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Development of Angina Pectoris Pain and Cardiac Events in Asymptomatic Patients with Myocardial Ischemia

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A total of 389 patients with angiographically determined coronary artery disease, who exhibited a complete absence of angina pectoris in the presence of reproducible myocardial ischemia, were studied in a follow-up investigation. After an initial coronary angiogram, anti-ischemic medication was prescribed as treatment. After a mean follow-up time of 4.9 years (maximum 13.4 years) patients were sent a questionnaire that assessed any new development of angina pectoris pain and cardiac events. In 48 of these patients a second angiogram was recorded after a mean period of 4.2 years. Asymptomatic patients had a worse prognosis than an age-adjusted normal population. After 5 and 10 years, 9 and 26% of the patients, respectively, had died, nonfatal cardiac events (myocardial infarction, bypass surgery or percutaneous transluminal coronary angioplasty) occurred after 5 and 10 years in 19 and 46%, respectively. A large number of initially asymptomatic patients developed angina pectoris pain over the follow-up period (34% after 5 years, 58% after 10 years). Novel angina pectoris pain often preceded cardiac events by months to years. Multivariate analysis indicated that vessel disease ($p = 0.0001$) and degree of ischemia (defined by ST-segment depression free exercise tolerance, $p = 0.04$) proved to have independent predictive value with respect to mortality rate. Newly developed angina pectoris was associated with an increase in objective signs of myocardial ischemia and a progression in coronary stenosis. The results indicate that patients who originally had myocardial ischemia with a marked absence of pain can develop angina pectoris over the course of years and that newly developed pain often precedes cardiac events.

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Some patients with coronary artery disease and myocardial ischemia have a marked lack of angina pectoris pain. The reasons for this absence of pain remain unclear. A series of investigations have shown that these patients have increased pain thresholds,[1–5] which suggest that the endogenous pain modification system may play a role. The questions that arise are whether these patients remain asymptomatic or develop angina pectoris pain on a long-term basis, and to what extent does pain precede cardiac events?

METHODS

Asymptomatic patients with myocardial ischemia: From January 1976 to June 1987, 508 patients were admitted to our hospital. These patients fulfilled the following criteria: In all patients coronary angiography was performed, and showed significant coronary artery disease (i.e., ≥50% stenosis in at least 1 of the 3 main coronary vessels). In no patient had coronary angiography been performed before. Patients with valvular disease were excluded from the study. In all patients ≥2 exercise tests (on average, 3.2 exercise tests per patient) were performed within a 3-month time period before coronary angiography, each of which showed significant signs of myocardial ischemia, without patients exhibiting any chest pain. Exercise tests were performed with the patient supine using a commercially available cycle ergometer (Elema Schönander) with a stepwise increasing watt level. Anti-ischemic medication was stopped the day before testing. In all patients, marked myocardial ischemia was demonstrated by a significant ST-segment depression (≥0.1 mV) in exercise electrocardiography tests. In 371 of the 508 patients (73%) the presence of myocardial ischemia was additionally evidenced by a significant increase in pulmonary capillary wedge pressure during floating catheter examination under physical exercise, at which time no patient reported chest pain. In addition to reproducible substantial silent myocardial ischemia during exercise testing, all patients reported a complete absence of angina pectoris pain dur-

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TABLE I Baseline Data of Asymptomatic Patients at Time of Initial Coronary Angiography

No. of patients (men/women)	389 (368/21)
Age (years)	50.3 ± 0.4
Height (cm)	172.5 ± 0.3
Weight (kg)	75.4 ± 0.5
Risk factors	
Cigarette smoking	272 (70%)
Hypertension (>160/95 mm Hg)	179 (46%)
Hyperlipidemia (>200 mg/dl total cholesterol)	266 (68%)
Diabetes mellitus	68 (18%)
Exercise electrocardiogram	
Exercise tolerance (W)	81 ± 2
Max. heart rate (beats/min)	126 ± 1
Max. blood pressure	
systolic (mm Hg)	190 ± 2
diastolic (mm Hg)	105 ± 1
Max. ST-segment depression (mV)	0.22 ± 0.01
Floating catheter examination	
Exercise tolerance (W)	93.6 ± 1.7
Pulmonary capillary wedge pressure (mm Hg)	
At rest	9.75 ± 0.22
Maximal	26.7 ± 0.5
Max. ST-segment depression (mV)	0.29 ± 0.01
No. of major coronary arteries narrowed >50% in diameter at angiogram	
1	131 (34%)
2	118 (30%)
3	140 (36%)
Left ventriculogram	
Ejection fraction	59.6 ± 7.4
Left ventricular function	
Normal	67 (17%)
Minimally impaired	190 (49%)
Severely impaired	132 (34%)
Previous myocardial infarction	335 (86%)
Heart volume (ml)	882 ± 8.5
Heart volume related to body weight (ml kg^{-1})	11.7 ± 0.09

Max. = maximal.

ing everyday activity in the 3-month period before coronary angiography. A total of 53% (n = 271) of these patients were completely asymptomatic and never experienced chest pain during everyday activities, and in 47% (n = 237) occasional reports of chest pain were evident in their past clinical history (≥3 months before coronary angiography). However, it could not be determined retrospectively in all cases whether the patients' chest pain reports were due to angina pectoris or to other noncardiac causes. These patients were all totally asymptomatic ≥3 months before the first coronary angiogram and were thus included in the present investigation.

One hundred nineteen of the 508 patients underwent coronary artery bypass surgery or percutaneous transluminal coronary angioplasty during a 6-month period after coronary angiography. These patients were excluded from the present study. In the remaining patients (n = 389) anti-ischemic medication was prescribed as treatment, and administered by the treating practitioners in most cases. These patients have been investigated in the present study. Table I lists coronary angiographic data, functional results and risk factors at the time of the initial angiogram.

A total of 86% of these patients (n = 335) already had myocardial infarction in their clinical history (>6 weeks before the coronary angiogram). On average, patients had pronounced myocardial ischemia with a substantial mean ST-segment depression of 0.22 mV and a mean maximal pulmonary capillary wedge pressure of 26.7 mm Hg. Only 18% of these patients had diabetes mellitus.

Procedure: After a mean follow-up period of 4.9 years (maximum 13.4), all 389 patients were sent a questionnaire, which assessed current medical treatment, the presence and frequency of chest pain, the point in time when, if at all, chest pain developed and under which circumstances, and whether myocardial infarction had occurred since coronary angiography, or whether bypass surgery or percutaneous transluminal coronary angioplasty was performed (>6 months after the initial coronary angiogram). The patients were asked to consult their treating practitioner in cases of uncertainty while responding to the questionnaire. Patients or their practitioners were consulted by telephone in cases of unclear responses to items in the questionnaire. Thus, we obtained a reliable estimate of the long-term follow-up in 98% of all cases.

The new development of angina pectoris pain was defined as the point in time (with a precision of a couple of months) when chest pain could be provoked in exercise tests for the first time (in most cases) and/or when the treating practitioner observed signs of angina pectoris in his/her patients.

If any patient died during follow-up, the circumstances of death were documented by a telephone call to the treating practitioner or to close relatives. The time of death was determined and whether symptoms occurred before death (>1 hour), or whether sudden death occurred (no symptoms or symptoms occurring within 1 hour before death). It was also determined whether in the months or years before death any new development of angina pectoris pain was observed.

A subgroup of patients (n = 48) underwent a second coronary angiography after a mean follow-up period of 4.2 years (maximal 12 years). This second angiography was performed in patients whose increase in myocardial ischemia was evident during exercise tests or in those whose maximal exercise capacity was markedly reduced, or exercise-induced angina pectoris had developed or any combination of these. Results of the second angiogram were compared with those of the first. It was determined whether the findings had changed or whether a regression or progression (a change of ≥2 degrees within the classification of the American Heart Association[6]) of stenoses was evident.

Data analysis: The follow-up data were analyzed according to the method of Cutler and Ederer.[7] An analysis of the prognostically relevant factors was conducted using the Cox hazards model.[8] A McNemar chi-square test was performed for testing symmetric distribution.[9] All values are presented as mean ± 1 SEM.

RESULTS

Asymptomatic patients with myocardial ischemia had a higher mortality rate over the follow-up period than the age-adjusted normal population.[10] Five years after the initial coronary angiography, 9% of these patients

had died, and approximately 26% died after 10 years (Figure 1a). A total of 3 patients died of noncardiac reasons. In the first 5 years, the annual mortality rate was relatively low (1.8%/year), and after the sixth follow-up year it was somewhat more pronounced (3.4%/year).

Figure 1b shows the incidence of nonfatal cardiac events in the surviving patients. In most cases the cardiac event was myocardial infarction (76%), and bypass surgery (17%) or percutaneous transluminal coronary angioplasty (7%). The annual nonfatal cardiac event rate was 3.7%/year for the first 5 years and afterward 5.6%/year.

Figure 1c shows the new development of angina pectoris pain. A high percentage (after 5 years 34%, after 10 years 58%) of the patients who were initially asymptomatic during all exercise tests and during the 3-month period before coronary angiography developed angina pectoris pain during the follow-up period (5.8%/year).

In 27% of the cases, nonfatal cardiac events were preceded by newly developed angina pectoris pain, which occurred months to years before the event (Table II). In 30% of the cases, angina pectoris pain occurred approximately at the same time as the nonfatal cardiac event (in most cases myocardial infarction), whereas newly occurring angina pectoris often preceded myocardial infarction by several days.

Figure 2 presents the mortality rates for patients who were grouped according to (a) number of diseased vessels ($p \leq 0.001$), (b) left ventricular function ($p \leq 0.005$), (c) maximal ST-segment depression during exercise testing ($p \leq 0.005$), and (d) ST-segment depression free exercise tolerance (i.e., exercise tolerance with ST-segment depression of <0.1 mV; $p \leq 0.01$). Patients with a 3-vessel disease, substantially impaired left ventricular function or pronounced ST-segment depression, or a combination of these, had the worst prognosis. Table III compares different factors with respect to their prognostic relevance. In a univariate analysis, vessel disease, left ventricular function, maximal ST-segment depression and ST-segment depression free exercise tolerance had a significant predictive value for mortality rate, and in part for nonfatal cardiac events. In a multivariate analysis, vessel disease accounts for most of the variance. However, ST-segment depression free exercise tolerance also had an independent predictive value with respect to mortality rate and to the incidence of nonfatal cardiac events.

TABLE II Outcome of 389 Initially Asymptomatic Patients with Reproducible Myocardial Ischemia During Follow-Up

	No.	% Per Year	Angina Pectoris Preceded Cardiac Event or Death
New developed angina pectoris	132	5.8	—
Nonfatal cardiac event	99	4.6	27 (27%)
Death	54	2.6	28 (52%)

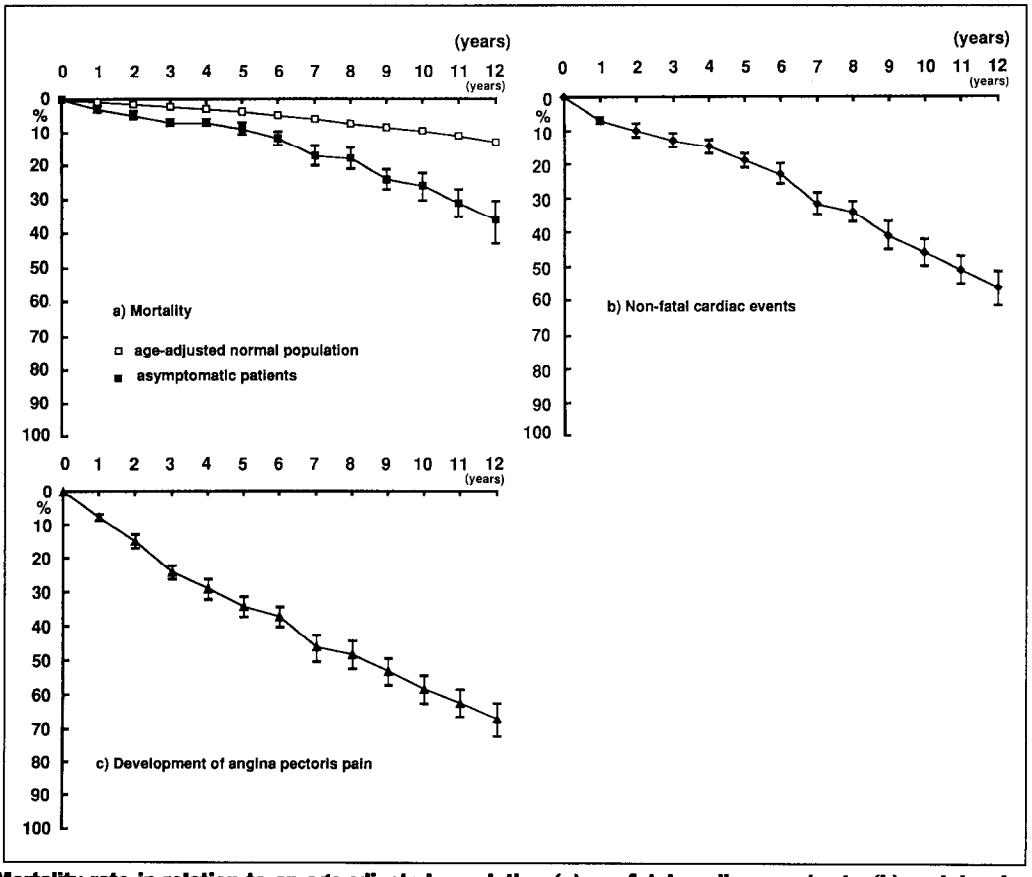

FIGURE 1. Mortality rate in relation to an age-adjusted population *(a)*, nonfatal cardiac event rate *(b)*, and development of angina pectoris pain *(c)* in asymptomatic patients with myocardial ischemia. The cumulative frequency of events is presented as a function of years after initial angiogram.

The new incidence of angina pectoris pain was also dependent on the severity of vessel disease (Table III). Patients with 3-vessel disease developed angina pectoris pain significantly more often during the follow-up period than did patients with 1- and 2-vessel disease ($p \leq 0.05$). Angina pectoris pain occurred more frequently

TABLE III Univariate and Multivariate Analysis of Prognostically Relevant Variables According to the Cox Hazards Model

	Univariate		Multivariate	
	χ^2	p Value	χ^2	p Value
Mortality rate				
Vessel disease	17.99	0.0000	15.88	0.0001
Left ventricular function	5.1	0.02		
Heart volume	1.55	NS		
Maximal ST-segment depression	6.02	0.01		
ST-segment depression				
Free exercise tolerance	6.36	0.01	4.24	0.04
Maximal exercise tolerance	3.14	(0.08)		
Nonfatal cardiac events				
Vessel disease	16.18	0.0001	15.27	0.0001
Left ventricular function	0.11	NS		
Heart volume	2.11	NS		
Maximal ST-segment depression	3.82	0.05		
ST-segment depression				
Free exercise tolerance	4.16	0.04	3.26	(0.07)
Maximal exercise tolerance	1.62	NS		
Development of angina pectoris pain				
Vessel disease	11.85	0.0006	11.85	0.0006
Left ventricular function	0.9	NS		
Heart volume	0.1	NS		
Maximal ST-segment depression	2.8	(0.09)		
ST-segment depression				
Free exercise tolerance	1.2	NS		
Maximal exercise tolerance	0.63	NS		

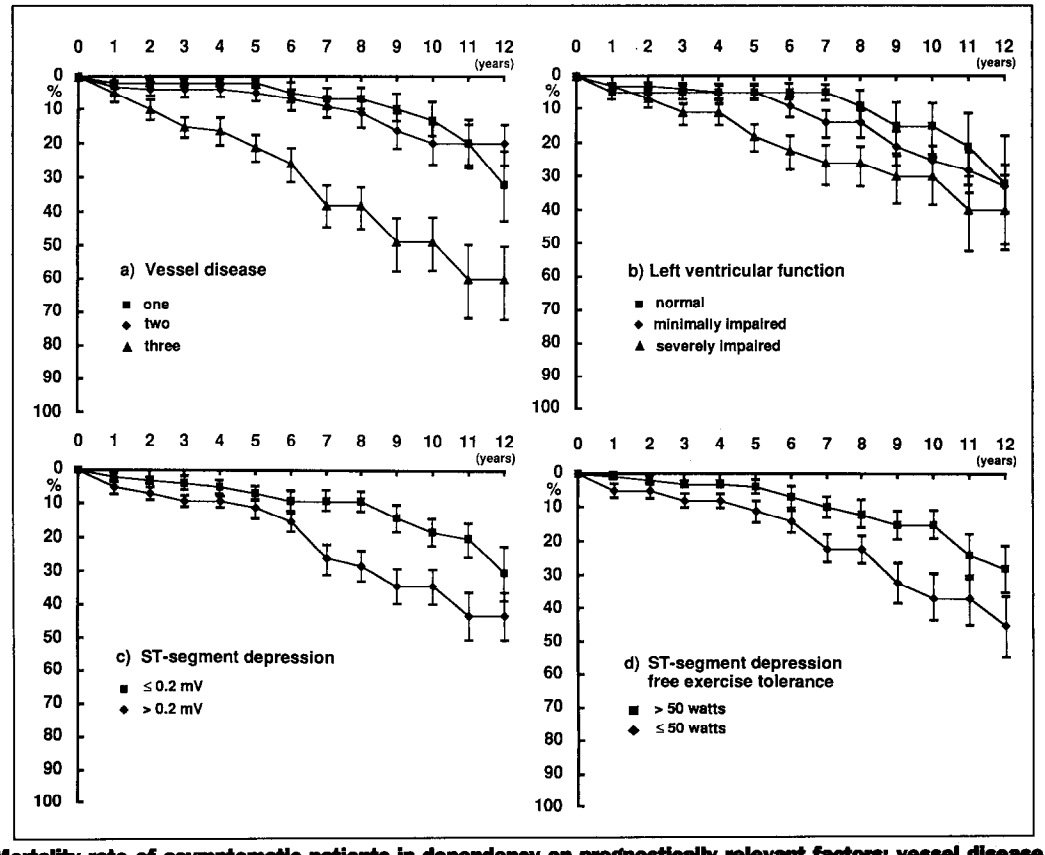

FIGURE 2. Mortality rate of asymptomatic patients in dependency on prognostically relevant factors: vessel disease *(a)*, left ventricular function *(b)*, ST-segment depression in exercise tests *(c)*, and ST-segment depression free exercise tolerance *(d)*.

during the follow-up period if the patient reported occasional chest pain in his clinical history before coronary angiography ($p \leq 0.001$; Figure 3). Among these patients ($n = 221$; 58% of the entire group) 50 and 70% after 5 and 10 years, respectively, reported angina pectoris pain. Patients who had never experienced angina pectoris pain ($n = 168$; 42% of the entire group), however, also developed anginal pain during the follow-up period (20% after 5 years, 47% after 10 years; Figure 3c). The occasional report of chest pain in the patients' past clinical history had no prognostic value with respect to mortality rate or the incidence of nonfatal cardiac events (Figure 3, a and b).

Figure 4 shows the functional parameters measured during exercise testing, a comparison of the coronary angiographic data, and the development of angina pectoris pain in the subgroup of 48 patients whose second coronary angiogram was obtained an average of 4.2 years after the first angiogram. During this time period, objective signs of myocardial ischemia had increased (maximal pulmonary capillary wedge pressure and maximal ST-segment depression) and exercise capacity had decreased in these patients. The results of the second angiogram indicated no regression in any patient, no change in 37% and a progression of coronary stenoses in 63%. Half of these patients reported angina pectoris pain during exercise testing before the second angiogram, whereas all these patients experienced no pain during exercise testing before the first angiogram. As shown by the McNemar chi-square test,[9] there was no difference between the patients who developed angina pectoris and asymptomatic patients with regard to progression of coronary stenosis.

During the follow-up period 54 patients died. More than half of the patients (52%) who were asymptomatic at the time of the initial coronary angiogram developed angina pectoris, frequently several years before death (Table II). Only 48% of the patients remained asymptomatic until the time of death. In these latter patients, 55% experienced sudden death and in another 25% symptoms first occurred <24 hours before death. However, 43% of patients who had developed angina pectoris pain some time before death experienced sudden death, and another 21% had occurrence of symptoms <24 hours before death. The frequency of sudden cardiac death did not differ between patients with and without newly developed angina pectoris pain as shown by the McNemar chi-square test.[9]

DISCUSSION

Coronary patients with myocardial ischemia indicate a worse prognosis than an age-adjusted normal population, even when they do not experience angina pectoris. This result of the present investigation is in agreement with observations of other investigators.[11–16] The annual mortality rate of the patients investigated here is <2%, at least in the first years. The patients studied in this study represent a select group; most were treated with an anti-ischemic medication. At the time patients responded to the questionnaire, 72% were receiving anti-ischemic medication (nitrates, β blockers, and/or calcium antagonists). Of these patients, 46% were being

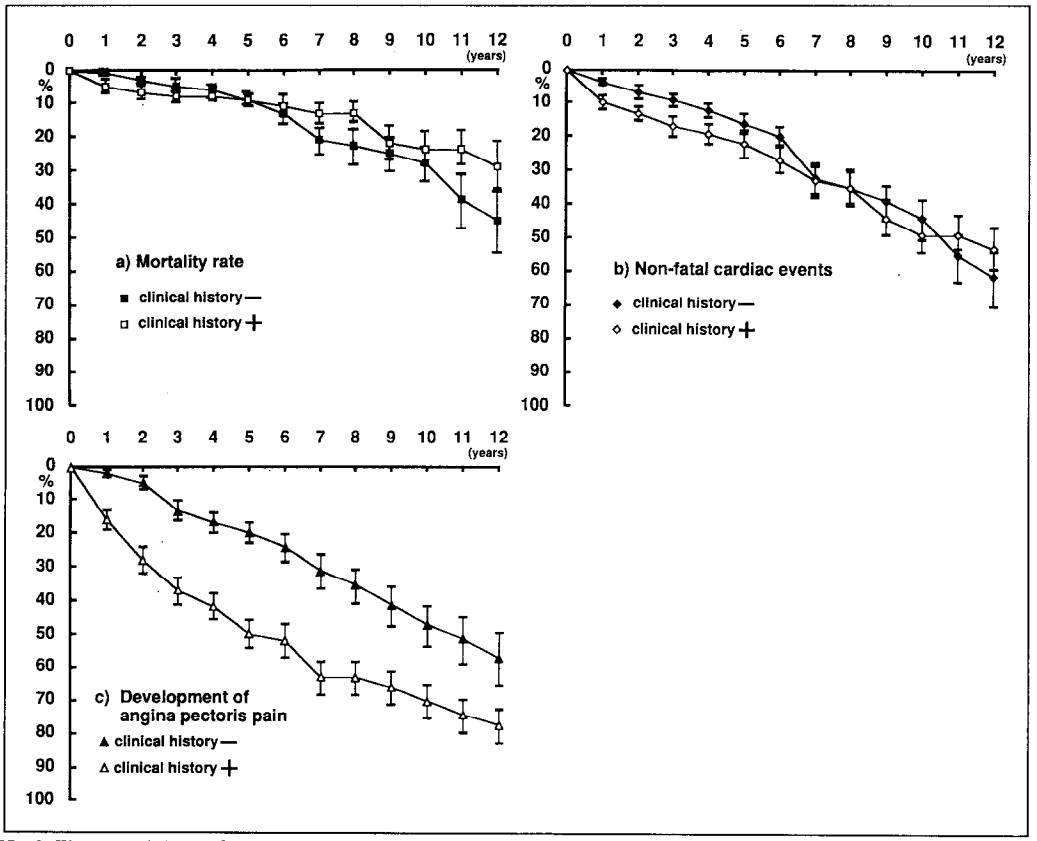

FIGURE 3. Mortality rate *(a)*, nonfatal cardiac events *(b)*, and development of angina pectoris pain *(c)* dependent on the presence or absence of chest pain in the clinical history ≥3 months before the initial coronary angiogram.

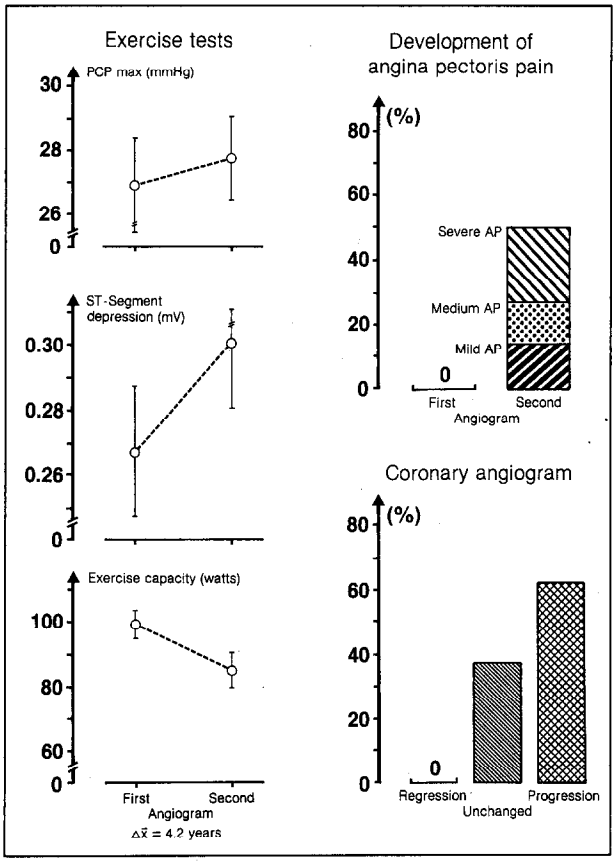

FIGURE 4. Results of exercise testing, development of pain during physical exercise, and coronary angiographic data at the time of the first and second angiogram. AP = angina pectoris; PCP = pulmonary capillary wedge pressure; $\Delta\bar{x}$ = mean time between first and second angiogram.

treated with a single substance, 39% with 2 of these substances, and 15% received all 3 substances.

The results indicate that the main factors that have earlier been found to determine the course of coronary artery disease in symptomatic patients (i.e., vessel disease and left ventricular function[17–22]), also have a substantial predictive value in asymptomatic patients. This finding is in agreement with studies examining asymptomatic patients.[12,14,15] The severity of myocardial ischemia, defined by the degree of ST-segment depression free exercise tolerance, has an independent predictive value in asymptomatic patients, as has also been reported by other investigators.[13,23] This was revealed by a multivariate analysis in which the independent contributions to the explained variance of mortality rate was computed. This observation suggests that the extent to which treatment should be given to asymptomatic patients should, at least in part, be oriented according to the degree of myocardial ischemia. In this study, we could not determine whether this suggestion would improve the asymptomatic patient's prognosis. This would require controlled prospective follow-up studies. The present results indicate that the degree of ischemia for asymptomatic patients is best represented by the exercise level reached before a significant ST-segment depression occurs and not by maximal exercise capacity. Because exercise testing in asymptomatic patients is not limited by angina pectoris pain, maximal exercise capacity did not show an independent predictive value. The lack of an independent predictive value for left ventricular function in the multivariate analysis of the present patient sample is most likely due to our selection criteria. One of the selection criteria was that the patients had a pronounced objective sign of myocardial ischemia. In patients with severely impaired left ventricular function, the objective signs of myocardial ischemia are often equivocal, thus leading to their exclusion from the present study.

Patients with myocardial ischemia, who were originally asymptomatic, do not remain asymptomatic in long-term follow-up studies. A large portion of these patients develop angina pectoris, which is in agreement with the observations of other workers.[11,24–30] The development of pain often precedes cardiac events by several months to years. The results from patients who received a second angiogram indicate that the development of pain is associated with a progression of coronary stenosis and an increase in the objective signs of ischemia. According to these observations, it can also be assumed that in patients who exhibit a pronounced absence of pain during ischemia, a stimulus-intensity mechanism plays a role. For such extremely asymptomatic patients, our earlier investigations[1,2] and those of other research groups[3–5] could demonstrate elevated pain thresholds. If the intensity of myocardial ischemia increases in the individual course of an originally asymptomatic patient, then this more severe ischemia apparently is sufficient to exceed the elevated pain threshold. Compared with symptomatic patients, asymptomatic patients have higher pain thresholds, requiring a more pronounced myocardial ischemia as a peripheral nociceptive stimulus to evoke pain.

It remains uncertain why asymptomatic and symptomatic patients with myocardial ischemia differ in their general sensibility to painful stimuli. The observation that patients who originally were characterized by a marked lack of pain over time also develop angina pectoris pain, suggests that regulative and quantitative factors such as individual sensibility to nociceptive stimuli,[3,31] pain modification by endorphines[32,33] and changes in individual pain thresholds[4,34,35] are responsible.

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