Evaluation of Clinical Factors Involved in Onset of Myocardial Infarction

TETSUYA SUMIYOSHI, M.D., KAZUO HAZE, M.D., MUNEYASU SAITO, M.D.

KENICHI FUKAMI, M.D., YOICHI GOTO, M.D.

AND KATSUHIKO HIRAMORI, M.D.

In order to discuss the mechanism of onset in myocardial infarction (MI), clinical cases were reviewed and various clinical findings were analyzed according to the premise that the onset of MI requires both a predisposition and a trigger. The majority of subjects did present conditions that constituted predispositions for MI, including a history of angina pectoris (especially unstable angina), poor therapeutic results for angina pectoris, organic stenosis of the coronary artery, life changes, and overwork. Patients with multiple factors tended to develop MI without a definite trigger, i.e., onset during sleep or rest whereas, in patients with fewer predisposing factors, it was obvious effort, excitation or stress that triggered MI. However, not a few of the patients presented with no organic stenosis of the coronary artery or no history of angina pectoris. There were patients without ST segment elevation at onset of MI, and patients in whom ST elevation was recorded after onset. These findings suggest the existence of mechanisms other than coronary occlusion in onset of MI. Occlusion of the coronary artery distributed to the infarct region occurred frequently among patients with delayed CPK efflux as well as prolonged chest pain and ST segment elevation. These lines of evidence suggest extension of infarction due to secondary coronary occlusion.

THE mechanism of onset in acute myocardial infarction (MI) has been the subject of controversy for decades and this ambiguity has produced a number of etiological hypotheses. For example, coronary artery thrombosis, coronary spasm and secondary coronary thrombi have all been considered: however, none has been conclusively proved. The process of formation of MI may be divided into three stages. In the first stage, predispositions for onset of MI in terms of coronary arteriosclerosis, angina pectoris and changed physical condition are consolidated.

The second stage is the instant at which MI is initiated by events or triggers such as coronary thrombi, coronary vasospasm, or abnormalities in the autonomic nervous system, among others. The third stage is the period between initiation and completion of MI, a stage related to extension or salvage of myocardial necrosis. Because of the difficulty of investigating the mechanism of onset of MI in patients directly, we were compelled to use indirect evaluations. With these limitations in mind, we delineated various clinical factors associated with onset of MI in the three stages in our study cases and described the significance of each factor in each stage.

Key Words:

Mechanism of onset in myocardial infarction (MI)
Predispositions for onset of MI
Triggers for onset of MI
Preinfarction angina
Infarct-related vessel

PATIENTS AND METHODS

The subjects were patients with MI or angina

National Cardiovascular Center, Osaka, Japan

Mailing address: Tetsuya Sumiyoshi, M.D., National Cardiovascular Center, 5-7-1 Fujishiro-dai, Suita, Osaka 565, Japan

pectoris who were hospitalized in the National Cardiovascular Center between October 1977 and February 1985. The following clinical parameters were evaluated.

I. Predispositions for onset of MI

1. Preinfarction angina and its therapeutic results

The presence or absence of preinfarction angina in the patient's history, the type of angina, and the results of medical treatment were examined in 310 patients with MI hospitalized between October 1977 and July 1981. As controls, the results of medical treatment and the incidence of MI were examined with regard to 285 patients with angina who required hospitalization for treatment during the same period.

2. Relationship between vasospastic angina and onset of MI

The presence or absence of MI in the patient's history and the prognosis during a mean three-year follow-up period were examined in 183 patients with angina in whom an attack with ST elevation was documented or in whom coronary arteriogram directly demonstrated spasm, indicating the involvement of coronary vasospasm. Of this population, 100 patients with organic coronary stenosis of 50% or less were evaluated for the relationship between continuation of medical treatment and prognosis during the mean five-year follow-up period.

3. Grade of stenosis of the coronary artery distributed to the infarct region (infarct-related vessel: IRV)

The grade of IRV stenosis was determined in 54 patients who had undergone coronary arteriography before onset of MI and 893 who underwent the examination after an interval of approximately four weeks after onset of MI.

4. Lifestyle of patients before onset of MI

By means of an interview and/or questionnaire, we surveyed the lifestyle and environmental changes occurring for one month before onset of

Fig.1. Preinfarction angina and results of its medical therapy in patients with acute myocardial infarction.

MI in 118 recent patients who were hospitalized between July 1984 and February 1985. There were 20 items, including job transfer, moving, illness of relatives, etc. These data were compared with those of the same patients during the one-month period one year previous to onset. The presence or absence of a feeling of overworking or abnormalities in physical condition immediately before MI onset was also surveyed.

II. Onset of MI

1. In 416 patients whose situation at the instant of onset of MI could be examined, the situations were classified according to the following items: during sleep; at rest; during light daily effort (walking, changing clothes, taking meals, defecating, etc.); during moderate to heavy exercise (jogging, carrying a heavy object, etc.); and during emotional stress or excitement (arguments, conferences, etc.). The relationship of the situations at onset to preinfarction angina and to coronary arteriographic findings was studied.

2. The distribution, at hourly intervals, of

TABLE 1 RESULTS OF MEDICAL THERAPY FOR ANGINA PECTORIS, AND THE NUMBERS OF PATIENTS WHO DEVELOPED MYOCARDIAL INFARCTION (MI)

Type of Angina	Total	Medically controlled	Medically uncontrolled
Unstable Angina	143 (11)	124 (1)	19 (10)
Non-unstable Angina	142 (6)	136 (1)	6 (5)
Total	285 (17)	260 (2)	25 (15)

() = number of patients who developed MI

TABLE II-a INCIDENCE OF MYOCARDIAL INFARCTION (MI) OR SUDDEN DEATH IN PATIENTS WITH VASOSPASTIC ANGINA

CAG findings	Number of cases	Cases with history of MI	Cases that developed MI or sudden death
with fixed* stenosis	64	5	4
without fixed stenosis	119	4	5 (2)
Total	183	9	9 (2)

*organic stenosis $\geq 75\%$
() = number of sudden deaths

TABLE II-b STATUS OF POST-DISCHARGE MEDICATION AND PROGNOSIS (PATIENTS WITH VASOSPASTIC ANGINA WITHOUT FIXED CORONARY STENOSIS)

Medication	Number of cases	Reccurent angina	MI or sudden death
continued	76	34	5 (2)
discontinued or reduced	24	19	0
Total	100	53	5 (2)

() = number of sudden deaths

time of MI onset was determined in 750 patients, from their history, on the basis of the initiation of typical symptoms, e.g. chest pain. In addition, this distribution was examined with reference to the type of preinfarction angina.

3. The presence or absence of early ST segment changes in the infarct area and the status of the final formation of abnormal Q waves were studied in 122 patients who were admitted within 4 hours after onset of MI and were available for serial electrocardiograms in the early stage. ST changes of 0.1 mV or more were considered significant. An abnormal Q wave was defined as being 40 msec or more in duration and 1/3 or more of the R wave in depth.

III. Completion of myocardial necrosis

We chose the accumulation curve of released CPK as the best clinical indicator of the process of completion of myocardial necrosis and investigated its relationship to the duration of chest pain (T_{cp}) and to that of ST segment elevation (T_{st}), both of which readily observed clinically, and to the presence or absence of occlusion of IRV. The subjects were 39 patients without congestive heart failure or other complications who underwent coronary arteriography, who were taken from the population without previous MI and who were available for observa-

tion of time-course changes of serum CPK activity. The accumulation curve of released CPK was constructed according to the method of Shell et al¹ and total released CPK (CPK_r) was obtained using this curve. These data produced, upon calculation, the mean CPK accumulation velocity for the initial stage (V_i) and the total CPK release time (Tr), as we have already reported^{2,3}. In the present study, we regarded V_i as a factor reflecting initial myocardial damage and Tr as an indicator reflecting indirectly the subsequent process of infarct extension.

Data were statistically analyzed by means of Student's t test or χ^2 test, and a p value of < 0.05 was regarded as significant.

RESULTS

I. Factors involved in forming the predispositions for onset of MI

1. Preinfarction angina and its medical therapeutic results

Of the 310 subjects, 99 (32%) developed MI from unstable angina as defined by the AHA criteria⁴ and 101 (33%) from the other forms of angina (non-unstable angina), 65% of the total population having a history of angina pectoris. The remaining 110 patients (35%) developed MI suddenly and had no previous history of angina.

Fig. 2. Incidence of non-significant stenosis of coronary artery distributed to the infarct region.

* % in the column indicate the grade of stenosis of coronary artery distributed to the infarct region. + IRV: coronary artery distributed to the infarct region. ++ non-IRV: coronary artery distributed to the non-infarct region. CAG: coronary arteriography.

Of the 200 patients with a history of angina, 93 had never been treated. Of the 107 medically treated patients, 76 were available for evaluation of the therapeutic results, and of these 76, MI occurred in 53 (70%), for whom the symptoms were unchanged or exacerbated (Fig. 1).

On the other hand, MI occurred in a total of 17 (6.0%) of the 285 angina patients who required hospitalization. Angina could not be controlled medically in 25 cases (8.8%), which included a majority (15 cases) of the patients with onset of MI (Table I).

2. Relationship between vasospastic angina and MI

Of the 183 patients with vasospastic angina, significant organic coronary stenosis (over 75%) was detected in 64 (35%), whereas 119 (65%) showed no significant stenosis. The former group included 5 patients with a history of MI; the latter 4. The numbers of patients with onset of MI or sudden death during hospitalization or after discharge were small: 4 out of 64, and 5 out of 119, respectively. Even when these figures were combined, the incidence of MI or sudden death associated with vasospastic angina was low: 18 cases (10%) (Table II-a). Of the patients

Fig. 3. Proportion of patients with life change events before onset of myocardial infarction.

a: Number of life change events.

b: Life change events constituting emotional and physical burdens.

without significant organic coronary stenosis, 100 were available for evaluation of the relationship between the status of continued medical treatment after discharge and prognosis. In this series, MI or sudden death occurred in 5 patient (5%) who belonged to the group in which, despite continued treatment, angina recurred and was uncontrollable (Table II-b).

3. Grade of stenosis of the coronary artery distributed to the infarct region

Significant stenosis of over 75% of the IRV was found in 41 (76%) of the 54 patients who had undergone coronary arteriography before onset of MI and 811 (91%) of the 893 who underwent the examination after an interval of approximately 4 weeks after onset of MI. Thus, MI was closely related to coronary stenosis. However, stenosis of the IRV was 50% or less in 13 (24%; four of them with completely normal IRV) of the 54 patients examined before onset of MI and 82 (9.2%; 37 of them with normal IRV) of the 893 examined after onset. In addition, there were 10 inconsistent cases with normal IRV but with significant stenosis of the coronary artery distributed to the non-infarct region (Fig. 2).

Fig.4. Classification of the situations at the instant of onset of myocardial infarction.

Fig.5. Relationships of the situations at onset of myocardial infarction to preinfarction angina and to severity of coronary lesions.

4. Life changes before onset of MI

Seventy-four (63%) of the 118 subjects responded that they had experienced at least one of the 20 items related to life changes during the period of one month before onset, and 21 (18% of a total) of these 74 had experienced two or more events. These frequencies were not particularly higher than those, 65 patients (55%) and 25 (21%), respectively, during the one-month period one year before onset (Fig. 3-a). However, if events are limited to those that constituted emotional and physical burdens, the frequency immediately before onset (58%) was significantly higher than that (34%) one year previously ($p < 0.01$; Fig. 3-b). As many as 52 patients (64%) had worked excessively or had an abnormal

physical condition immediately before onset, and 24 (20%) of them mentioned that these events were unusual. The younger the group, the higher the frequency of these events.

II. Onset of MI

1. Situation at the instant of onset

Figure 4 shows a classification of the situation at onset of MI. MI occurred during sleep in 22% and at rest in 31%. When these two items were combined with onsets during mild effort (20%), during or immediately after a meal (12%) and during defecation (4%), the incidence of onset under usual light work or less reached as much as about 90%. The sum percentage of the incidences during moderate to heavy exercise (6%) and

Fig. 7. Serial ST segment changes in 122 patients who were admitted within 4 hours after onset of myocardial infarction and were available for early stage electrocardiograms.

Fig. 6. Distributions at hourly intervals of time of onset of myocardial infarction.

during emotional stress or excitement (3%) did not amount to 10%. In the questionnaire we asked the 118 patients whether or not the situation at onset was unusual. Only 31% developed MI under unusual circumstances, e.g., having a nightmare, bathing after consuming too much alcohol and so on.

The population was roughly divided into four groups according to the type of situation at onset in order to compare the proportions of patients without preinfarction angina. The proportion increased in the following order: (1) during sleep: 23% of the group, (2) at rest: 27%, (3) during mild effort (including meals and

defecation): 40% and (4) during moderate to heavy exercise, or emotional stress or excitement: 53% ($p < 0.01$; Fig. 5). Furthermore, a comparison of the number of diseased vessels between these four groups revealed that the rate of three-vessel disease was higher in the sleep and rest groups, being 23%, 26%, 14% and 9%, respectively, and also that normal coronary artery was not necessarily frequent in the sleep group, the frequency being 7%, 6%, 7% and 9%, respectively.

2. Time of onset of MI

Figure 6 shows the number of cases according to the time of onset of MI at hourly intervals. A double-peaked distribution with peaks in the morning period from 6–8 o'clock and in the evening period from 7–10 o'clock was noted, with a tendency for the incidence during the active diurnal zone to be rather low. In relation to the type of preinfarction angina, the group without previous angina included a few more cases during the daytime than late at night, and the group which developed MI from unstable angina, particularly cases with rest angina, included more cases during the period from midnight to early morning. The frequencies during the period from late evening (past the active diurnal zone) to night was high in the group with effort angina. Thus, each type of preinfarction angina indicated a characteristic distribution of times of onset.

3. ST changes in the early stage after onset

ST segment elevation was detected in the initial ECG record in 76 (62%) of the 122 patients on whom serial ECG recording was initiated in the early stage after onset. There were 33 cases (27%) of non-Q wave MI that never demonstrated ST elevation and 13 cases (11%) that showed delayed ST elevation (Fig. 7).

Fig.8. Comparisons of CPK parameters in the three groups divided according to the grade of stenosis of coronary artery distributed to the infarct region.
Tr = total CPK release time; Vi = mean CPK accumulation velocity for the initial stage; CPKr = total released CPK

Fig.9. Comparisons of duration of chest pain (T_{cp}) and of ST segment elevation (T_{st}) in the three groups divided according to the grade of stenosis of coronary artery distributed to the infarct region.

III. Evolutional process of myocardial necrosis in terms of the accumulation curve of released CRK

Sixteen of the 39 subjects showed IRV stenosis of 90% or less, 12 showed stenosis of 99%, and 11, complete occlusion. These three groups showed no significant differences with regard to total released CPK (CPKr) or mean CPK accumulation velocity for the initial stage (Vi), whereas the total CPK release time (Tr) was

significantly longer in the complete occlusion group (23.2 ± 4.9 hr) than in the group with stenosis of under 90% (17.3 ± 6.0 hr) ($p < 0.05$; Fig. 8). Neither CPKr nor Vi had any significant correlation to the duration of chest pain (T_{cp}), or of ST elevation (T_{st}). However, Tr significantly correlated to both T_{cp} ($r = 0.42$) and T_{st} ($r = 0.52$) ($p < 0.01$). T_{cp} was 3.2 ± 1.5 hr in the group with stenosis of $\leq 90\%$, and 7.2 ± 2.7 hr ($p < 0.01$) in the complete occlusion

group. Tst was 3.9 ± 1.7 hr and 7.0 ± 3.2 hr ($p < 0.05$), respectively. Both of these parameters were significantly longer in the complete occlusion group (Fig. 9).

DISCUSSION

Myocardial infarction (MI) has been defined as ischemic myocardial necrosis caused by occlusion of the coronary artery⁵ and a variety of etiological hypotheses have been proposed for this. Influential among these are views based on coronary arteriographic and histopathological evidence, that hold coronary thrombosis as the primary cause of MI⁶⁻⁸ and views that coronary spasm produces direct or indirect coronary occlusion to cause MI⁹⁻¹¹. Both attribute the cause of MI to complete occlusion of the coronary artery. Based on clinicopathological studies, some authors believe that, since the incidence of obstructive thrombi in the early stage after onset of MI is not as high as has been claimed, coronary occlusion due to coronary artery thrombi is a result, rather than a cause, of MI.¹²⁻¹⁵ The more MI patients we encounter clinically, the more we have come to realize that there is a notable number of cases in which onset of MI cannot be accounted for on the basis of coronary occlusion alone. For example, there is a considerable number of patients who develop MI suddenly without a history of angina and in whom coronary arteriography provides no visualization of stenotic lesions.

In 1982, Kaneko et al. proposed a new theory of selfdestruction concerning the mechanism of MI onset.¹⁶ Their histopathologically based view of the mechanism of onset of MI is as follows: Myocardial cells undergo supercontraction for some reason and are instantly destroyed, resulting in cardiac cell death, i.e., kinetic death. This kinetic death is at the essence of MI. Coronary artery thrombi are formed subsequently, and ischemic cell death, i.e., static death, supervenes. They also demonstrated that MI similar to that in humans could be produced experimentally in dogs by preparing a basis, using a drip infusion of calcium (calcium setting), followed by an intravenous injection of a small dose of caffeine or catecholamine as a trigger, without occluding the coronary artery. Since we had observed histologically this same kinetic death in our cases, we reviewed our clinical cases with the self-destruction theory as a working hypothesis. Our assumption was that onset of

MI requires predispositions equivalent to the calcium setting as well as a trigger equivalent to caffeine or catecholamine in Kaneko's experimental model. Our data showed that a majority of patients had a history of angina, especially unstable angina, before onset of MI, and that the incidence of MI was higher among those whose angina had been poorly treated. These findings suggest that myocardial ischemia is an important factor in setting the onset of MI. On the other hand, there were many patients (35%) with no history of angina, calling for an investigation of factors other than ischemia involved in creating the setting. For example, the influence of some "abnormalities," such as those indicated by our present study and studies in Helsinki,¹⁷ i.e. life changes or overwork, on myocardial metabolism might be studied.

Patients with IRV stenosis of less than 25% were not rare, the frequency being 7.4% among those with preinfarction and 4.1% among those with postinfarction coronary arteriography. Coronary spasm is a persuasive clue to explaining the onset of MI in individuals with normal coronary artery and may actually be valid in some cases. However, a survey of our 183 cases indicated that onset of MI in patients with vasospastic angina was relatively rare. In addition, these rare cases had frequent angina attacks which could not be controlled, even under medical treatment. Thus, there appear to be considerable differences between the clinical pictures of patients with vasospastic angina and those of patients with normal coronary arteries who suffered a sudden onset of MI without any previous angina attacks.

Since it is difficult to witness the instant of onset of MI clinically, we attempted to infer factors that could serve as a trigger for MI by examining the time and situation of onset. Onsets during sleep or rest accounted for more than half of the cases. A definite trigger, such as effort or excitement linked directly to onset, was identified in less than 10% of the entire series, and about 70% of our patients developed MI under normal circumstances. These figures are similar to those of the analysis of 530 cases by Master et al. in 1937.¹⁸ A predominant number of our patients who had onset during sleep or rest had a past history of angina, especially unstable angina, and a relatively large proportion of these patients had three-vessel disease. These data indicate that onset itself is facile in patients who have a broad predisposing basis

such as preinfarction angina and coronary artery lesion, i.e., the threshold for onset is low in these patients; while patients with a less extensive basis need a stronger trigger for onset, i.e., they have a higher threshold.

There are few reports¹⁸ available on detailed examinations of the time of onset of MI. A relatively small number of our patients developed MI during the active diurnal time zone, but a double-peaked distribution involving an early morning interval and an interval from evening to night was brought to light. The early morning peak was formed primarily by the population with anamnesis of unstable angina or rest angina, and the peak in the interval from evening to night by the population with no history of angina or with a history of effort angina. It is noteworthy that depending on the type of preinfarction angina, the hours at which MI onset was most likely to occur differed. In the case of angina pectoris, hourly distribution of attacks has been used as a basis for the investigation of attack-inducing factors¹⁹; for example, the incidence of attacks of vasospastic angina is highest early in the morning when the tone of autonomic nerves fluctuates. Concerning MI as well, the possibility exists that a similar relationship exists between causes and factors that show circadian variation, such as the tone of autonomic nerves or plasma catecholamine levels. This will deserve further study.

ST segment elevation is thought to be an indicator of complete occlusion of the coronary artery.²⁰ A study of ECG in the early stage after onset revealed the presence of considerable numbers of patients with no ST elevation at onset and those with a delayed recording of ST elevation after onset. Therefore, the possibility exists that mechanisms other than coronary occlusion are involved in onset of MI.

Based on the analysis of the accumulation curve of released CPK, we have already published our speculation that MI consists of initial myocardial necrosis and secondary necrosis which occurs additionally around the initial lesions.^{2,3} Even when the initial infarct sizes were identical, the duration of chest pain and ST elevation were longer with CPK efflux more extended in patients with obstructed IRV than in those with patent IRV. It appears that IRV obstruction is closely related to the increment of infarct size, suggesting an incremental process in infarct size due to secondary coronary occlusion, this being consistent with the static death proposed by

Kaneko et al.

Clinical observation of large number of MI patients disclosed a number of facts that could not entirely be understood on the exclusive basis of the theory that coronary occlusion is the primary cause of MI. In conclusion we suggest that it is necessary to take into account other theories, including Kaneko's self-destruction theory, in the investigation of the mechanism of MI onset.

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