Impairment of Myocardial Perfusion and Function During Painless Myocardial Ischemia

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Left ventricular (or pulmonary and systemic arterial) hemodynamics were measured for a mean of 13.6 hours during continuous electrocardiographic monitoring in 14 patients admitted to the coronary care unit because of angina at rest. Of 293 episodes of transient ST segment and T wave changes identified, 247 (84%) were completely asymptomatic. Sixty-three percent of asymptomatic episodes were associated with an elevation of the left ventricular end-diastolic or pulmonary artery diastolic pressure of 5 mm Hg or more; in 15% there were smaller elevations (2 to 4 mm Hg) and in 22% there were no changes or less than a 2 mm Hg elevation of pressure. The peak contraction and relaxation dP/dt (first deriviative of left ventricular pressure) were reduced to 100 mm Hg/s or more in 84 and 81% of asymptomatic episodes, respectively. Great cardiac vein oxygen saturation measured in three patients showed an increased myocardial oxygen extraction similar to that seen in painful episodes, which preceded and accompanied asymptomatic electrocardiographic changes. These results indicate that asymptomatic electrocardiographic changes represent transient myocardial ischemia.

Comparison of asymptomatic and symptomatic episodes revealed that asymptomatic episodes were generally shorter (253 ± 159 versus 674 ± 396 seconds, probability [p] < 0.001) and produced less impairment of left ventricular function: there were smaller elevations of left ventricular end-diastolic or pulmonary artery diastolic pressure (5.9 ± 5.0 versus 16.5 ± 6.9 mm Hg, p < 0.001), and smaller reductions of peak left ventricular contraction dP/dt (252 ± 156 versus 395 ± 199 mm Hg/s, p < 0.001) and relaxation dP/dt (259 ± 191 versus 413 ± 209 mm Hg/s, p < 0.001). In individual patients, however, asymptomatic and symptomatic episodes of similar duration and severity were observed. The duration and severity of ischemia appear important for the genesis of anginal pain, but additional factors must be involved.

Pain is the clinical manifestation of ischemic heart disease that most often causes the patient to seek medical attention. Yet, observations during exercise stress testing occasionally show the development of typical ischemic electrocardiographic changes in the absence of anginal pain or long before its appearance (1,2). Similar observations have also been made during continuous ambulatory electrocardiographic monitoring (3–7). Preliminary evidence suggests that these electrocardiographic changes may indeed represent transient acute myocardial ischemia that, for reasons so far unexplained, is not accompanied by typical chest pain (8–11).

We present here the results of a series of measurements of left ventricular contractile function and coronary sinus oxygen saturation performed in a large number of episodes of transient asymptomatic electrocardiographic changes observed during continuous monitoring in a coronary care unit. Our observations show that in the group of patients we studied, asymptomatic episodes of transient ischemic ST segment and T wave changes are associated with alterations of myocardial perfusion and function similar to those observed in painful episodes.

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Methods

Study patients. We performed a retrospective analysis of analog tape recordings obtained during continuous hemodynamic monitoring of patients with unstable angina admitted to the coronary care unit. Partial reports of these studies have been previously published (9–11). The recordings were selected from 14 patients with a high daily frequency of ischemic episodes at rest (≥ 10/day). Their clinical characteristics and electrocardiographic and angiographic findings are shown in Table 1.

Hemodynamic monitoring. Routine antianginal medications

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were discontinued for at least 24 hours before the hemodynamic study. Nitrates were given when required for chest pain both before and during the study. The lead showing the greatest ST segment change on a 12 lead electrocardiogram recorded during angina was selected for continuous monitoring during the hemodynamic study. Patients were instructed to report immediately any symptom such as chest discomfort or dyspnea that might represent ischemia and were questioned about the presence of symptoms when electrocardiographic changes were apparent on the monitoring screen.

Details of the patient monitoring are summarized in Table 1. In 10 of the patients, the left ventricular pressure was continuously recorded; in the remaining 4 (Cases 4, 5, 9 and 10) only pulmonary and brachial artery pressures were monitored. Three patients (Cases 12, 13 and 14) with anterior ischemia also had continuous recording of great cardiac vein oxygen saturation. The techniques of hemodynamic monitoring have been described previously (9,11).

Data analysis. Left ventricular, or pulmonary and systemic arterial pressure and the electrocardiogram were continuously recorded on a multichannel FM tape recorder. At the end of each study, the stored data were replayed on a photographic recorder at low paper speed, so that transient episodes of ST segment elevation or depression ($\geq$ 0.15 mV) or pseudonormalization or peaking of inverted or flat T waves lasting more than 30 seconds could be identified for subsequent computer analysis. These segments of the recording were again replayed for analog to digital conversion and analysis with a Hewlett-Packard 21 MX digital computer, as previously described (12,13). The program was designed to calculate, on a beat to beat basis, the heart rate, ST-T positive and negative areas, left ventricular systolic and diastolic pressures (or pulmonary diastolic and systemic systolic pressures) and first derivative of left ventricular pressure (peak left ventricular contraction and relaxation dP/dt). No correction was made for the response of the catheter because we were interested only in relative transient changes of peak dP/dt. The values of the derived variables were averaged over 5 second periods and plotted with their standard deviation against time (Fig. 1).

Table 1. Clinical, Electrocardiographic and Angiographic Findings and Details of Hemodynamic Monitoring in the 14 Patients

		Electrocardiogram		Coronary Angiogram		Hemodynamic Monitoring								
											Episodes			
Case	Age (yr)	Control	Angina	Control	Spasm	Duration (h)	AP PAP	LVP	O_2 Sat	ECG	Total	S	A	%S
1	52	Normal	ST⇅ V_2–V_4	75% LAD, 90% LCx, 100% RC	LAD	13	—	Yes	—	V_3	34	4	30	12
2	59	Neg T wave V_1–V_4	ST↑ V_1–V_4 T↑ V_1–V_4	90% LAD	LAD	15	—	Yes	—	V_3	36	—	36	0
3	57	Neg T wave V_2–V_4	ST↑ V_3–V_6	90% LAD, 100% LCx, 100% RC	—	12	—	Yes	—	V_4	9	7	2	78
4	47	Normal	ST↑ V_1–V_4	90% LAD	LAD	12	Yes	—	—	V_3	10	7	3	70
5	56	Normal	ST⇅ II,III,aVF	90% LAD, 90% RC	RC	20	Yes	—	—	III	17	—	17	0
6	68	Neg T wave V_5–V_6	ST↓ V_3–V_6, II,III,aVF	90% LAD, 100% LCx, 90% RC	—	9	—	Yes	—	V_4	17	1	16	6
7	52	Old anterior + inferior MI	ST↓ V_3–V_6, T↑ II,III, aVF	100% LAD, 90% LCx	LCx	11	—	Yes	—	III V_4	25	7	18	28
8	52	Neg T wave V_1–V_3	ST↑ V_2–V_4, T↑ V_2–V_4	90% LAD, 75% RC	LAD	18	—	Yes	—	V_3	6	4	2	67
9	63	Normal	ST↑ V_2–V_4	90% LAD	LAD	8	Yes	—	—	V_3	9	1	8	11
10	62	Neg T wave V_4–V_6	ST↓ V_3–V_6	90% LAD, 75% LCx, 50% RC	—	20	Yes	—	—	V_4	18	7	11	39
11	59	Normal	ST↓ V_3–V_6	90% LAD, 75% LCx, 75 % RC	—	18	—	Yes	—	V_4	6	3	3	50
12	43	Normal	ST↑ V_2–V_4, T↑ V_1–V_4	75% LAD, 50% RC	—	10	—	Yes	Yes	V_3	22	3	19	14
13	47	Normal	ST↑ V_2–V_4, T↑ V_2–V_4	75% LAD, 90% RC	LAD	10	—	Yes	Yes	V_3	19	1	18	5
14	34	Neg T wave V_1–V_3	ST↑ V_1–V_3, T↑ V_1–V_4	90% LAD	LAD	15	—	Yes	Yes	V_2	65	1	64	2

A = asymptomatic episodes, AP = arterial pressure, ECG = electrocardiogram, LAD = left anterior descending coronary artery, LCx = left circumflex coronary artery, LVP = left ventricular pressure, MI = myocardial infarction, neg = negative, O_2 Sat = great cardiac vein oxygen saturation, PAP = pulmonary artery pressure, RC = right coronary artery; S = symptomatic episodes, ST↑ = ST segment elevation, ST↓ = ST segment depression, T↑ = pseudonormalization or peaking of T wave

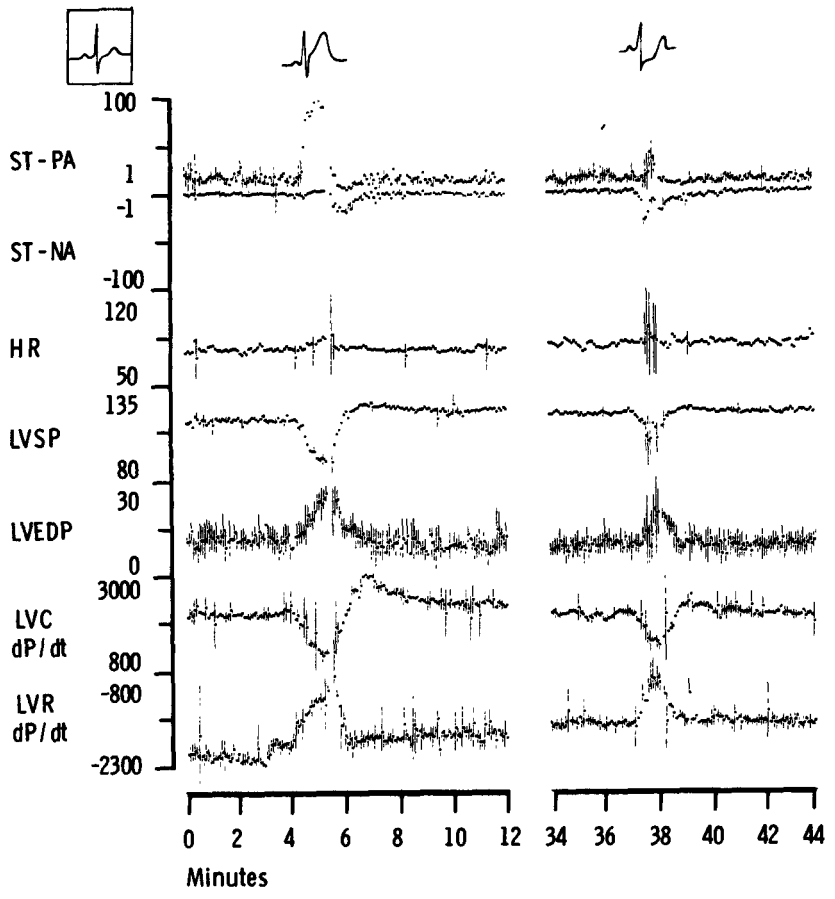

Figure 1. Computer plot of two asymptomatic ischemic episodes in the same patient. The averaged values of each derived variable are plotted with their standard deviation against time. The variables (**top to bottom**) were ST segment positive (PA) and negative areas (NA), heart rate (HR), left ventricular systolic (LVSP) and end-diastolic pressures (LVEDP) and left ventricular peak contraction (LVC) and relaxation (LVR) dP/dt. In the episode on the **left**, transient ST segment elevation (increase in ST segment positive area) was accompanied by an increase in left ventricular end-diastolic pressure, and decreases in both contraction and relaxation peak dP/dt. Similar impairment of left ventricular function accompanied the asymptomatic episode of ST segment depression (increase in ST segment negative area) in the same electrocardiographic lead shown on the **right**. There was no increase in the variables controlling myocardial oxygen demand before either episode.

Student's *t* test was used to test the significance of differences between asymptomatic and symptomatic episodes. Probability (p) values of less than 0.01 were considered statistically significant.

Results

A total of 191 hours of hemodynamic and electrocardiographic recording were obtained in the 14 patients (mean 13.6 hours per patient, range 9 to 20). No complications resulted from any of the procedures. A total of 293 episodes of transient ST segment and T wave changes were identified: 88 with ST segment elevation, 100 with ST segment depression and 105 with T wave pseudonormalization. Three patients showed only ST segment elevation and three showed only ST segment depression during the hemodynamic study. In the remainder, more than one electrocardiographic pattern was seen in the monitored lead during different episodes. Only 16% of episodes (46 of 293) were accompanied by anginal pain (percentages for the individual patients are shown in Table 1). Fewer episodes of ST segment depression were symptomatic than were episodes of ST segment elevation (19 and 38%, respectively). All episodes of T wave pseudonormalization were asymptomatic.

Asymptomatic episodes: hemodynamic findings. Asymptomatic episodes of ST-T wave changes were observed during hemodynamic monitoring in all 14 patients. The 247 asymptomatic episodes analyzed included 208 with left ventricular pressure tracings and derived contraction and relaxation peak dP/dt and 39 with pulmonary and systemic arterial pressures. No episodes were preceded by an increase in the heart rate or left ventricular or arterial systolic pressure. The results of computerized measurements are shown in Table 2. Overall, 63% of asymptomatic episodes were associated with an increase in left ventricular end-diastolic or pulmonary diastolic pressure of 5 mm or greater. The proportion was greater for the episodes with ST segment elevation (89%) than for those with ST segment depression (53%) or T wave pseudonormalization (56%). The peak contraction and relaxation dP/dt were reduced by 100 mm Hg/s or more in 84 and 81% of episodes, respectively. In 15% of episodes, there was a small increase in left ventricular end-diastolic or pulmonary diastolic pressure (3 to 4 mm) and in 22% there was no change or less than a 2 mm increase in pressure. Of the latter group of 47 episodes with less than a 2 mm increase in end-diastolic pressure, a reduction of either contraction or relaxation peak dP/dt by 100 mm Hg/s or more was noted in 23, leaving only 24 asymptomatic episodes without noticeable hemodynamic evidence of transient left ventricular dysfunction.

Table 2. Hemodynamic Changes During Transient Asymptomatic Episodes of ST Segment or T Wave Changes

Category	Δ LVEDP or Δ PADP (mm Hg)				Δ dP/dt ≥ 100 (mm Hg/s)			Δ LVEDP < 2 Plus ΔdP/dt C or R ≥ 100
	n	≥ 5	3 or 4	< 2	n	C	R	
ST ↑	61	54	6	1	50	50	49	1/1
ST ↓	81	43	14	24*	55	44	43	11/17
T ↑	105	59	17	29	105	83	79	11/29
Total	247	156	37	54*	210	177	171	23/47

* Seven had pulmonary diastolic pressure measurements only

Δ dP/dt C or R = change in peak left ventricular contraction or relaxation dP/dt; Δ LVEDP or Δ PADP = change in left ventricular end-diastolic pressure or pulmonary artery diastolic pressure; ST ↑ or ↓ = transient ST segment elevation or depression ≥ 0.15 mV. T ↑ = transient pseudonormalization or peaking of inverted or flat T waves

Great cardiac vein oxygen saturation. In three patients (Cases 12, 13 and 14), the changes in left ventricular pressure were documented together with the great cardiac vein oxygen saturation during 101 asymptomatic episodes. A reduction in oxygen saturation always preceded the electrocardiographic and hemodynamic changes, indicating that reduced coronary blood flow was the cause of asymptomatic episodes. The mean reductions of oxygen saturation for three subclasses of hemodynamic change are shown in Table 3. The episodes with the greatest degree of left ventricular hemodynamic impairment (class 1) showed a correspondingly greater decrease in oxygen saturation, with smaller decreases in oxygen saturation for classes 2 and 3. A decrease in percent oxygen saturation of at least 10 was seen in all 17 episodes without hemodynamic impairment (class 3). The computerized plot of one such episode is shown in Figure 2.

Comparison of asymptomatic and symptomatic episodes. The hemodynamic changes during the 46 symptomatic and 247 asymptomatic episodes are compared in Figure 3. The comparisons for the total group are further subdivided according to the type of electrocardiographic change. Overall, the mean duration of the symptomatic episodes (674 ± 396 seconds) was significantly longer than the asymptomatic episodes (253 ± 159 seconds, $p < 0.001$). There was an almost threefold greater increase in left ventricular end-diastolic or pulmonary artery diastolic pressure (16.5 ± 6.9 mm Hg) in the symptomatic episodes than in the asymptomatic episodes (5.9 ± 5.0 mm Hg, $p < 0.001$). The degree of impairment of left ventricular contractility was also greater in the symptomatic episodes. The reduction in peak contraction dP/dt was 395 ± 199 mm Hg/s in the symptomatic and 252 ± 156 mm Hg/s in the asymptomatic episodes ($p < 0.001$); the reduction in peak relaxation dP/dt was 413 ± 209 mm Hg/s in the symptomatic and 259 ± 191 mm Hg/s in the asymptomatic episodes ($p < 0.001$).

These data indicate that in this group of patients, asymptomatic episodes are usually characterized by a shorter duration and a lesser degree of ischemic left ventricular dysfunction than are the symptomatic episodes, although there is a considerable degree of overlap both in the group data (Fig. 3) and in the results from individual patients. When symptomatic and asymptomatic episodes were compared within the same patient, four showed asymptomatic episodes of duration comparable with their symptomatic episodes, with a similar elevation of the end-diastolic pressure; five patients had asymptomatic episodes with elevation of the end-diastolic pressure similar to that of their symptomatic episodes, but of a shorter duration.

Discussion

The mechanisms responsible for cardiac pain are still speculative and little progress has been made since 1965 when Gorlin (14) discussed the possible causes of pain. Because our understanding of the basis of cardiac pain is limited, it is not surprising that the occurrence of transient asymptomatic ischemic-like electrocardiographic changes has been regarded with caution and skepticism. However, in the Framingham study (15), 23% of myocardial infarctions occurred in the absence of symptoms. Additionally, strongly positive exercise tests have been documented in completely asymptomatic patients with severe coronary ar-

Table 3. Changes in Great Cardiac Vein Oxygen Saturation Based on Hemodynamic Subclass

Class	Hemodynamic Changes	No. of Episodes	Δ SO_2 GCV (mean ± SD)	Range
1	Δ LVEDP ≥ 5	56	24.7 ± 7.4	(13–45)
2	Δ LVEDP 0–4 and Δ LV dP/dt C or R ≥ 100	28	19.3 ± 5.4	(10–30)
3	Δ LVEDP 0–4 and Δ LV dP/dt C and R < 100	17	14.9 ± 3.1	(10–20)

Δ LVEDP = change in left ventricular end-diastolic pressure (mm Hg); Δ LV dP/dt C or R = change in peak left ventricular contraction or relaxation dP/dt (mmHg/s). Δ SO_2 GCV = change in percent oxygen saturation in the great cardiac vein.

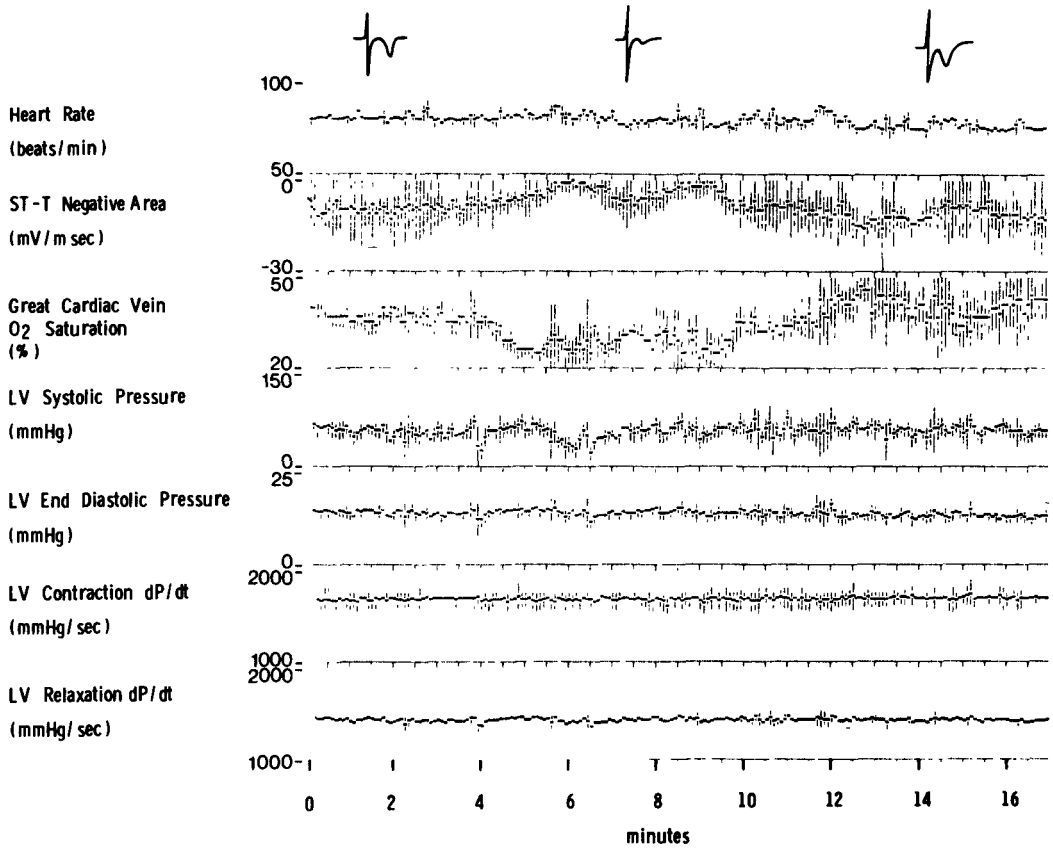

Figure 2. Computer plot of an asymptomatic episode of pseudonormalization of an inverted T wave (decrease in ST-T negative area) in a patient with anterior ischemia. There was no increase of left ventricular (LV) end-diastolic pressure and the peak contraction and relaxation dP/dt were not altered, although there was a reduction of great cardiac vein oxygen saturation preceding and accompanying the electrocardiographic change.

tery disease, supporting the view that myocardial ischemia can occur without anginal pain (2). Our data fully confirm this possibility and demonstrate that asymptomatic ischemic events, which outnumber those accompanied by pain, are associated with similar disturbances of myocardial perfusion and function.

Animal experiments have shown that increased myocardial oxygen extraction (16) and impairment of left ventricular function (17,18) are early manifestations of acute myocardial ischemia. In our patients, these alterations were observed in all episodes with pain and in the large majority of episodes without pain. None of the asymptomatic episodes occurring at rest were preceded by an increase in myocardial oxygen demand; instead we observed an increase in myocardial oxygen extraction before the onset of electrocardiographic changes, supporting the hypothesis that a reduction of coronary blood flow was responsible for asymptomatic episodes in our patients.

Asymptomatic versus symptomatic ischemic episodes. Asymptomatic episodes were generally shorter in duration and produced relatively less impairment of left ventricular hemodynamics than symptomatic episodes. It is tempting to speculate that asymptomatic episodes may therefore represent lesser degrees of myocardial ischemia, as previously suggested (1). The absence of pain in the brief episodes of T wave pseudonormalization and in those other episodes with minor or no measurable left ventricular impairment could probably be explained in this manner. However, the wide overlap in duration of episodes and degree of left ventricular impairment observed both in the group data and in comparisons of the episodes within individual patients suggests that the severity of ischemia represents a predisposing, but not necessarily sufficient, condition for production of symptoms. Therefore, additional factors must be involved in the genesis of anginal pain.

Transient asymptomatic electrocardiographic changes representing transient myocardial ischemia are commonly seen in patients with ischemic heart disease when continuous electrocardiographic recordings are performed. The proportion of all episodes that are asymptomatic varies from patient to patient and in the present study represented 84% of the total. This proportion is similar to the findings in a number of other studies of ambulatory patients (3–7) in which asymptomatic episodes outnumbered symptomatic episodes. This means that patients with angina may experience ischemia significantly more often than the frequency of symptoms would suggest.

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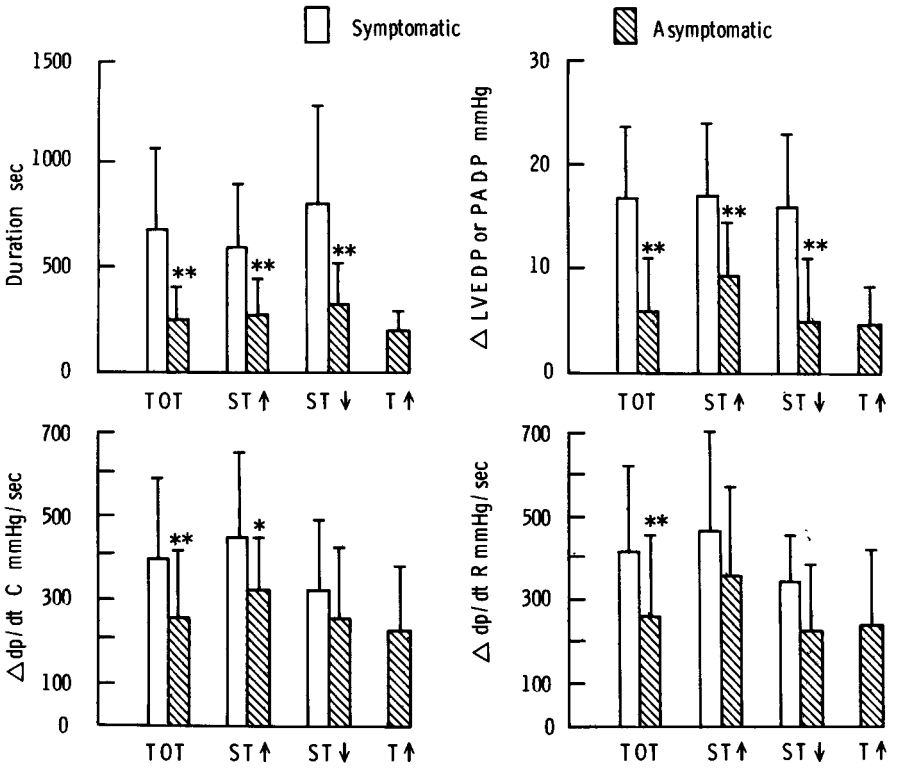

Figure 3. Comparison of symptomatic and asymptomatic episodes of ST segment and T wave changes. The mean values and standard deviation are plotted for the duration of episodes, the increases in left ventricular end-diastolic (LVEDP) (or pulmonary artery diastolic [PADP]) pressure and reductions of left ventricular peak contraction (C) and relaxation (R) dP/dt. P values for comparison of symptomatic and asymptomatic episodes: * = < 0.01. ** = < 0.001. Overall, asymptomatic episodes were shorter and were accompanied by lesser degrees of left ventricular impairment. ST ↑ or ↓ = transient ST segment elevation or depression; T ↑ = transient pseudonormalization or peaking of inverted or flat T waves; TOT = total.

The asymptomatic episodes of ST segment and T wave changes documented in this study were derived from a group of patients hospitalized because of typical anginal pain associated with ischemic changes on the electrocardiogram. The findings in these patients cannot necessarily be extrapolated to an asymptomatic population undergoing exercise stress testing or continuous electrocardiographic recording by the Holter technique (19,20). However, the significance of asymptomatic transient electrocardiographic changes in such a group must be assessed by methods capable of detecting transient regional myocardial ischemia, rather than by the presence or absence of coronary atherosclerosis.

Clinical implications. Asymptomatic episodes of ST segment elevation or depression or T wave pseudonormalization or peaking are common when appropriately searched for in patients with ischemic heart disease. Hemodynamic monitoring indicates that these episodes represent painless myocardial ischemia, so that the majority of ischemic events may be unrecognized by the patient. In these patients, continuous electrocardiographic monitoring is useful to determine the frequency of ischemic events for the evaluation of prognosis and response to therapy.

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