ROLE OF PERCEPTIVE THRESHOLD IN MYOCARDIAL INFARCTION PATIENTS WITHOUT PREVIOUS ANGINA

NAGAHARU FUKUMA, M.D., HIROSHI KISHIDA, M.D.
AND HIDEMASA OKUMURA, M.D.

The purpose of this study is to clarify the mechanism of sudden onset myocardial infarction (MI) without previous angina and the relationship of MI without previous angina to the mechanism of onset of postinfarction asymptomatic myocardial ischemia. The mean initial time of ischemic pain in the upper arm under the tourniquet test was significantly prolonged in the MI patients without previous angina, compared with that for the MI patients with previous angina and normal control subjects, although there are some overlapping cases (74 ± 37 sec versus 52 ± 20 sec ($p < 0.01$), and versus 56 ± 15 sec ($p < 0.05$), respectively). The tolerance time for ischemic pain also was similarly prolonged. There was no significant difference between the groups of MI patients (with and without previous angina) with respect to age, frequency of complications of diabetes mellitus, severity of coronary artery lesions or site of MI. The incidence of post-infarction myocardial ischemia was 50% for the previous angina group and 39.5% for the group without previous angina, but the frequency of asymptomatic ischemia was significantly higher in patients without previous angina, at 66.7%, than in those with previous angina, 32.3% ($p < 0.05$). These results suggest that there is a close relationship between the mechanism of MI with sudden onset and that of asymptomatic myocardial ischemia during the pre- and post-infarction periods in patients with low sensitivity to pain.

IT is hardly necessary to say that the majority of myocardial infarction (MI) patients have a history of angina pectoris before the onset of acute MI, but it is also known that in some patients without previous angina pectoris acute MI is triggered by the first episode of chest pain. The incidence of MI without prodrome is approximately 48% to 67%,¹⁻⁵ and silent MI accounts for 20% to 60% of MI patients.⁶ The onset of MI may be unaccompanied by

subjective symptoms, as pointed out by several investigators,⁷⁻⁹ due to various factors such as advanced age, disturbance of the anginal warning system in complications of diabetes mellitus and some type of neuropathy, hyposensitivity to pain, site of MI and small infarctions.

On the other hand, in cases where the onset of acute MI is not preceded by subjective symptoms such as chest pain, dyspnea, vomiting and cold sweat, it is possible that the patients have already had transient attacks of myocardial ischemia without subjective symptoms before the onset of MI. The purpose of this study is to elucidate the mechanism of development of MI without

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The First Department of Internal Medicine, Nippon Medical School, Tokyo, Japan

Mailing address: Nagaharu Fukuma, M.D., The First Department of Internal Medicine, Nippon Medical School, 1-1-5 Sendagi, Bunkyo-ku, Tokyo 113, Japan

Fig.1. Reproducibility of tourniquet test (16 cases).

The left-hand panel shows the initial times of onset of ischemic pain, and the right-hand panel the tolerance times of ischemic pain. The abscissa shows the time determined in the first session of the tourniquet test and the ordinate the time obtained in the second session.

Fig.2. Initial times recorded during tourniquet tests in control, myocardial infarction and angina pectoris patients.

Group A consisted of patients with previous angina prior to myocardial infarction, group B of patients without previous angina. Group C comprised angina pectoris patients with symptomatic myocardial ischemia, group D patients with asymptomatic myocardial ischemia. * $p < 0.05$, ** $p < 0.01$

previous angina in cases where MI manifests itself with the first anginal episode, and to investigate the relationship between MI without previous angina and transient

asymptomatic myocardial ischemia which manifests itself during the follow-up of MI. To achieve the aim, patients with MI were classified according to the presence or abs-

Fig. 3. Tolerance times recorded during tourniquet tests in control, myocardial infarction and angina pectoris patients.

The distribution of patients in groups A, B, C and D is the same as in Fig. 2.

* $p < 0.05$

ence of previous angina, and their response to the tourniquet test for ischemic pain threshold and clinical features were compared between the 2 groups. Furthermore, the angina pectoris patients without a history of MI were classified into a group with symptomatic episodes and one with asymptomatic episodes for the purpose of comparison.

MATERIALS AND METHODS

1. Subjects

This investigation was carried out on 100 patients with old MI (85 males and 15 females averaging in age 60 ± 10 years; for periods averaging 52 ± 43 months). They were selected from patients with a stable clinical course treated by antianginal drugs at the outpatient clinic of Nippon Medical School. The patients were classified into a group of 62 with previous angina (group A) and a group of 38 with no previous angina (group B). The observation periods from the onset of MI were 54 ± 42 months in group A and 49 ± 43 months in group B. Ambulatory electrocardiographic monitoring was conducted on all 100 patients for at least 48h during the periods of the stable clinical course, and the patients who had transient ST-segment depression on the ECG at least once were classified as positive for myocar-

dial ischemia. The MI patients who had transient ST-segment depression with symptoms at least once were classified as positive for symptomatic myocardial ischemia, and the patients who had transient ST-segment depression with no symptoms were classified as positive for asymptomatic myocardial ischemia.

Meanwhile, of 44 patients (36 males and 8 females averaging in age 60 ± 8 years) with chronic stable angina pectoris, those who were symptomatic in at least one episode of transient ST-segment depression on 48h ambulatory electrocardiographic monitoring were classified as group C, and those who were asymptomatic in all episodes were classified as group D, according to the criteria of Kishida et al.¹⁰ Group C consisted of 31 patients, group D 13 patients.

Two 24h sessions of ambulatory electrocardiographic monitoring were performed with a Del-Mar Avionics tape recorder (Model 445). ECG tracings were obtained through 2 channels, one of them showing a maximum ST-segment depression except for leads exhibiting QS patterns and Q waves. An ischemic episode was defined as a transient (≥ 1 mm) horizontal or downsloping ST-segment depression of at least 60 sec duration. An episode was classified as symptomatic if it was accompanied by subjective

TABLE I CLINICAL FEATURES IN PATIENTS WITH AND WITHOUT A HISTORY OF PREVIOUS ANGINA PRIOR TO MYOCARDIAL INFARCTION

	Group A	Group B	p value
Number of cases	62	38	
Age (years)	59±10	61±11	NS
Complication of diabetes mellitus	30	12	NS
Site of myocardial infarction			
Anterior	21	10	NS
Antero-inferior	15	10	
Inferior	26	18	
Number of diseased coronary arteries			
Single vessel	32	18	NS
Multi-vessel	26	17	
Left ventricular ejection fraction (%)	52±6	48±12	NS
Tourniquet test			
Initial time (seconds)	52±20	74±37	p<0.01
Tolerance time (seconds)	131±41	151±44	p<0.05

Group A: Case with previous angina prior to myocardial infarction

Group B: Cases with no previous angina prior to myocardial infarction

TABLE II CLINICAL FEATURES IN GROUPS WITH SYMPTOMATIC AND ASYMPTOMATIC MYOCARDIAL ISCHEMIA

	Group C	Group D	p value
Number of cases	31	13	
Age (years)	60±7	59±11	NS
Complication of diabetes mellitus	7	2	NS
Number of diseased coronary arteries			
Single vessel	9	3	NS
Multi-vessel	9	4	
Left ventricular ejection fraction (%)	62±10	65±8	NS
Mean maximum ST-segment depression (mm)	1.6±0.5	1.9±0.6	NS
Tourniquet test			
Initial time (seconds)	55±24	67±20	NS
Tolerance time (seconds)	137±36	150±37	NS

Group C: Cases with symptomatic myocardial ischemia

Group D: Cases with asymptomatic myocardial ischemia

symptoms or as asymptomatic if no symptoms were present on ST-segment depression. Excluded from the study were patients with: 1) anemia or valvular heart disease, which show electrocardiographic responses similar to that of angina in response to stress; 2) left bundle branch block, WPW syndrome etc., which can interfere with the interpretation of ST-segment changes during angina episodes.

Coronary arteriography and left ventriculography were performed on 93 of 100 MI

patients and 25 of 44 angina pectoris patients. A fixed narrowing of more than 75% of the luminal diameter was defined as significant coronary artery stenosis. According to this criterion, 50 patients had single-vessel disease and 43 patients multi-vessel disease in MI, and 12 and 13 patients, respectively, in angina pectoris.

The left ventricular ejection fraction was calculated by the area-length method, using right anterior oblique projection from left ventriculography.

Fig. 4. Relationship between the presence or absence of angina prior to myocardial infarction and the occurrence of myocardial ischemia following myocardial infarction.

There was a significant difference in frequency between symptomatic and asymptomatic myocardial ischemia depending on the presence or absence of angina ($p < 0.05$).

2. Tourniquet Test

A sphygmomanometer cuff was inflated and maintained at 180 mmHg over the left upper arm. The time required for pain and/or tingling to manifest itself in the left forearm or left hand following the start of the tourniquet test was defined as the initial time of ischemic pain, and the time required for the symptom to reach its limit during squeezing was defined as a tolerance time for ischemic pain. The upper limit of the duration of inflation was set at 3 min. This test was also conducted in 28 normal control subjects (19 males and 9 females averaging in age 57.1 ± 9.2 years) matched for age with patients with MI and angina pectoris. Systolic blood pressure was within 140 mmHg in all the MI and angina pectoris patients and 28 normal control subjects.

3. Statistical Analysis

All data were expressed as mean $\pm$ standard deviation, and the reproducibility of the tourniquet test was assessed by linear regression analysis. The other data were assessed by the Student's t-test and the Chi-square test for the significance of differences, and the differences were considered statistically significant when $p < 0.05$.

RESULTS

Reproducibility of Tourniquet Test

Figure 1 shows the reproducibility of the initial and tolerance times for ischemic pain in the upper arm determined by the tourniquet test. A close correlation between the first and second measurements of both initial and tolerance time for ischemic pain was indicated in the results obtained by the same physician.

Tourniquet Test in Patients with MI

Figure 2 shows the initial time obtained by the tourniquet test in MI and angina pectoris patients. The initial times for group A with previous angina, group B without previous angina and the control group were 52 ± 20 sec, 74 ± 37 sec and 56 ± 15 sec, respectively. The initial time for group B was prolonged significantly, compared with that for group A or the controls ($p < 0.01$ and $p < 0.05$, respectively). With angina pectoris, on the other hand, the initial times for group C and group D were 55 ± 24 sec and 67 ± 20 sec, respectively, a difference that was not statistically significant.

On the other hand, as shown in Fig. 3, the tolerance times were 131 ± 41 sec, 151 ± 44 sec, 137 ± 36 sec, 150 ± 37 sec and 134 ± 31 sec.

sec, respectively, for groups A, B, C and D and the control group, group B showing a significant prolongation, compared with group A ($p < 0.05$) and the control group ($p < 0.05$). The tolerance time for group D was also prolonged, but the difference was not significant, compared with control group. The number of subjects in each group whose tolerance time reached 3 min was 12 of 62 in group A (19.4%), 17 of 38 in group B (44.7%), 5 of 31 in group C (16.1%) and 7 of 13 in group D (53.8%), with a significantly greater number in group B than in group A ($p < 0.01$) and in group D than in group C ($p < 0.01$).

Clinical Features in Patients with MI and Angina Pectoris

Table I summarizes the clinical features of the patients with MI. No significant difference was observed between groups A and B with respect to age, frequency of complications of diabetes mellitus, site of MI, severity of coronary artery lesion or the ejection fraction.

Table II summarizes the clinical features of the patients with angina pectoris. No significant difference in clinical features was observed between groups C and D.

Myocardial Ischemic Episodes Following MI

Figure 4 shows the frequency of transient myocardial ischemia during the follow-up of MI. As determined by Holter monitoring the frequency of transient myocardial ischemia was 31 of 62 for group A (50%) and 15 of 38 for group B (39.5%). However, the reverse pattern was seen in the frequency of asymptomatic myocardial ischemia in patients with manifest myocardial ischemia, with asymptomatic myocardial ischemia observed in 10 of 31 (32.3%) for group A and 10 of 15 (66.7%) for group B, ($p < 0.05$).

DISCUSSION

It is reported that about half of MI patients exhibit sudden onset without prodromal symptoms!¹⁻⁵ Of these patients, the mechanism of development of MI may be due to the sudden onset with or without asymptomatic episodes. It has been pointed out that asymptomatic myocardial ischemia is associated with the sudden onset of MI!^{1,12}

According to these reports, the frequency of MI is higher in patients with asymptomatic myocardial ischemia than in those who have negative exercise tests. Therefore, in cases where myocardial ischemia occurs before manifestation of MI, the onset of MI may be prevented by treating myocardial ischemia, since it is known that the patients without previous angina carry a more favorable prognosis of MI than those with previous angina!¹³⁻¹⁶

One of the aims of this study, although approached was to determine whether or not such cases are included among patients without previous angina by the tourniquet test to measure ischemic pain threshold!^{17,18} Our results indicated that, although the 2 groups partially overlapped each other, the initial and tolerance times for ischemic pain were significantly longer in the group without previous angina than in the group with previous angina. These findings lead us to conclude that transient asymptomatic myocardial ischemia precedes the onset of MI, thus being the cause of sudden or silent MI in cases where these times are prolonged to a significant extent. This conclusion is in agreement with findings demonstrating that in angina pectoris patients initial and tolerance times for ischemic pain tended to be longer, though not significantly so, in patients with asymptomatic episodes than in those with symptomatic ones.

Glazier et al!¹⁸ state that generalized defective perception induced by painful stimuli is a cause of painless myocardial ischemia, adding that this defective perception in painless myocardial ischemia, observed in this study in the overlapping cases, stems from the endorphin-mediated analgesic system which produces a selective suppression of nociceptive dorsal horn neurons and consequent analgesia.

All the subjects of this study had symptoms of acute MI at its onset, regardless of whether they had previous angina. This fact rules out the possibility that neural pathways responsible for the transmission of painful stimuli from the heart had been damaged or was absent. However, since no investigation was made as to endorphins in this study, the influence of the endorphinic mechanism upon the transmission of painful stimuli cannot be discussed here.

On the other hand, the frequency of transient myocardial ischemia, observed by Holter monitoring conducted during the follow-up of MI, was higher in the group with previous angina, which carried a more unfavorable prognosis, than in the group without previous angina.¹³⁻¹⁶ Bosch et al,¹⁹ pointed out that cardiac events occurred more frequently in patients with early ischemia, defined as transient myocardial ischemia 24h or more after acute MI during hospitalization, than in those without early ischemia.

The frequency of isolated asymptomatic ischemia was 20 of 46 patients with transient myocardial ischemia after MI. One recent investigation²⁰ pointed out that the prognosis of MI was more unfavorable in patients with transient myocardial ischemia than in those without it, irrespective of the presence of subjective symptoms. Furthermore, therapeutic strategy for myocardial ischemia is particularly important in light of reports²¹ showing that the incidence of asymptomatic myocardial ischemia is higher in angina pectoris patients with a history of MI than with those without a history of MI.

The ischemic pain threshold and the frequency of transient asymptomatic ischemia after MI were higher in the group without previous angina than in the group with previous angina. Moreover, the ischemic pain threshold in angina pectoris patients was higher in patients with asymptomatic episodes than in those with symptomatic ones, though the difference was not significant because of the small sample of angina pectoris patients. This finding may justify the conclusion that low sensitivity to pain prior to MI is the cause of transient asymptomatic myocardial ischemia following MI.

The relationship between asymptomatic ischemia and factors including age, complications of diabetes mellitus, severity of coronary artery lesions and site of MI was also investigated, but no significant relationship was noted.

In conclusion, it may be postulated that asymptomatic myocardial ischemia is associated with sudden onset of MI without previous angina and that generalized defective perception is a possible mechanism. It is also suggested that this mechanism provides a partial explanation of asymptomatic myocardial ischemia following MI.

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