Circadian Variations of Onset of Acute Myocardial Infarction and Efficacy of Thrombolytic Therapy

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Objectives. The present study investigated whether the onset of acute myocardial infarction and resistance to thrombolysis have similar circadian variations.

Background. Circadian variations of the onset of acute myocardial infarction and resistance to thrombolysis in the early morning have been reported. Some studies have also reported a secondary peak incidence in the late evening; however, it is not known whether the resistance to thrombolysis has a similar circadian variation in these patients.

Methods. Six hundred eighty Japanese patients with an acute myocardial infarction were the subjects of the study. Two hundred forty-four of the 608 patients were treated with thrombolysis within 12 h of the onset of symptoms. One hundred thirteen patients received urokinase, and 131 patients received tissue-type plasminogen activator (t-PA) over 60 min. Patency of the infarct-related artery, the primary end point of the study, was evaluated at 60 min after the initiation of thrombolytic therapy, and Thrombolysis in Myocardial Infarction (TIMI) grade 0, 1 or 2 was defined as resistant to thrombolysis.

Results. The onset of acute myocardial infarction and resistance to thrombolysis showed circadian variations with early morning and late evening peaks (p < 0.001 and p < 0.05, respectively). These circadian patterns showed similar distributions as evaluated with Spearman's method (r = 0.70, p < 0.05), although resistance to thrombolysis showed a phase difference of about 2 h earlier than the infarction incidence. The circadian variation of the resistance to thrombolysis was independent of the type of thrombolytic agents (urokinase or t-PA).

Conclusions. These findings suggest that adjustment of treatment based on the time of the onset of symptoms may be warranted for the patients with acute myocardial infarction.

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were treated with thrombolytic agents within 12 h of the onset of acute myocardial infarction, after the evaluation of the infarct-related artery by coronary angiography. One hundred thirteen patients were treated with urokinase, and 131 patients were treated with t-PA. Exclusion criteria were cardiogenic shock (systolic blood pressure < 80 mm Hg unresponsive to fluids and vasopressors), uncontrolled hypertension (> 180/110 mm Hg), prior cerebrovascular accident and evidence of recent or active bleeding.

Study protocol. Patients with acute myocardial infarction who were found to satisfy eligibility criteria for the thrombolytic therapy were transferred to the cardiac catheterization laboratory, where coronary angiography was performed to evaluate the infarct-related artery. Arterial access was obtained through the femoral route. Heparin (5,000 U) was administered immediately after access was established, and patients received oral aspirin (81 mg). When the infarct-related artery remained occluded after intracoronary administration of 200 µg of nitroglycerin or 2 mg of isosorbide dinitrate, patients received one of the following thrombolytic agents according to the attending physician's decision: 1) intracoronary urokinase, a total of 240,000 to 1,200,000 IU, over 60 min; 2) intravenous t-PA (Alteplase), a total of 0.50 to 0.75 mg/kg body weight (290,000 to 435,000 IU/kg), over 60 min with 10% given as a bolus. Patency of the infarct-related artery, the primary end point of the study, was evaluated at 60 min after the initiation of thrombolytic therapy. The flow pattern of the infarct-related artery was graded according to the Thrombolysis in Myocardial Infarction (TIMI) classification (29,30), and TIMI 0, 1 or 2 was defined as resistant to thrombolysis. All cineangiograms were evaluated by cardiologists who had no knowledge of patient characteristics. The protocol for the thrombolytic therapy was approved by the Institutional Review Board of the Osaka Mishima Critical Care Medical Center, and written informed consent was obtained from all patients or their family members, or both, after the purpose of therapy was fully explained.

Statistical analysis. Comparisons between total cohort and patients treated with thrombolytic agents were made using the unpaired Student t test to compare interval scales and using the chi-square test for goodness of fit (31). The circadian patterns of the onset of acute myocardial infarction as the total cohort did.

Table 1. Clinical Characteristics for Total Cohort and Patients With Thrombolysis

<table>
<thead>
<tr>
<th></th>
<th>Total Cohort (n = 608)</th>
<th>Patients With Thrombolysis (n = 244)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr) (mean ± SD)</td>
<td>61 ± 11</td>
<td>59 ± 10</td>
</tr>
<tr>
<td>Men/women (no.)</td>
<td>465/143</td>
<td>198/46</td>
</tr>
<tr>
<td>Location of AMI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anterior</td>
<td>329 (54.1)</td>
<td>139 (57.0)</td>
</tr>
<tr>
<td>Inferior</td>
<td>235 (38.7)</td>
<td>95 (38.9)</td>
</tr>
<tr>
<td>Lateral</td>
<td>44 (7.2)</td>
<td>10 (4.1)</td>
</tr>
<tr>
<td>History of angina</td>
<td>147 (24.2)</td>
<td>52 (21.3)</td>
</tr>
<tr>
<td>History of AMI</td>
<td>66 (11.9)</td>
<td>23 (9.4)</td>
</tr>
<tr>
<td>Coronary risk factors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoking</td>
<td>324 (53.3)</td>
<td>159 (61.5)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>269 (44.2)</td>
<td>95 (38.9)</td>
</tr>
<tr>
<td>DM</td>
<td>109 (17.9)</td>
<td>40 (16.4)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>78 (12.8)</td>
<td>40 (16.4)</td>
</tr>
</tbody>
</table>

p = NS for all comparisons. Data presented are number (%) of patients, unless otherwise indicated. AMI = acute myocardial infarction; DM = diabetes mellitus.

Results

The patient characteristics in the total cohort and in patients treated with thrombolytic therapy were well matched, as shown in Table 1. The number of women was slightly lower among patients treated with thrombolysis than in the total group, although the difference was not statistically significant. The circadian distribution of the onset of acute myocardial infarction in the overall cohort and the resistance to thrombolysis in the patients treated with thrombolytic agents are shown in Figure 1. According to the statistical test of uniformity, the circadian distribution of the onset of acute myocardial infarction and the circadian distribution of the resistance to thrombolysis differed significantly from random with early morning and late evening peaks (p < 0.001 and p < 0.05, respectively), as shown in Figure 1. The patients treated with thrombolysis showed the same circadian viability in incidence of myocardial infarction as the total cohort did.

The circadian patterns of the onset of acute myocardial infarction and the resistance to thrombolysis showed similar distributions as evaluated with a Spearman's rank correlation analysis (r = 0.70, p < 0.05), although the resistance to thrombolysis showed a phase difference of about 2 h earlier than infarction incidence as shown in Figure 1. There was no difference in the circadian variation of the resistance to thrombolysis between patients treated with urokinase and patients treated with t-PA, as shown in Figure 2. There were no differences in doses of either urokinase or t-PA at the various times of day, as shown in Figures 3 and 4. The time from the onset of symptoms to thrombolytic therapy was longer at 2 AM to 4 AM than at other times of day, and there was no relation either to dosing of thrombolytic therapy or to thrombolytic efficacy, as shown in Figure 5.
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Figure 1. Temporal distribution of onset of acute myocardial infarction and resistance to thrombolysis showed significant circadian variations with early morning and late evening peaks (p < 0.001 and p < 0.05, respectively). These circadian variations were similar (r = 0.70, p < 0.05), although resistance to thrombolysis showed a phase ~2 h earlier than the infarction incidence. Patients treated with thrombolysis showed the same circadian viability in incidence of myocardial infarction as did the total cohort. AMI = acute myocardial infarction; t-PA = tissue-type plasminogen activator; UK = urokinase.

Discussion

The present study demonstrated that the onset of acute myocardial infarction and the resistance to thrombolysis have similar circadian variations with early morning and late evening peaks, although the resistance to thrombolysis showed a phase difference of about 2 h earlier than infarction incidence. This circadian variation of the resistance to thrombolysis was independent of the types of thrombolytic agents (urokinase or t-PA).

Figure 2. Circadian variations of resistance to thrombolysis in patients treated with urokinase (UK) and those treated with tissue-type plasminogen activator (t-PA). Resistance to thrombolysis showed similar circadian variations in the two groups. AMI = acute myocardial infarction. Data are expressed as mean value ± SE.

Circadian variation of onset of acute myocardial infarction.

The onset of acute myocardial infarction has been reported to have circadian variations. A majority of large scale reports (1-4) have shown a peak incidence between 6 AM and noon, although a secondary peak incidence in the late evening has also been reported in some studies (5-11). In the present study, the onset of acute myocardial infarction had a circadian variation with early morning and late evening peaks, which was consistent with the reports of others (5-11). These differences could in some instances reflect the small study cohort, different customs regarding meals or work habits in reported countries, or differences in various other patient factors. The morning increase in sympathetic activity may cause vasoconstriction and may lead to plaque rupture in atherosclerotic coronary arteries in combination with mechanical factors such as elevated blood pressure (11-15). The increased platelet aggregability (16,17).

Figure 3. Doses of urokinase used at different times of the day showed no significant variation. Data are expressed as mean value ± SE.

Figure 4. Doses of tissue-type plasminogen activator (t-PA) used at different times of the day showed no significant variation. Data are expressed as mean value ± SE.
and reduced plasma fibrinolytic activity in the morning (18-24) may facilitate or accelerate thrombus formation. The reasons for the late evening peak incidence are less clear. It was reported that patients >70 years of age, smokers, diabetic patients, those receiving beta-blockers at the time of symptom onset and women had a secondary peak incidence in the late evening (9). In the present study, >50% of the study population were smokers, which may be related to a second peak incidence in the late evening. Although increased platelet aggregability, reduced plasma fibrinolytic activity or increased plasminogen activator inhibitor-1, or both, may play important roles for the genesis of the onset of acute myocardial infarction, we did not evaluate these factors; therefore, the exact mechanism of the circadian variation of the onset of acute myocardial infarction was not clearly elucidated in the present study.

Circadian variation of resistance to thrombolysis. Circadian fluctuation with a morning increase in the resistance to thrombolysis by intravenous t-PA (25,26) and intracoronary urokinase (28) has been reported. In the present study, the resistance to thrombolysis showed a circadian variation similar to that of the onset of acute myocardial infarction, with early morning and late evening peaks, with a phase ~2 h earlier than that of infarction incidence. This circadian pattern of the resistance to thrombolysis was independent of the types of thrombolytic agents (urokinase or t-PA) in the present study. The highest doses of intracoronary urokinase were given between 6 and 8 AM, which was expected because intracoronary urokinase was given for occluded vessels, and more resistant occlusions received more urokinase. Although dosing of thrombolytic therapy was not statistically different at any particular time of day, the dose of t-PA was slightly lower during the 6 to 8 AM and 8 to 10 AM time periods than at other times of the day, which could influence the resistance to t-PA during these hours. However, dosing of t-PA did not affect the later peak in resistance to thrombolysis. It was reported that there was a greater patency with a shorter time to thrombolytic therapy (25); however, the resistance to thrombolysis in the early morning and the late evening was not caused by the longer time to thrombolytic therapy after symptom onset; therefore, the time to thrombolytic therapy was not found to play an important role in the circadian variation of the resistance to thrombolysis in the present study.

The morning resistance to thrombolysis was reported to be associated with elevation of plasminogen activator inhibitor-1 in the morning (25-27). The reasons for the late evening resistance to thrombolysis are not clear. The plasminogen activator inhibitor-1 was not reported to be increased in the late evening (19-24). The large number of smokers in the present study may be related to the observed late evening resistance to thrombolysis. The same factors that may affect the onset of acute myocardial infarction may also affect the resistance to thrombolysis; however, the exact mechanism of a circadian variation of the resistance to thrombolysis was not clearly elucidated in the present study.

Patency of the infarct-related artery was evaluated at 60 min after the initiation of thrombolytic therapy instead of at 90 min because thrombolytic agents were delivered over 60 min, which might influence the patency rate in the present study. However, overall 60-min patency rate in the patients treated with thrombolytic therapy was 54.1% in the present study, which was compatible with the 90-min patency rates of other reports using the same definition of the patency as the present study (25).

Clinical implications. A number of potential therapeutic implications based on the time of the onset of symptoms can be presented, each of which would require further investigation. The dose of thrombolytic agents should be adjusted on the basis of time of day; however, a higher dose of thrombolytic agents might increase the risk of side effects such as intracerebral hemorrhage. Thrombolytic agents resistant to plasminogen activator inhibitor-1 and adjunct pharmacologic agents, including potent anticoagulants or antiplatelet agents, might improve the resistance to thrombolysis. Mechanical recanalization such as a direct angioplasty might be a better option for treatment in the early morning and late evening.

Conclusions. The onset of acute myocardial infarction and the resistance to thrombolysis had similar circadian variations with early morning and late evening peaks, although the resistance to thrombolysis preceded the onset of acute myocardial infarction. The circadian variation of the resistance to thrombolysis was independent of the type of thrombolytic agent (urokinase or t-PA). These findings suggest the adjustment of the treatment based on the time of onset of symptoms may be warranted for the patients with acute myocardial infarction.

References


