

Experimental Pain Measurement in Patients With Asymptomatic Myocardial Ischemia

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Men with substantial coronary heart disease determined angiographically and with reproducible myocardial ischemia were studied. During exercise electrocardiography, 22 patients exhibited significant ST segment depression with concomitant angina pectoris (that is, symptomatic myocardial ischemia) and 20 patients demonstrated significant ST segment depression without any symptoms (that is, asymptomatic myocardial ischemia). No significant differences were found between the patient groups in functional variables, coronary angiographic data or coronary risk factors. In contrast, various experimental

pain measures (for example, electrical pain threshold, according to Notermans' method, cold pressor test and tourniquet pain test) yielded significant differences between groups. Results indicate that patients with asymptomatic myocardial ischemia demonstrated significantly higher electrical pain thresholds and ischemic pain thresholds, as well as more tolerance to cold and ischemia, so that individual differences in sensibility to pain may partly explain lack of pain in patients with asymptomatic myocardial ischemia.

Although it has been known for some time that myocardial infarction can occur silently, an increasing number of reports (1-3) suggest that myocardial ischemia may also occur without angina pectoris. Investigations utilizing ST segment depression on the exercise electrocardiogram as an indirect indication of ischemia, nuclear imaging studies and direct determination of lactate in coronary venous blood have demonstrated that exercise-induced myocardial ischemia can be exhibited without accompanying symptoms (4). Why pain is lacking in this so-called asymptomatic or silent myocardial ischemia remains equivocal. A possible reason for this absence of the perception of pain may be found in individual differences in a patient's sensibility to pain.

Methods

Subjects. Forty-two men (mean age 51 years) were examined. All patients demonstrated severe coronary artery disease ($\geq 75\%$ stenosis in at least one major coronary vessel) as determined angiographically. In addition, all patients exhibited substantial ST segment depression (> 0.1 mV) during several exercise conditions. Patients were divided into two groups depending on the occurrence of angina pectoris: 22 demonstrated symptomatic myocardial ischemia (the simultaneous occurrence of ST segment depression and angina pectoris); 20 exhibited asymptomatic myocardial ischemia

(no pain experienced during ST segment depression). For both patient groups, and especially for the asymptomatic patients, evidence for the reproducibility of ischemia was present. Other factors that could have indicated spurious ST segment depression in any patient (that is, digitalis medication, hypopotassium levels, myocardial hypertrophy, valvular disease) were excluded.

Procedures. Three different pain-receptive modalities were employed to measure pain experimentally. 1) An electrical pain test described by Notermans (5), in which pain thresholds are determined by the magnitude of current (in mA) needed to perceive pain. Pain thresholds were determined at three sites on the left thigh by means of 10 incremental and 10 decremental measurements. Skin resistance was simultaneously controlled. The value of thresholds is given according to the degree of stimulation (current in mA). 2) A cold pressor test in which the left arm was submerged in 4°C water that was stirred. 3) An ischemic pain test using a modified form of the submaximal effort tourniquet technique (6,7). Pain was elicited from ischemia produced in the working muscle of the left arm.

For the last two procedures, the time that elapsed before the patient either perceived pain (threshold test) or was no longer able to tolerate pain (tolerance test) was measured. In addition, patients were asked to rate the intensity of the pain experienced (reaction value). For this purpose, a 10 step pain intensity rating scale was presented. Along with the experimental measurement of pain, some neurologic examinations (for example, determination of tactile thresholds using Frey's hairs) as well as psychologic questionnaires (for example, Freiburger personality inventory [8]) were administered.

Coronary angiography was conducted according to the Sones technique (9). Exercise electrocardiograms were obtained with the

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Table 1. Comparison of Selected Medical Variables Measured in Patients With Symptomatic and Asymptomatic Myocardial Ischemia

	Myocardial Ischemia	
	Symptomatic (n = 22)	Asymptomatic (n = 20)
1 vessel disease	9	3
2 vessel disease	3	3
3 vessel disease	10	14
Friesinger score	8.6 ± 3.1	10.4 ± 2.6
Ejection fraction (%)	60 ± 16	58 ± 12
Heart volume (ml)	816 ± 142	856 ± 220
Heart volume related to body weight (ml/kg)	10.9 ± 1.2	11.1 ± 2.5
Previous myocardial infarction (no. of patients)	17	16
Risk factors		
Age (yr)	51 ± 5.8	52 ± 9.6
Smoking	17	10
Hypertension (>140/>95 mm Hg)	8	8
Diabetes	1	2
Cholesterol (mg/dl)	240 ± 40	237 ± 65
Triglycerides (mg/dl)	195 ± 83	174 ± 79

All data are ± standard deviation values.

Differences between the symptomatic and asymptomatic groups for each variable were not significant.

patient supine using a bicycle ergometer. The data were statistically analyzed with use of the *t* test, Mann-Whitney U test and chi-square test.

Results

Patients exhibiting either symptomatic or asymptomatic myocardial ischemia did not differ significantly with respect to coronary angiographic data or coronary risk factors (Table 1). These findings concur with results previously reported (10). The two patient groups did not demonstrate any significant differences in any cardiologic functional variable (Table 2). During maximal effort, asymptomatic patients had more substantial ST segment depression in more electrocardiographic leads than did the symptomatic patients.

Previous myocardial infarction and angina. Of the 20 patients with asymptomatic myocardial ischemia, 16 exhibited electrocardiographic evidence of previous infarction. In four of these patients, the infarction occurred silently. The anamnestic data indicated that another six of these patients noticed their infarction; for example, they felt weak or nauseated, but experienced no direct pain. Thus, in 10 (62.5%) of 16 patients with asymptomatic myocardial ischemia, the occurrence of infarction was also asymptomatic or silent. In contrast, only one silent and one asymptomatic

Table 2. Comparison of Functional Variables (exercise electrocardiography) Between Symptomatic and Asymptomatic Patient Groups

	Myocardial Ischemia		p Value
	Symptomatic	Asymptomatic	
Rest			
Heart rate (beats/min)	69 ± 11	75 ± 11	NS
Blood pressure (mm Hg)			
Systolic	142 ± 22	135 ± 10	NS
Diastolic	88 ± 8	86 ± 8	NS
Ischemia			
Watts	43 ± 35	27 ± 21	NS
Heart rate (beats/min)	103 ± 17	103 ± 15	NS
Blood pressure (mm Hg)			
Systolic	169 ± 26	157 ± 16	NS
Diastolic	99 ± 10	96 ± 14	NS
Rate-pressure product	17,591 ± 4,809	16,405 ± 3,566	NS
Maximal effort			
Watts	75 ± 30	61 ± 42	NS
Heart rate (beats/min)	118 ± 16	120 ± 37	NS
Blood pressure (mm Hg)			
Systolic	186 ± 27	173 ± 23	NS
Diastolic	103 ± 11	102 ± 11	NS
Rate-pressure product	21,957 ± 5,110	21,579 ± 6,282	NS
ST segment depression mV	0.21 ± 0.09	0.38 ± 0.15	<0.001
No. of leads exhibiting ST depression	3.3 ± 1.8	4.7 ± 1.8	<0.02

All data are ± standard deviation values
NS = not significant.

infarction were recorded in the control group with symptomatic ischemia. Furthermore, asymptomatic patients showed substantial differences from the symptomatic group in the effects of ischemia on daily life. Among 16 patients, no angina pectoris was experienced during everyday living. Six patients had complained of chest pain several months or years earlier, but later the complaints were no longer present.

Pain tests. Significant differences were found between the symptomatic and asymptomatic groups for all pain tests. Symptomatic patients demonstrated a mean electrical pain threshold of 0.57 mA (Fig. 1, top). This finding is in agreement with the results of Notermans' investigation (5), in which 4,000 measurements were obtained in normal subjects. Asymptomatic patients exhibited a significantly higher mean threshold of pain that was greater than 1.0 mA (Fig. 1, bottom).

Figures 2 and 3 illustrate mean threshold and tolerance levels for stimulus intensity and subjective experience of pain for the symptomatic and asymptomatic groups. Subjective reports were obtained by means of a 10 step intensity scale for the pain experienced (reaction value).

Cold pressor and ischemic pain tests. On the cold pressor test (Fig. 2), asymptomatic patients showed significantly higher values for pain tolerance than did symptomatic patients, but did not show any difference for pain threshold. In terms of rated pain intensity, asymptomatic patients estimated the stimulus that they could endure as significantly less painful.

The results of the ischemic pain test (Fig. 3) were similar to those of the cold pressor test. Asymptomatic patients had a higher ischemic pain threshold and pain tolerance than did symptomatic patients; the difference in pain threshold reached a significant level. For the symptomatic patients, ischemic

pain occurred after an average of 70.6 seconds, while asymptomatic patients first reported pain after an average of 96.9 seconds. In this test, similar to the cold pressor test, asymptomatic patients estimated a higher stimulus as less painful. The difference in the rated intensity for ischemic pain tolerance was significant.

Neurologic and psychological tests. We did not find any differences in neurologic variables. There is no evidence to suggest polyneuropathy (for example, higher alcohol consumption or influence of toxic substances) or differences in tactile threshold test with Frey's hairs at four sites on the body surface. The results of the Freiburger personality inventory test indicated a significantly lower score for the asymptomatic patients on the "nervousness" ($p < 0.001$) and "excitability" ($p < 0.001$) scales and a significantly higher score on the masculinity scale ($p < 0.001$). Very little difference between groups was evident for the remaining scales (Table 3).

Discussion

Factors responsible for lack of pain. Three arguments are presented as a possible explanation of the underlying factors responsible for the lack of pain in asymptomatic or silent myocardial ischemia.

The nociceptive pathways projecting from the heart may be destroyed by substantial myocardial infarction, very diffuse coronary heart disease or polyneuropathy at a more central location. This argument appears, however, less likely to apply to the present patient group. Symptomatic and asymptomatic patients exhibited no significant differences in frequency of prior myocardial infarction. Furthermore,

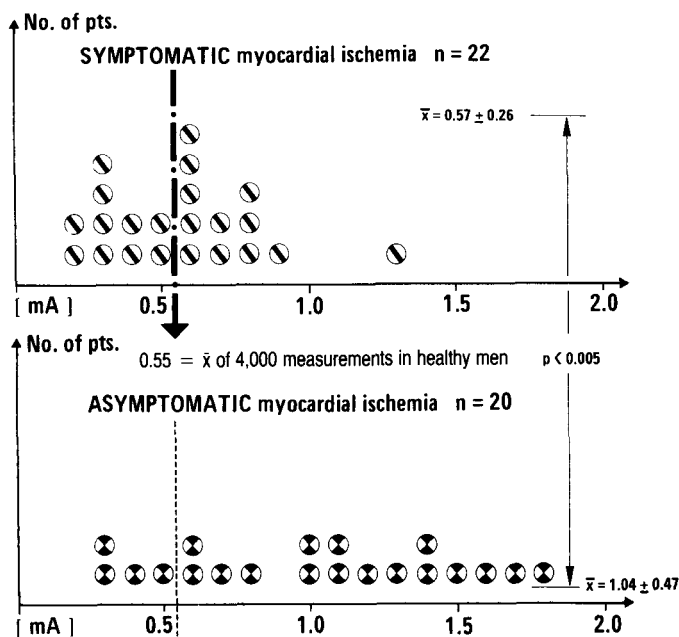


Figure 1. Electrical pain threshold in symptomatic and asymptomatic patients determined according to Notermans' procedure (5). n = number of patients; p = probability; \bar{x} = mean value \pm standard error (standard deviation value).

COLD PRESSOR TEST

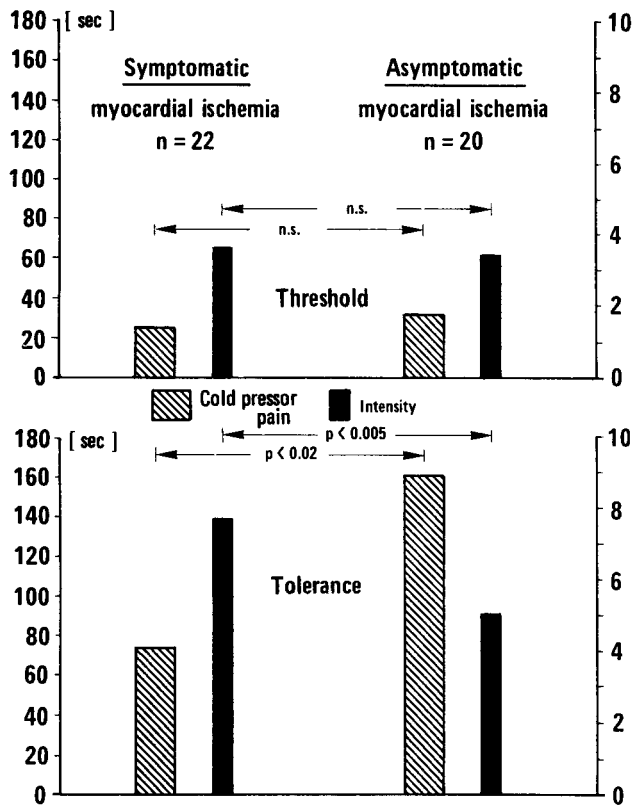


Figure 2. Cold pressor test: group differences for threshold and tolerance levels (stimulus intensity = hatched columns; subjective experience of pain = solid columns). n.s. = not significant.

the number and degree of diseased coronary vessels showed no significant differences between groups. Anamnestic data also indicated no evidence in the asymptomatic patients that might suggest polyneuropathy, that is, previous alcohol consumption or diabetes. Findings ensuing from denervation after aortocoronary bypass indicate that only subsequent to an extremely radical procedure or autotransplantation (11) is a measurable change evident in the pain experienced, that is, absence of angina pectoris. Less radical methods only slightly change the amount of pain experienced by the patient over time (12). These observations also refute the notion that the phenomenon of asymptomatic myocardial ischemia can be explained by the morphologic destruction of nociceptive pathways.

Patients with asymptomatic myocardial ischemia may not obtain the intensity of ischemia needed to elicit angina pectoris (13). This argument also does not seem likely for the present patient sample. The asymptomatic patients exhibited especially substantial signs of ischemia compared with the control symptomatic group. For example, during maximal exertion ST segment depression occurred in more electrocardiographic leads in asymptomatic patients (Table 2). All

remaining functional variables were not significantly different for the two groups. Some of the patients examined exhibited reproducible asymptomatic ST segment depression of 0.5 mV amplitude.

The notion that an insufficient level of ischemia could explain the lack of angina pectoris pain may apply to patients who only sometimes exhibit asymptomatic myocardial ischemia (1). For example, patients exhibiting asymptomatic ischemia in only a single examination, whereas pain generally does occur, may fall in this category. This may also hold for patients who demonstrate asymptomatic episodes observed with electrocardiographic monitoring techniques (3).

Asymptomatic patients may exhibit a hyposensitivity to pain in general. Our present results support this notion. Earlier clinical observations of patients with painless myocardial infarction (14,15) suggest that these patients have an unusually low sensibility to pain. Although these earlier results were only partly quantified (16), Keele (17) and Procacci et al. (18) reported higher pain thresholds in patients with silent myocardial infarction. Furthermore, the observation that in most of the asymptomatic patients, asymptomatic ischemia was reproducible and also was found

Figure 3. Ischemic pain test: group differences for threshold and tolerance levels (stimulus intensity = hatched columns; subjective experience of pain = solid columns).

ISCHEMIC PAIN TEST

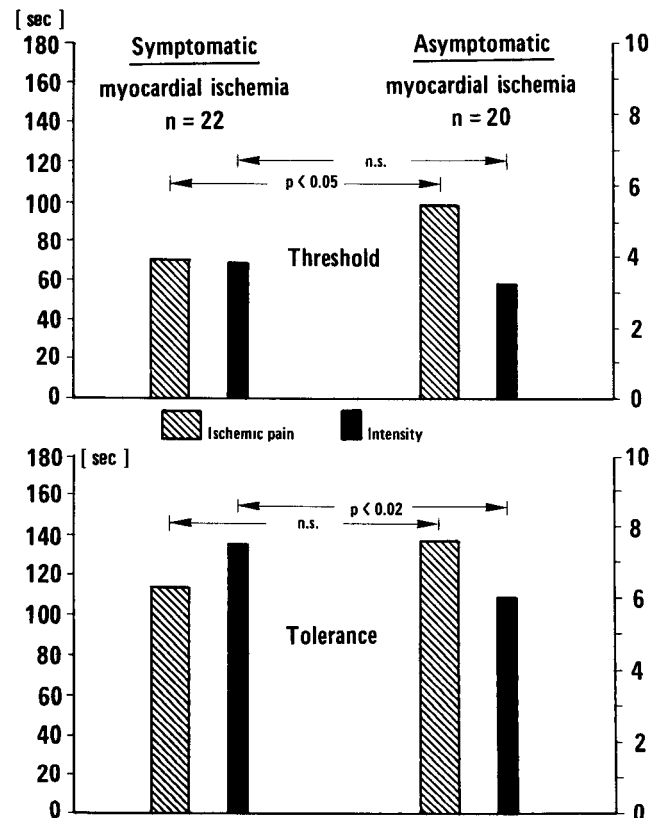


Table 3. Comparison of Personality Questionnaire Data (Freiburger personality inventory [8]) in Patients With Symptomatic and Asymptomatic Myocardial Ischemia

		Myocardial Ischemia		p Value
		Symptomatic (n = 22)	Asymptomatic (n = 20)	
Nervousness	FPI-1	2.9 ± 1.6	1.0 ± 1.2	< 0.001
Aggression	FPI-2	1.1 ± 1.2	1.1 ± 1.5	NS
Depression	FPI-3	2.6 ± 2.3	1.4 ± 1.8	NS
Excitability	FPI-4	4.7 ± 1.9	2.1 ± 2.5	< 0.001
Sociability	FPI-5	4.7 ± 1.9	3.8 ± 2.1	NS
Calmness	FPI-6	3.5 ± 2.0	4.7 ± 1.9	NS
Dominance	FPI-7	2.5 ± 1.9	1.2 ± 1.3	< 0.02
Inhibition	FPI-8	2.1 ± 1.9	1.7 ± 2.3	NS
Openness	FPI-9	3.1 ± 1.7	2.6 ± 2.2	NS
Extraversion	FPI-10	4.3 ± 2.2	3.4 ± 2.1	NS
Emotional lability	FPI-11	2.5 ± 2.2	0.9 ± 1.6	NS
Masculinity	FPI-12	3.1 ± 1.6	5.1 ± 1.7	< 0.001

FPI = Freiburger personality inventory, NS = not significant.

in daily life as well as during infarction itself, speaks for a more person-related than a situation-dependent cause. It may be argued that a hyposensitivity to pain may play a role only for patients who demonstrate substantial and reproducible forms of asymptomatic myocardial ischemia; other explanations may be more adequate for less severe forms, for example, for a partial asymptomatic ischemia. Note, however, that in our patients, no general innate insensitivity to pain was evident. All of these patients could experience pain and did not show any obvious neurologic deficits.

Mechanisms of diminished sensitivity to pain. The question may then be posed as to which mechanisms are involved in this differential sensitivity to pain. Recent research on pain discriminates between two essential factors: 1) differences in the patient's neurophysiologic ability to discriminate pain, and 2) differences in individual response tendencies that categorize a stimulus as pain (concept of a general tendency to complain).

The significant differences in the electrically determined pain thresholds and the thresholds for ischemic pain suggest that differences exist between the patient groups in discriminating pain. Furthermore, the differences in the questionnaire data for the "excitability" scale may be similarly interpreted. On the other hand, asymptomatic patients rated the pain they experienced from a stimulus tolerated by them much longer than by the symptomatic group as significantly less intense than did the symptomatic group. This difference further suggests differences in the response tendencies. Simultaneously, asymptomatic patients generally exhibited a very modest tendency to complain about problems in the various body areas. This tendency can be seen in the significantly low scores obtained by these patients on the "nervousness" scale, as well as in the significantly higher scores

on the factor-analytically derived construct of "masculinity." The personality questionnaire data support the present experimental results. Whether differences in the discrimination or response tendencies are responsible for the hyposensitivity found in patients with asymptomatic myocardial ischemia cannot be decided from the present data. It should be kept in mind, however, that these two factors are not independent of each other.

Recent investigations have attempted to analyze inter-individual differences in sensitivity to pain by considering the influence of endorphinic mechanisms (19,20). The results of these reports suggest that varying concentrations of endorphins in plasma and cerebrospinal fluid or varying amounts of endorphinic secretion in intersynaptic fluid may represent the chemical substrate responsible for interindividual differences in pain sensitivity. Van Rijn and Rabkin (21) have shown that after injection of the opioid antagonist, naloxone, angina pectoris pain occurred significantly earlier in relation to onset of ischemia. These findings lend support to the possible role played by endorphinic mechanisms in asymptomatic myocardial ischemia. Further investigations are necessary, however, before unequivocal conclusions can be drawn.

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