlier the PTCA, the better the autonomic profile (Fig. 5).

Clinical response to rehabilitation. The left ventricular ejection fraction and dimensions (two-dimensional echocardiography) at baseline did not significantly differ among groups (Table I) and were not changed by rehabilitation in groups 2 and 3. Interestingly, group 1 patients showed a significant improvement in their left ventricular function after rehabilitation (ejection fraction 47 ± 5 to 59 ± 4%, p < 0.02). All

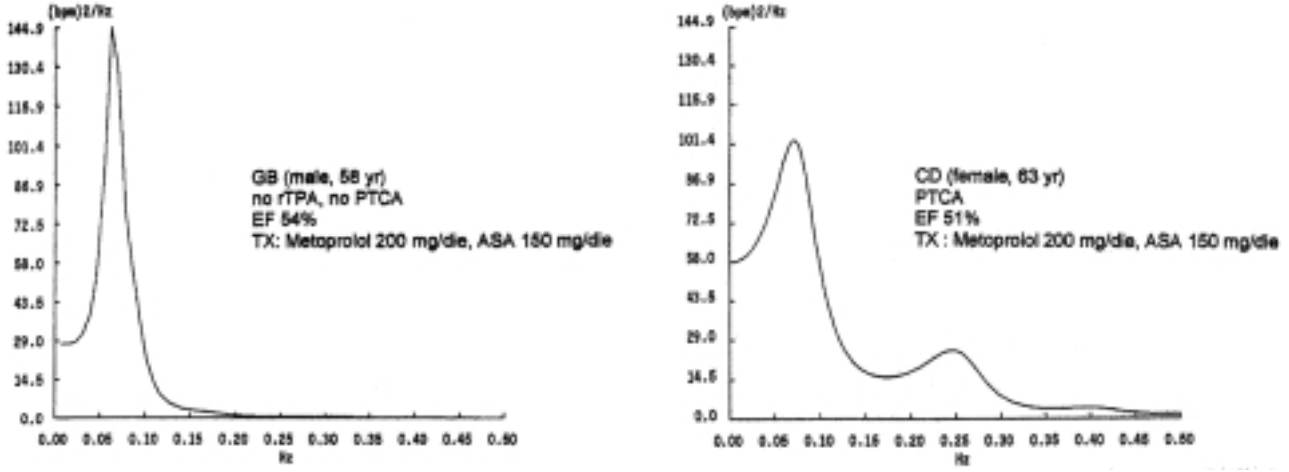

Figure 1. *Spectral profiles of 2 patients. Despite similar clinical characteristics, they had received a different treatment (TX) in the acute phase.* Left panel*: a patient in whom no acute reperfusion was performed, due to the delay prior to coronary care unit admission.* Right panel: *a patient who underwent primary coronary angioplasty (PTCA) (door-to-balloon time 125 min). The higher high-frequency component and smaller low-frequency oscillation are evident in the latter case, indicating a better sympathovagal balance. ASA = acetylsalicylic acid; EF = ejection fraction; rTPA = recombinant tissue-type plasminogen activator.*

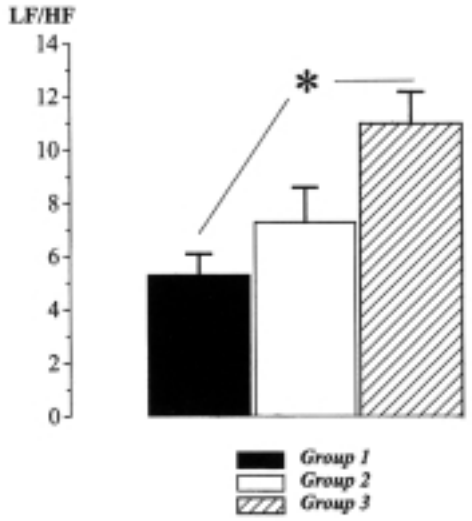

Figure 2. *Mean baseline low frequency/high frequency (LF/HF) ratio in the three groups of patients. Three different autonomic profiles are evident, indicating that restoring antegrade flow leads to less adrenergic activation as expressed by a lower LF/HF ratio in group 1. * p < 0.05 vs groups 2 and 3.*

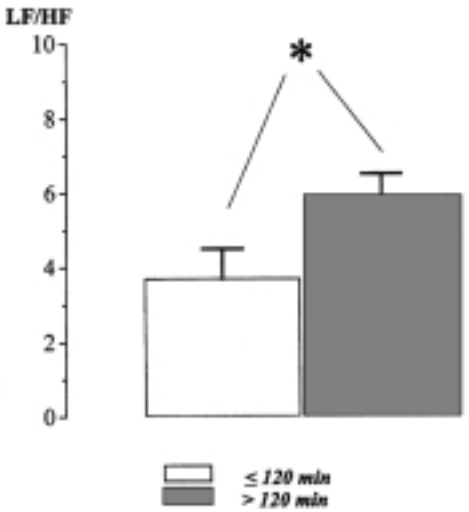

Figure 3. *Average values of the low frequency/high frequency (LF/HF) ratio in patients submitted to primary coronary angioplasty (group 1), divided according to their door-to-balloon time. Patients submitted to primary coronary angioplasty earlier than 2 hours following symptom onset had a significantly lower LF/HF ratio. * p < 0.05.*

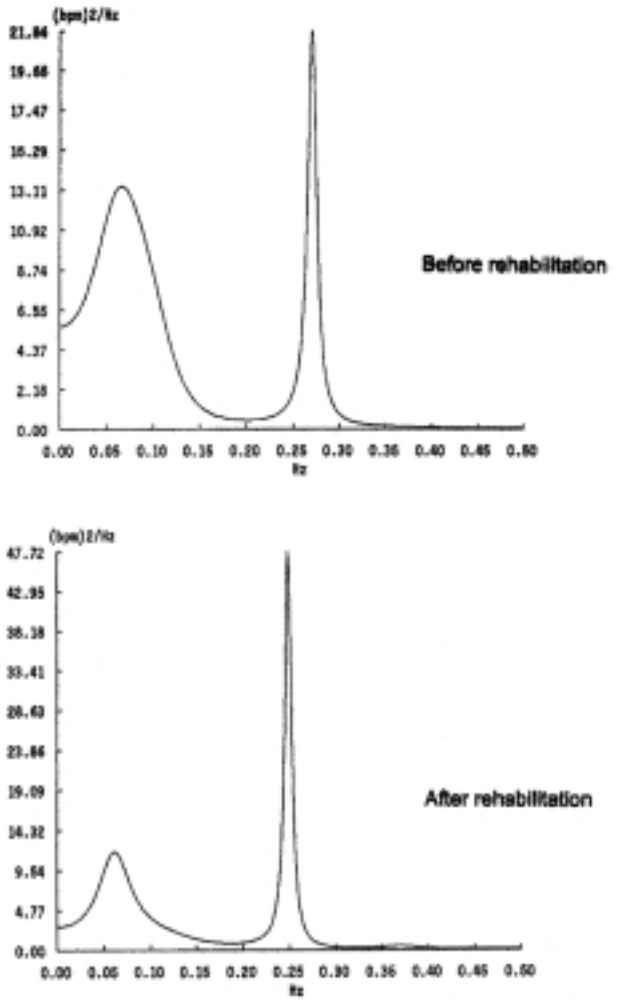

Figure 4. *Spectral profiles of a patient in whom coronary angioplasty was successfully performed 45 min following symptom onset, before and after rehabilitation.* Upper panel*: at baseline, 17 days after coronary angioplasty, a small low-frequency and a prominent high-frequency component are evident, suggesting a preserved sympathovagal balance.* Lower panel: *after rehabilitation, a further decrease in the low-frequency component may be seen in the spectrum. This is due to the vagomimetic effects of training.*

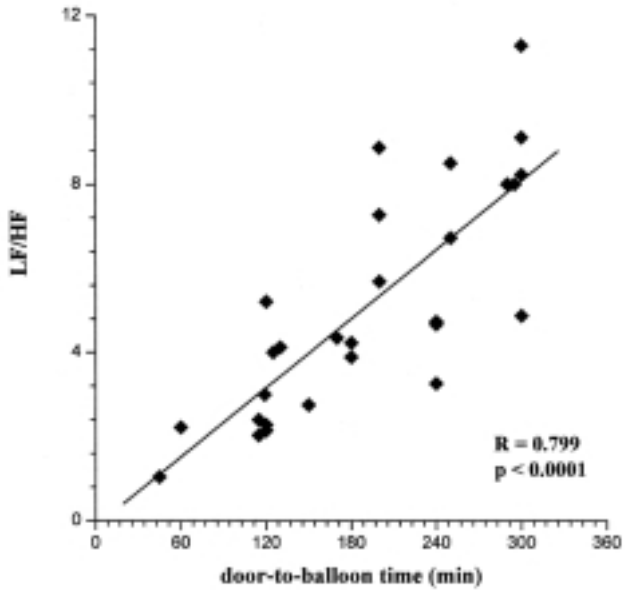

Figure 5. *Linear positive relationship between the door-to-balloon time and the low frequency/high frequency (LF/HF) ratio: the less the delay, the less the adrenergic activation observed before rehabilitation, 17 ± 3 days after acute myocardial infarction.*

patients had a good training effect with rehabilitation, whilst none reported complications. Group 1 patients achieved a good exercise capability, as shown by the duration of the exercise stress test performed at the end of the training period, about 3 months after the infarction and PTCA (Table II). Patients in groups 2 and 3, in whom a stress test could be performed before rehabilitation, showed a significant improvement in exercise duration (Table II). Overall, only 4/51 patients had an abnormal ST-segment response to intense exercise (> 100 W).

Autonomic response to rehabilitation. After the training period, a significant improvement in the LF/HF ratio was observed in all groups (Figs. 4 and 6). The absolute value of the LF/HF ratio was lower in group 1 ($p < 0.05$): these patients showed the strongest vagal modulation (LF/HF ratio 3.3 ± 0.9 nu); however, the most marked reduction in the LF/HF ratio was observed in subjects with the highest baseline values, that is, group 3 patients. In group 1, no relationship was found between the improvement in the autonomic profile, expressed as the percent change in the LF/HF ratio, and the change in ventricular function expressed as the percent change in ejection fraction ($r = 0.13$, $p = 0.21$), nor with the door-to-balloon time in minutes ($r = -0.14$, $p = 0.15$).

Table II. Effects of rehabilitation (R) on clinical variables.

	Group 1 (n=26)		Group 2 (n=11)		Group 3 (n=14)	
	Before R	After R	Before R	After R	Before R	After R
Heart rate (b/min)	62 ± 4	56 ± 3	70 ± 11	64 ± 10§	67 ± 11	60 ± 9§
Ejection fraction (%)	47 ± 5	59 ± 4§	51 ± 6	55 ± 8	52 ± 7	54 ± 6
Workload (W)	*	133 ± 16	103 ± 15	135 ± 22§	100 ± 17	129 ± 11§

* no test was performed after 2-3 weeks due to the likelihood of false-positive results; § $p < 0.05$ vs baseline.

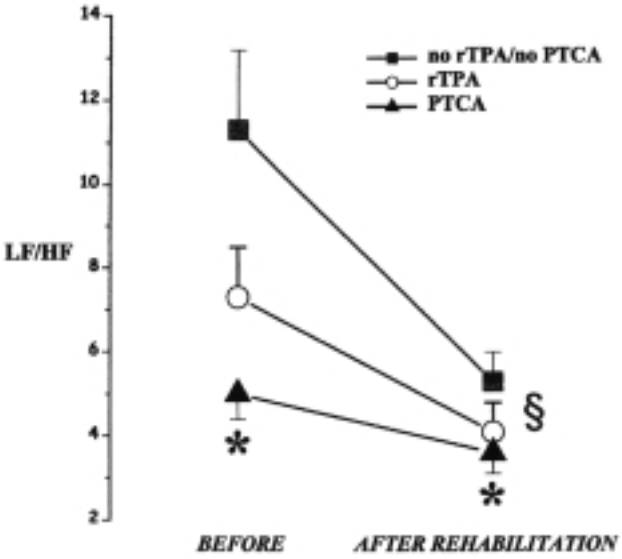

Figure 6. *Changes in the low frequency/high frequency (LF/HF) ratio with rehabilitation in the three study groups. All patients showed a strong autonomic modulation with training (§ $p < 0.05$ vs baseline). Group 1 patients retained the highest vagal tone (* $p < 0.05$ vs other groups), even though the greatest reduction in the LF/HF ratio was observed in subjects with the highest values before rehabilitation (group 3 patients). PTCA = coronary angioplasty; rTPA = recombinant tissue-type plasminogen activator.*

Discussion

The early and aggressive reopening of the infarct-related artery in patients at their first anterior myocardial infarction is associated with an almost "normal" autonomic profile. Moreover, a subsequent period of cardiovascular rehabilitation further modulates the sympathovagal balance, leading all patients to an improved neural cardiac control. These findings will be discussed separately.

Critique of the study. An appraisal of the limits of this study is warranted. It is an observational study with no randomization and no control group: thus, one may argue that the observed autonomic changes could simply reflect the recovery from myocardial infarction with time, rather than the effects of rehabilitation. We do not believe this is the case: in our first studies we reported the results of control groups who did not undergo rehabilitation showing that the influence of time on the sympathovagal balance is not relevant[14].

Why anterior infarction? We studied only patients after a first myocardial infarction localized in the anterior wall. There were two reasons for this choice. First, with respect to infero-posterior AMI, where sympathetic activation may follow transient signs of vagal hyperactivity[20,21], anterior AMI is constantly followed by strong and stable signs of enhanced adrenergic tone[20]; thus, we avoided any potential flaw in the interpretation of the changes in vagal and sympathetic effects. In addition, the effects of cardiac rehabilitation have been extensively studied in patients with anterior myocardial infarction and reduced ejection fraction in whom concern for adverse ventricular remodeling has been expressed[22,23]. In our study, we safely applied a training protocol in patients with clinical characteristics similar to those of the EAMI study[23] (the ventricular function was indeed slightly worse in group 1 patients). Moreover, cardiac rehabilitation did not hinder the improvement in ventricular function expected in patients after PTCA[24].

Restoration of antegrade flow and autonomic tone. In previous reports, a higher baroreflex sensitivity[12] or a higher time-domain heart rate variability[13] was reported for patients in whom the infarct-related artery was opened by means of thrombolysis. More recently, PTCA was also shown to modify heart rate variability early after myocardial infarction[25]. Our data, relating to short-term recordings and to a different technique of spectral analysis, are in agreement with these findings. Moreover, we show that a more complete and earlier reopening leads to a more favorable autonomic profile: patients with a very short door-to-balloon time had the best outcome, and patients with no reperfusion had the highest degree of sympathetic activation. On the other hand, patients who underwent thrombolysis – a group where no TIMI flow data were available, and therefore a variable degree of infarct-related artery opening could be anticipated[12] – had an intermediate spectral profile. The latter observation explains why in other studies[20] and in our previous analysis[26], no differences in sympathovagal balance were found between patients with and without reperfusion: in these papers, most "reperfused" patients had undergone thrombolysis without subsequent definition of the coronary flow[20,26]. The mechanism by which the early opening of the infarct-related artery improves autonomic control is a matter of speculation. No relationship was found between the impairment in ventricular function and the sympathovagal balance, while a higher parasympathetic tone was observed in patients with the shortest period of ischemia. Thus, it is unlikely that stretching of nerve endings is the pathophysiological mechanism which determines the autonomic tone in this clinical setting. A relevant role may in fact be played by chemical activation of polymodal adrenergic nerve endings, known to mediate excitatory cardio-cardiac reflexes[27], and to increase sympathetic drive in case of ischemia, stunning or hibernation[28].

Cardiovascular rehabilitation after coronary angioplasty. The introduction of primary PTCA for AMI has significantly reduced its morbidity and mortality, even though whether this intervention is really superior to thrombolysis, and whether it should be the treatment of choice in case of an anterior AMI is still subject of debate[10,29,30]. The issues regarding recurrent ischemia, restenosis, and the progression of the underlying coro-

nary artery disease are still unsolved. Thus, even if their functional status is good and they do not need hospitalization, it is important that patients be kept under observation after PTCA. This may be achieved by means of a secondary prevention program involving exercise training and aggressive treatment of risk factors. In fact, Belardinelli et al.[31] recently reported that rehabilitation, after PTCA and/or coronary stenting, reduces hospital admissions, improves quality of life and lipid control, and reduces the extent of induced ischemia. In our report, we did not study a control group of patients not following a rehabilitation program after PTCA; thus, we could not assess the effects of rehabilitation *per se* in this clinical setting. Instead, we compared the impact of training in three groups of patients who had been acutely treated in different ways: not only did physical exercise not result in any complication after PTCA, but we demonstrated a synergistic effect of early coronary reopening and rehabilitation on the autonomic tone. The powerful vagal modulation – already evident soon after AMI, and further enhanced after 8 weeks of regular physical exercise – could have been due to the combined central and peripheral effects of training and reperfusion respectively.

Conclusions. Restoring the patency of the infarct-related artery by means of primary PTCA determines an early significant modulation of the cardiac autonomic control, in a direction associated with a more favorable outcome. The subsequent further improvement in sympathovagal balance determined by a period of physical training indicates that a multidisciplinary approach (involving interventional and clinical cardiologists) is fundamental in designing effective strategies of secondary cardiovascular prevention.

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