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Beta-Endorphins During Coronary Angioplasty in Patients With Silent or Symptomatic Myocardial Ischemia

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Objectives. **The aims of this study were to correlate beta-endorphin plasma levels and anginal pain in patients with ischemia induced by percutaneous transluminal coronary angioplasty and to detect eventual endorphin variations during balloon occlusion.**

Background. **The opioid system appears involved in the absence of pain occurring in silent myocardial ischemia.**

Methods. **Beta-endorphin plasma levels were measured 24 h before, just before, during and after coronary angioplasty (performed on the left anterior descending artery) in 53 men with documented coronary artery disease and exercise-induced myocardial ischemia.**

Results. **Group 1 (33 patients) reported symptoms; group 2 (20 patients) was asymptomatic during angioplasty. In these patients, the prevalence of exercise-induced silent ischemia was 57%. The occurrence of angina during exercise or angioplasty was related to the frequency of angina during daily life when patients were subgrouped. The severity and distribution of coronary artery disease did not differ between the two groups. During angioplasty, the number of balloon inflations and the inflation time and pressure were similar in symptomatic and asymptomatic patients. In each group, no short-term variability of baseline beta-endorphin plasma levels was observed during 2 consecutive days. Corresponding beta-endorphin plasma levels (at baseline and during and after angioplasty) were significantly higher in Group 2. During balloon occlusion, the levels decreased significantly in the symptomatic group at the onset of angina but remained stable in the asymptomatic group.**

Conclusions. **Methodologic variables and the severity of coronary artery disease did not influence the presence of symptoms during angioplasty-induced ischemia. Beta-endorphin plasma levels were higher and more stable in patients with silent ischemia during angioplasty, suggesting that opiate levels and their variation during ischemia are associated with individual attitude toward anginal pain.**

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Balloon dilation during percutaneous transluminal coronary angioplasty is an ideal model to induce reversible myocardial ischemia in patients. The relation between electrical and clinical manifestations of ischemia induced by decreased blood supply may be evaluated in the extreme condition of transient complete vessel occlusion. More often, during daily life and also during exercise tolerance testing, ischemia is largely demand-related, is associated with a predominant sympathetic tone activation and involves subendocardial layers, whereas coronary angioplasty usually causes transmural ischemia. However, it is more difficult to grade the degree of myocardial involvement and to control the provoked ischemia during exercise testing than during balloon dilation at angioplasty. Studies (1–8) on electrocardiographic (ECG) changes and their correlations with symptoms have been conducted in patients during angioplasty. The timing of ECG changes, pain and wall motion abnormalities have also been documented (3–8).

It is well known that spontaneous or provoked myocardial ischemia can occur without pain (9–14), but the explanations for this phenomenon are controversial. Although the occurrence of pain seems to be related to the duration and intensity of ischemia and left ventricular dysfunction, these are not absolute determining factors (11–13,15,16). The presence or absence of angina may be partly explained by individual differences in pain threshold. A generalized hyposensitivity to various pain stimuli has been reported in patients with silent myocardial ischemia as compared with the response of symptomatic patients (13,17–19).

Beta-endorphin, one of the most potent endogenous opioid-like peptides, is believed to play an important role in the modulation of pain in the endogenous analgesic system (20–23) and appears to be involved in silent myocardial ischemia as well (24–26).

The objectives of this study were to determine any correlation between beta-endorphin plasma levels and the presence or absence of anginal pain during coronary angioplasty–induced ischemia, detect eventual beta-endorphin variations during angioplasty and compare the

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prevalence of symptoms during angioplasty and during exercise in the same group of patients.

Methods

Fifty-three consecutive men who underwent coronary angioplasty for clinical indications were studied. The criteria for inclusion in the study were as follows: 1) reproducible positive ECG response to an exercise tolerance test; 2) angiographically documented coronary artery disease; 3) angioplasty indicated, suitable and successful on a single vessel (left anterior descending coronary artery); 4) coronary angioplasty–provoked myocardial ischemia (ECG changes) in areas not involved in previous myocardial infarction; and 5) consistency of plasma endorphin values in two determinations performed on each sample.

The study group of 53 patients comprised 41 patients with coronary artery disease and a history of angina and 12 patients who had never experienced angina. Of the 12 asymptomatic patients, 2 were referred because of a history of syncope, 6 exhibited silent myocardial ischemia during a routine physical examination and 4 had silent myocardial ischemia discovered during a routine postinfarction examination. Ten patients had a previous (>6 weeks old) myocardial infarction.

Exercise-induced myocardial ischemia was documented in all 53 patients by an ergometric stress test; it was associated with pain in 23 patients, whereas 30 patients had no symptoms. Coronary angiography showed one-vessel disease in 38 patients, two-vessel disease in 8 and three-vessel disease in 7. In all patients, the vessel dilated during coronary angioplasty was the left anterior descending coronary artery. Mean ejection fraction, calculated by the standard area-length method, was 64.2 ± 6.3%. Mean left ventricular end-diastolic pressure was 12.4 ± 3.6 mm Hg.

Exercise tolerance test. All patients performed a multistage bicycle ergometric test 1 to 7 days before coronary angioplasty. The test was performed in the supine position with an initial work load of 25 W and subsequent stepwise increments of 25 W every 3 min at a pedaling frequency of 60 rpm. A 12-lead standard ECG was recorded before the test, every minute during the test, at the end of exercise and every minute of recovery. Leads V_4, V_5 and V_6 were monitored continuously throughout the test. Blood pressure was measured by means of a standard sphygmomanometer at 3-min intervals. During the test, patients were asked about chest pain or discomfort; when present, it was quantified on a scale of 1 to 10 and timed in seconds. The test was terminated when moderate to severe angina, dyspnea, exhaustion or >3-mm ST segment depression occurred. A positive ECG response was defined as the occurrence, for a 0.08-s duration, of ≥1-mm flat or downsloping ST segment depression compared with the baseline tracing. Ischemia threshold was defined as 1-mm ST segment depression. Tests were performed in pharmacologic "washout," with antianginal medication being suspended ≥24 h before exercise; no patient received beta-adrenergic blocking agents or digitalis. Patients with diabetes, systemic hypertension or neuromuscular disease and those whose clinical condition did not permit temporary withdrawal of antianginal therapy were excluded from the study.

Coronary arteriography. Arteriography was performed using the Sones technique 1 to 15 days before coronary angioplasty. A 50% stenosis in a major coronary vessel was defined as significant coronary artery disease.

Percutaneous transluminal coronary angioplasty. Angioplasty was performed by the femoral approach with a Shiley soft-tip guiding catheter and a MicroHartzler ACS balloon catheter system or Bonzel Monorail balloon catheter over 0.012 in. (0.015-cm) steerable guide wire. Balloon size ranged from 2.5 to 3 mm. Two or more inflations were made, and pressure was progressively increased (from 2 to 6 atm) until disappearance of the lesion. Each inflation was monitored for 20 to 60 s. All procedures were performed in the morning between 9 and 11 AM. Patients received 5 mg of diazepam orally as premedication. All antianginal medications were stopped ≥24 h before coronary angioplasty was started. Throughout the procedure, a 12-lead ECG was obtained every 30 s while 6 leads were continuously recorded at low (10 mm/s) paper speed on a Mingograf recorder. Aortic pressure was monitored before, during and after angioplasty.

Patients were asked during the procedure about the occurrence of symptoms. If present, symptoms were reported on a graduated linear scale and timed in seconds. Onset of ST segment displacement and any variations were carefully observed and calculated independently by two cardiologists. Coronary angioplasty was performed only on a single vessel (left anterior descending artery) in each patient; successful angioplasty was defined as a diameter gain of 20% without complications.

Beta-endorphin plasma level determination. To determine beta-endorphin plasma levels, 10-ml venous blood samples were taken between 9 and 11 AM the day before coronary angioplasty with the patient in a comfortable supine position and after a rest period of 15 min. On the day of coronary angioplasty, blood samples were taken (in the catheterization laboratory using a peripheral cannula) just before the procedure (after a rest period of 15 min) and during balloon inflation at the time of onset of ischemia (and symptoms). Another blood sample was taken 15 min after the end of the procedure. The samples were immediately centrifuged at 4°C, purified by C18 Sep-Pack Cartridges-Waters and analyzed by a radioimmunoassay method (beta-endorphin-1125, RIA Kit-Incstar) (26,27). Each sample was divided in two and analyzed separately by a different team of pharmacologists who had no knowledge of the patients' clinical characteristics. Quality control was performed for each determination. The normal range of beta-endorphin plasma levels in 15 healthy men aged 38 to 70 years was 2.2 to 7.5 pg/ml (mean 4.3 ± 3.2). By applying a pulpal test, which is a short noxious stimulus (18), in the same healthy subjects, the

following results were obtained: before the test, the mean plasma level was 4.6 ± 2.9 pg/ml; during stimulation, it was 5.1 ± 3.4 pg/ml, and 5 min after the test, it was 4.9 ± 3.1 pg/ml. Cardiac catheterization did not significantly modify the baseline beta-endorphin plasma levels in 10 patients with coronary artery disease who underwent coronary angiography without coronary angioplasty; at baseline and during catheterization, values in these patients were 4.4 ± 2.3 and 4.7 ± 3.5 pg/ml, respectively.

All patients gave informed consent before the study and before any procedure. The study protocol was approved by the Ethics Committee of the hospital.

Statistical analysis. The Kolmogorov-Smirov test was used to determine whether the studied continuous variables fit the normal distribution. Because all variables were normally distributed, it was possible to use parametric tests in further analyses. An unpaired *t* test was performed for analysis of two independent samples. The Mann-Whitney test was used for two independent nonparametric samples.

To analyze the variations of beta-endorphin plasma levels in the two patient groups studied (those with [group 1] and without [group 2] angina during angioplasty-induced ischemia), repeated measures analysis of variance was carried out using the sequential times (at baseline and during and after coronary angioplasty) as a within-subject factor and pertaining to group 1 or 2 as a between-subjects factor. To focus on the time intervals at which the most relevant modifications occurred, the contrast among endorphin values at several times was analyzed (basal levels vs. levels during angioplasty and the levels during angioplasty vs. levels after angioplasty in both groups).

A p value < 0.05 was considered statistically significant. All analyses were performed with the SPSS/PC+ statistical package.

Results

Patients were classified into two groups according to the occurrence of angina during coronary angioplasty–induced ischemia. Group 1 included 33 patients (62%) with anginal symptoms. Group 2 comprised 20 patients (38%) without symptoms during balloon dilation.

The mean age was 52 ± 3 years (range 35 to 65) in group 1 and 54 ± 2 years (range 38 to 63) in group 2. Previous myocardial infarction was diagnosed in six patients (18%) in group 1 and four (20%) in group 2; in the latter group, the infarction was always asymptomatic. A history of angina was present in 32 of the 33 patients in group 1 and in 9 of the 20 patients in group 2. All symptomatic patients had class III or IV angina (Canadian Cardiovascular Society classification).

The extent of coronary artery disease was similar in the two groups: 22 patients in group 1 and 16 patients in group 2 had single-vessel disease, whereas 9 in group 1 and 6 in group 2 had multivessel disease. Ejection fraction and left ventricular end-diastolic pressure also showed no significant differences between the two groups (61.2 ± 11% vs. 62.6 ± 13% and 13.1 ± 2 vs. 12.1 ± 3 mm Hg, respectively).

Angioplasty procedures. Groups 1 and 2 were treated similarly (p = NS) with respect to the number of balloon inflations (2.8 ± 1.4 vs. 3.1 ± 1.7), inflation time (76 ± 21 vs. 86 ± 16) and maximal inflation pressure (4.9 ± 2.4 vs. 5.1 ± 2.1 atm). The mean baseline values of heart rate and blood pressure were 72.8 ± 13 beats/min and 132.8 ± 18 mm Hg, respectively. During balloon occlusion, they were 85.2 ± 21 beats/min and 146.6 ± 15 mm Hg, respectively. There was no statistical difference in mean heart rate and blood pressure between groups 1 and 2. The onset of ECG changes was observed at similar inflation pressures in the two groups of patients (3.7 ± 1.3 vs. 3.9 ± 1.4 atm; p = NS). Electrocardiographic abnormalities occurred in 28 patients during the first balloon inflation, in 12 patients during the second inflation and in 13 at the third or fourth inflation. The onset of ST segment shift occurred 27 ± 12 s after balloon inflation and disappeared 24 ± 10 s after balloon deflation. In group 1, 29 patients exhibited ST segment elevation, averaging 2.6 ± 0.9 mm, and in 4 patients there was ST depression of 1.5 ± 1.2 mm. In group 2, 18 patients had ST elevation of 3.9 ± 1.8 mm, whereas ST depression of 1.8 ± 0.9 mm was present in 2 patients. The ECG changes lasted an average of 23 ± 8 s in group 1 and 21 ± 9 s in group 2 (p = NS).

Pain, if present, appeared in all patients at maximal balloon dilation. The mean time of onset of angina from the start of inflation was 37.9 ± 16.4 s. In group 1, the onset of angina coincided with the appearance of ST segment changes in 27 patients, but in 5 patients the ECG signs of ischemia occurred before pain.

Exercise tolerance test. All patients had a positive response to exercise tolerance testing as an inclusion criterion. At the exercise test preceding coronary angioplasty, 23 patients (43%) reported angina and 30 (57%) had no anginal symptoms during exercise-induced myocardial ischemia. During exercise testing, heart rate and blood pressure at the ischemia threshold and peak exercise were 112.9 ± 13 beats/min and 164.3 ± 21 mm Hg and 115.8 ± 19 beats/min and 170.1 ± 20 mm Hg, respectively. The rate-pressure product at baseline (9,256 ± 1,123 and 8,993 ± 1,743 mm Hg × beats/min) and that calculated at ischemia threshold (1-mm ST segment depression) were similar in the two groups (18,540 ± 3,562 vs. 18,931 ± 2,643 mm Hg × beats/min) (p = NS). Patients with and without symptoms during exercise-induced myocardial ischemia did not differ with respect to the extent and distribution of coronary artery disease.

Twenty-two of the 23 patients who were symptomatic during exercise were also symptomatic during coronary angioplasty. Of 30 asymptomatic patients during exercise, only 10 reported angioplasty-related symptoms and 20 were asymptomatic. All patients who were symptomatic during exercise tolerance testing and angioplasty (22 patients) had reported a history of angina; 11 of 12 patients with pain only at coronary angioplasty (11 patients) or at exercise testing

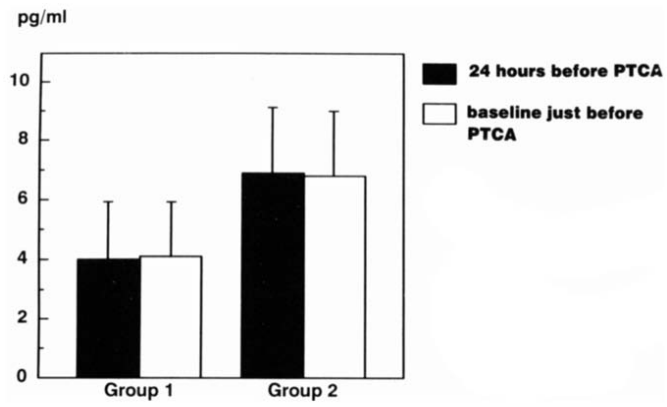


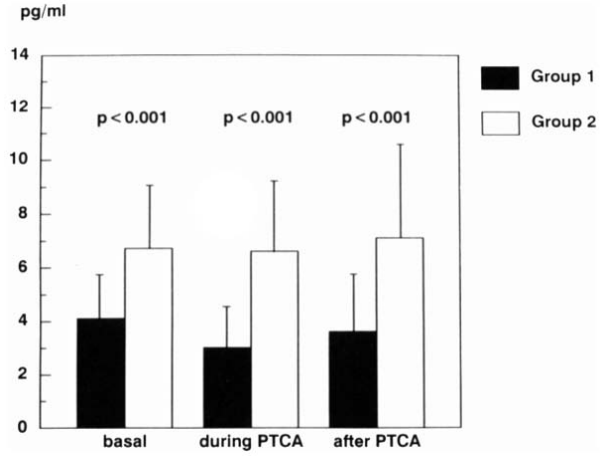
Figure 1. Beta-endorphin plasma levels in patients with (Group 1) and without (Group 2) symptoms during coronary angioplasty (PTCA). Endorphin levels were obtained both 24 h before angioplasty and again at baseline conditions just before the procedure. No short-term variability in beta-endorphin plasma levels was observed in either group over 2 consecutive days.

(1 patient) had anginal symptoms during normal daily life, whereas 8 of 19 patients with silent ischemia both at exercise testing and angioplasty had a previous history of angina. Of the 12 patients who were asymptomatic during everyday life, all remained asymptomatic during exercise testing; 11 of these 12 patients were also symptomless during angioplasty.

Beta-endorphin plasma levels. In each group, baseline beta-endorphin plasma levels on the 2 consecutive days of analysis were similar (Fig. 1). However, baseline levels were higher (6.72 ± 2.42 pg/ml) in asymptomatic patients than in those with symptoms during coronary angioplasty (4.10 ± 1.95 pg/ml) ($p < 0.001$) (Fig. 2).

The mean beta-endorphin plasma levels in group 2 remained significantly higher ($p < 0.001$) during and after the procedure (6.60 ± 2.80 pg/ml, 7.10 ± 3.60 pg/ml, respectively) compared with corresponding levels in group 1

Figure 2. Beta-endorphin plasma levels in symptomatic (Group 1) and asymptomatic (Group 2) patients before, during and after coronary angioplasty (PTCA). The asymptomatic patients showed higher opiate levels during basal conditions, during balloon occlusion and after the procedure as compared with patients in Group 1.



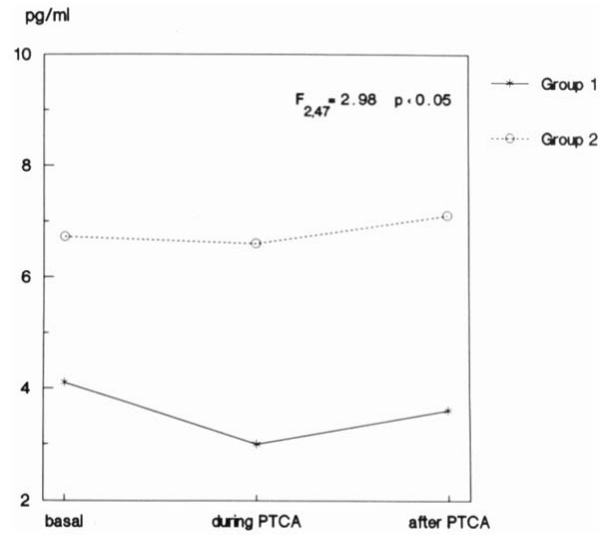


Figure 3. Beta-endorphin plasma levels decreased significantly in symptomatic patients (Group 1) during coronary angioplasty (PTCA) but remained more stable in asymptomatic patients (Group 2). After angioplasty, the levels tended to increase in both groups but to a significant degree only in the asymptomatic group.

(3.00 ± 1.84 pg/ml and 3.60 ± 2.45 pg/ml, respectively) (Fig. 2). Beta-endorphin plasma levels had a different temporal trend in the two groups. During coronary angioplasty, plasma levels decreased in both groups, but the reduction was significant only in patients in group 1; during recovery, the levels tended to increase to preangioplasty values in both groups. Analysis of variance confirmed that the temporal trend was different in the two groups ($F_{2,47} = 2.98$ $p < 0.05$) (Fig. 3); the analysis of contrasts underlined that significant variations occurred during angioplasty in group 1 ($p < 0.05$), whereas beta-endorphin plasma levels were stable during and after angioplasty in group 2 (Fig. 3).

By subgrouping the patients according to the occurrence of symptoms during exercise tolerance testing and coronary angioplasty, three groups were defined: 22 patients with angina at both exercise testing and angioplasty, 12 patients with a mixed profile (symptoms at either angioplasty or exercise testing but not both) and 19 patients with no symptoms (during both exercise testing and angioplasty). The highest baseline mean opiate level was found in the group with no symptoms (7.05 ± 3.7 pg/ml), the lowest level in the group with symptoms during both the exercise testing and angioplasty (3.01 ± 1.72 pg/ml) and an intermediate level in the group with a mixed profile (5.63 ± 3.3 pg/ml). During angioplasty, the difference between the three groups remained statistically significant; the intragroup variation during the procedure, though more marked in the group with mixed findings, did not achieve statistical significance.

Discussion

The prevalence of silent myocardial ischemia during coronary angioplasty varies from 16% to 47% (2,4,6,8). In

our study, 38% of the patients were asymptomatic at the time of ECG changes induced by the procedure. Previous studies (3–8) showed that during ischemia after balloon occlusion, ECG abnormalities occurred 15 to 45 s after balloon inflation. Anginal pain is reported (3,5,7,8) to occur from 27 to 43 s after complete vessel occlusion. In our study, the time to ECG changes and symptoms was 27 ± 12 and 37.9 ± 16.4 s, respectively.

Beta-endorphin levels during coronary angioplasty. Beta-endorphin is involved in the endogenous pain-modulating system (20–23,28–30). Activation of the descending system of pain modulation by opiates inhibits nociceptive dorsal horn neurons, producing analgesia (20,23,28); local actions of opiates at the spinal level also influence pain (29). A more complex endorphin-mediated modulation of pain seems to occur in analgesia related to environmental, attention and conditioning factors (22,30).

Although still controversial, there is evidence that beta-endorphin plasma levels play an important role in determining anginal symptoms in patients with coronary artery disease (24–26). In some studies (25,31) using the opioid antagonist naloxone, symptoms appeared earlier than those reported for the first time, whereas other studies (32,33) failed to show such differences in patients with coronary artery disease. Some investigators (33) have found no significant differences in endogenous opiate levels in symptomatic and asymptomatic groups during exercise-induced ischemia. However, a negative correlation was observed between postexercise beta-endorphin plasma levels and the duration and occurrence of angina (24). In a previous study in our own center (26), the evaluation of 74 men with reproducible exercise-induced ischemia revealed higher baseline plasma levels in the asymptomatic group. A nonstringent selection of patients in the various studies may explain the heterogeneous nature of the data reported; when completely asymptomatic patients were considered, the difference in the opioid values became evident.

In this study, the beta-endorphin plasma levels determined over 2 consecutive days were consistent in patients with silent and symptomatic angioplasty-induced ischemia, indicating short-term stability in individual levels. Although psychologic stress is known to cause variations in beta-endorphin plasma levels (34), the angioplasty procedure probably did not represent a source of additional severe stress for patients in the present study because they had had coronary angiography not long before angioplasty.

In patients who were asymptomatic during coronary angioplasty, higher ($p < 0.001$) mean baseline beta-endorphin plasma levels were observed and remained significantly higher in these patients during and after the procedure as compared with levels in symptomatic patients. During angioplasty, beta-endorphin plasma levels decreased significantly only in the symptomatic group. In healthy subjects, the endorphin profile did not show any significant variation with a noxious stimulus, as demonstrated by collateral finding in our laboratory.

Although cardiovascular functions may influence the mechanisms involved in the control of pain sensation (35–40), blood pressure and heart rate were similar during the procedure in the two groups. The reason for the opioid reduction found at balloon occlusion is unknown. Coronary angioplasty is a very short stressor and the decrease in beta-endorphin plasma levels observed in most patients may be caused by an immediate increase in demand and uptake at receptor sites. These results suggest that the reduction in circulating opioids may provoke pain in the symptomatic group or, more likely, that receptor uptake of beta-endorphins is accentuated in the presence of anginal symptoms. Differences in the regulation and metabolism of beta-endorphins have also been related to the presence of chronic pain (40,41). In this study, the symptomatic patients had a greater instability in beta-endorphin plasma levels, as shown by the significant variations that occurred in group 1, whereas the patients with silent ischemia showed more stable values during the procedure.

Intensity of the ischemic stimuli. Although it has been reported (11,13,15,16) that the presence of angina correlates with the duration and degree of ischemia, similar duration of balloon inflations has been reported (7) in patients with silent and symptomatic coronary angioplasty–induced ischemia. In our study, the number of balloon inflations, the inflation time and inflation pressure during angioplasty did not differ between patients with and without symptoms. The severity and distribution of coronary artery disease were also similar.

The similarity of the methodologic variables used during the procedure with different symptom outcome and degrees of ECG changes confirms that the intensity of the stimulus is not a determinant in provoking anginal pain. In this study, the subgroup of asymptomatic patients had greater ST segment deviation during coronary angioplasty, whereas previous publications (2,7) showed similar ECG abnormalities in patients with and without symptoms.

Coronary angioplasty–induced versus exercise-induced ischemia characteristics. In our study, the prevalence of coronary angioplasty–induced silent myocardial ischemia (38%) was lower than that induced by exercise (57%). During coronary angioplasty, the ECG changes were associated with chest pain in 33% of the patients who were asymptomatic during exercise-induced ischemia, and all patients (except one) with symptoms at the ergometric test were also symptomatic during coronary angioplasty. At least initially, exercise-related myocardial ischemia involves only subendocardial layers. In contrast, coronary angioplasty more frequently provokes transmural myocardial ischemia. The stronger ischemic stimulus of coronary angioplasty, represented by balloon occlusion, may have been the cause of the appearance of symptoms in those patients who were asymptomatic during exercise. Thus, in individual patients, the intensity of the ischemic stimulus seems to be relevant. Because blood pressure values were higher at peak exercise than during balloon occlusion, the baroceptor regulatory system might also have played a role in the higher preva-

lence of silent ischemia during exercise. However, in 39.6% of patients, no angina was provoked either by exercise or by coronary angioplasty–induced ischemia, suggesting that some patients are likely not to have symptoms no matter how severe the ischemia.

Anginal symptoms and sensitivity to pain. The importance of the individual's attitude to various forms of pain has already been pointed out. Patients with silent ischemia are less prone to complain of experimentally induced pain (for example, electrical skin stimulation, cold pressor test, modified submaximal effort tourniquet test and dental pulp stimulation) than are patients who are usually symptomatic (17–19).

The results of this study confirm an individual trend in pain perception and, in particular, indicate that a patient's report of anginal pain during exercise and coronary angioplasty tends to be constantly predictable for a given patient and may be related to individual characteristics. In fact, the great majority of the patients without symptoms during balloon occlusion also had no symptoms during exercise-induced ischemia. Moreover, the history of anginal pain was more frequent in the subgroup of patients who were symptomatic during exercise and coronary angioplasty, whereas patients with silent ischemia were less likely to report pain during everyday life.

A great number of central and peripheral mediators have been recognized in the modulation of pain, including endorphins, metenkephalins, serotonin, gamma-aminobutyric acid, catecholamines, adenosine and any other peptide or molecule that can influence the complex afferent and efferent pathways of pain perception (23). A link between cardiovascular regulation and endorphin-related hypalgesia has been recognized and also seems of relevance in the perception of anginal symptoms (35–40).

In our study, asymptomatic patients were found to have higher beta-endorphin plasma levels than those of their symptomatic counterparts not only at rest, but also during and after coronary angioplasty–induced ischemia in the presence of similar blood pressure and heart rate values. In addition, the baseline opiate levels in patients without symptoms at both angioplasty and exercise were the highest; patients with pain only at angioplasty (or exercise tolerance testing) also had higher values than the subgroup with anginal symptoms during both procedures. These results confirm a primary role of circulating opioids in anginal pain perception. Moreover, the symptomatic patients had a greater instability in beta-endorphin plasma levels as shown by the significant reduction at the onset of symptoms during coronary angioplasty; in contrast, the patients with silent ischemia showed more stable values during the procedure.

Conclusions. The important factors for the occurrence of pain during ischemia may be not only absolute beta-endorphin plasma levels, but also their variations; opiate levels and their variability may represent the individual characteristic associated with the attitude to anginal pain sensation.

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