Role of Beta-Endorphins in Silent Myocardial Ischemia

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The reason for the absence of pain perception in silent myocardial ischemia is unknown. A role of increased endorphinic activity in patients with silent ischemia has been postulated. To further investigate this hypothesis, 10 men with documented coronary artery disease and previous positive electrocardiographic findings during exercise without anginal pain were studied. Six healthy volunteers served as control subjects. The protocol included 2 bicycle exercise tests, the first test serving as baseline and the second performed after administration of naloxone, a specific opiate antagonist. Plasma β-endorphin levels were measured by radioimmunoassay in both tests at rest, at peak exercise level and after recovery. All patients underwent thallium-201 scintigraphy after coronary vasodilation to provide an additional independent marker of ischemia. All patients showed stress-induced reversible perfusion abnormalities. No patient reported pain after naloxone application. Exercise duration, blood pressure and heart rate were not significantly altered by naloxone. Plasma β-endorphin levels ranged from 18 ± 6 pg/100 μl (mean ± standard deviation) at rest to 22 ± 6 pg/100 μl during exercise in the patient group and from 20 ± 5 to 27 ± 9 pg/100 μl in the control subjects. Thus, there was no significant increase of plasma β-endorphins during exercise or after naloxone administration, nor was there any difference observed between patients and control group. These data support the view that endorphinic activity does not play an essential role in the pathophysiology of silent myocardial ischemia.

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Silent myocardial ischemia is an increasingly observed and accepted manifestation of coronary artery disease (CAD) and may occur in both symptomatic and asymptomatic patients.[1–5] Its pathophysiology, however, remains controversial.[6–12] There is evidence that endorphins, endogenous opioid peptides, play a significant role in modifying individual pain threshold.[13–15] This finding led to the use of naloxone, a specific opiate antagonist, with the expectation that this substance could provoke the appearance of anginal pain in patients with silent myocardial ischemia. Investigations based on these considerations showed controversial results.[11,12] The present study was performed to further investigate the role of endorphins in silent myocardial ischemia by measuring plasma β-endorphins before and after naloxone administration in patients with CAD and exercise-induced silent ischemia.

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Methods

Ten men (mean age 57 years) with previous positive electrocardiographic findings during exercise (horizontal or downsloping ST-segment depression 2 mm or more) without anginal pain during the test were studied. All patients had documented CAD. The diagnosis was established by a history of myocardial infarction and corresponding perfusion defects on thallium-201 scintigraphy in 4 patients and by coronary arteriography in 6 patients. The latter revealed 3-vessel CAD in 3 patients (2 of whom had additional left main disease), 2-vessel CAD in 2 patients and 1-vessel CAD in 1 patient. Two patients who underwent coronary arteriography had prior myocardial infarction and coronary bypass grafting (Table I). Exclusion criteria were electrocardiographic signs of left ventricular hypertrophy, treatment with digitalis, valvular heart disease, hypokalemia and insulin-dependent diabetes mellitus.

Five patients (2 with previous infarction) had both symptomatic and asymptomatic episodes of myocardial ischemia, 4 patients were asymptomatic after an infarction and 1 patient was asymptomatic.

Eight patients underwent thallium-201 scintigraphy after pharmacologic coronary vasodilation[16,17] within 6

TABLE I Documentation of Coronary Artery Disease and Myocardial Ischemia

Pt	Events	Angio	TI-201 Scintigraphy	Max ST↓ (mm)	Termination Criterion
1	0	LM 40% and 3-VD	—	4	BP drop
2	Inferior MI	—	* †	2.5	Dyspnea
3	0	2-VD	0	3	Fatigue
4	Anterior MI	—	* ††	2	BP drop
5	Inferior MI	—	* †	2.5	BP drop
6	0	LM 50% and 3-VD	—	3	BP drop
7	0	1-VD	†††	3	Leg pain
8	Inferior MI Triple CBG	3-VD	* ††	2	Exhaustion
9	Anterior MI	—	*	2	Fatigue
10	Anterior MI Double CBG	2-VD	* †	2	Dyspnea

* Reversible perfusion defect in infarct zone; † reversible ischemia in noninfarcted myocardial segment.

Angio = angiography; BP = blood pressure; CBG = coronary bypass grafting; LM = left main; MI = myocardial infarction; ST↓ = ST-segment depression; TI-201 = thallium-201; VD = vessel disease.

weeks after the positive exercise stress test results. This showed stress-induced reversible perfusion defects in 7 patients. In 5 patients, these defects were located in the infarct area and in 1 or 2 other myocardial segments, and in 1 patient in the infarct zone only. In another patient without prior infarction, stress-induced perfusion defects involved 3 different myocardial segments. In 1 patient, thallium uptake was normal in all segments, but regional thallium-201 washout kinetics were abnormal (Table I). In 2 patients, no stress scintigraphy was performed because of 3-vessel CAD with left main involvement.

The study protocol included 2 symptom-limited bicycle exercise tests in the upright position. The exercise level was increased by 25 W every 2 minutes.[18] The baseline test was performed without naloxone and the second exercise test was started 5 minutes after intravenous injection of 1.2 mg of naloxone. The electrocardiogram (precordial leads V_4, V_5 and V_6) was recorded continuously, and heart rate and blood pressure were measured every 2 minutes during exercise and after 1, 3 and 5 minutes of the recovery period. The tests were stopped when the maximum capacity or any other criterion for termination was reached.[18] The patients were questioned as to the perception of anginal pain during or after exercise. The mean interval between both tests was 3.5 ± 2 days. Tests were performed at comparable times of the day to minimize eventual diurnal influences.

Plasma β-endorphins were measured by radioimmunoassay[19] (New England Nuclear Kit) in both tests at rest, at peak exercise level and after 5 minutes recovery. Blood was drawn through an indwelling cannula placed in a large antecubital vein.

Statistical methods: The differences of plasma β-endorphin levels and of exercise variables in both tests were analyzed by the Student *t* test for paired observations.

TABLE II Plasma Beta-Endorphin Levels (pg/100 μl) Without (Test 1) and With Naloxone Stimulation (Test 2)

	Patients		Control Group		
	Test 1	Test 2	Test 1	Test 2	p Value
Rest	21 ± 6	18 ± 6	23 ± 9	20 ± 5	NS
Rest after naloxone	—	20 ± 6	—	22 ± 7	NS
Max. workload	21 ± 7	23 ± 6	24 ± 9	27 ± 9	NS
Recovery	21 ± 5	21 ± 5	26 ± 7	23 ± 9	NS
p value	NS	NS	NS	NS	

Max = maximum; NS = not significant.

Results

No patient reported anginal pain during either test. The reasons for termination were reduction in blood pressure in 4 patients, dyspnea in 2, leg pain or fatigue in 3 and exhaustion in 1 patient. Exercise duration, blood pressure, heart rate and ST-segment depression between the baseline and the second exercise test were not significantly different in either group (Fig. 1).

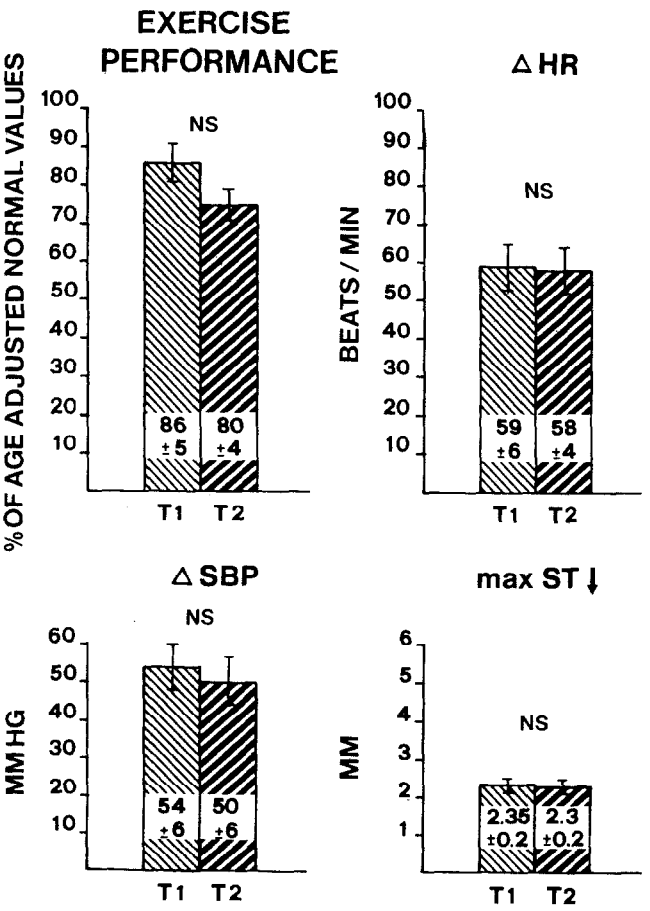

FIGURE 1. Exercise variables (mean ± standard deviation) of the baseline test (T1) and the test with naloxone (T2) in the patient group. Δ HR = difference of maximum and minimum heart rate; NS = not significant; Δ SBP = difference of maximum and minimum systolic blood pressure; max ST ↓ = maximal ST-segment depression.

Mean plasma β-endorphin levels ranged from 18 ± 6 to 22 ± 6 pg/100 μl (± standard deviation) in the patients and from 20 ± 5 to 27 ± 9 pg/100 μl in the control group. Although a tendency to higher β-endorphin levels during exercise was observed in both groups, the differences in mean values were not statistically significant (Table II).

Discussion

Three main factors have been postulated as being responsible for the occurrence of silent myocardial ischemia: a smaller amount of myocardium affected by ischemia,[7,8] a defective anginal warning system[9] and a lower pain threshold and sensibility in general.[10]

One cause of a lower pain threshold could be an increased endorphinic activity, leading to enhanced inhibition of pain-producing stimuli. Two studies using naloxone as a specific opiate antagonist in patients with exercise-induced silent ischemia brought controversial results: Droste and Roskamm[11] reported the appearance of anginal pain in 2 of 10 patients with silent ischemia. Conversely, in a study performed by Ellestad and Kuan,[12] naloxone failed to induce anginal pain in 10 patients with silent ischemia.

In an attempt to document endorphinic activity in a more direct approach, our study protocol included the measurement of plasma β-endorphins in 2 consecutive exercise tests with and without naloxone application. In addition to the electrocardiogram, we have applied an independent marker of ischemia by the use of thallium-201 scans. These scans exhibited significant reversible perfusion defects, making a true ischemic response during the exercise test much more likely. Similar findings have been reported by Deanfield et al[4] who used rubidium-82 and positron emission tomography in patients with CAD and stable angina pectoris, demonstrating that perfusion defects do occur independent of the presence of pain and concluding that ST-segment depression is a reliable marker of ischemia in this patient population.

None of our patients responded with anginal pain after naloxone. Correspondingly, plasma β-endorphin levels showed neither a homogeneous pattern nor a significant increase during exercise in either group. The following factors as possible causes for these negative results are discussed.

Inadequate exercise protocol: A longer duration of submaximal exercise could lead to a higher catecholamine level and, thus, endorphinic stimulation. Although an endocrine relation between pituitary-adrenocortical and endorphinic activity has been demonstrated,[20,21] to our knowledge no data support the hypothesis that exercise of longer duration leads to a stronger catecholamine and endorphinic stimulation.[22]

Insufficient naloxone dose: Although the naloxone dose (1.2 mg) used in our study lies in the middle of the dose range cited by other investigators,[11,12,23] larger amounts of opiate receptors or larger endorphin concentrations in these patients may require a larger dose of naloxone for complete antagonization.[24]

Other agents in pain modification: Naloxone binds mainly to the μ-opioid receptors.[25] Recently, however, other opioid receptors as well as opioid peptides, such as dynorphins, have been identified.[25,26] Thus, more agents must be considered as responsible for individual pain modification, all of which may not be antagonized by naloxone.

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