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

TATSUJI KONO, MD, HIROSHI MORITA, MD, TAKUYA NISHINA, MD, MASASHI FUJITA, MD,
YUZO HIROTA, MD,* KEISHIRO KAWAMURA, MD,* AKIRA FUJIWARA, MD

Takatsuki, Japan

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 late evening; however, it is not known whether the resistance to thrombolysis has a similar circadian variation in these patients.

Methods. Six hundred eight 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 types 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.

(J Am Coll Cardiol 1996;27:774–8)

The frequency of onset of acute myocardial infarction has been reported to have a circadian variation. 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). These differences could result in some instances from small study groups, from different customs regarding meals or work habits of various countries, or from differences in other modifying patient factors. The morning increase in ischemia is related to an imbalance between myocardial oxygen supply and demand reflecting sympathetic/vagal balance (12–15), increased platelet aggregability (16,17) and reduced plasma fibrinolytic activity in the morning (18–24). The reasons for the late evening peak incidence are less clear.

Circadian fluctuation has also been reported in the efficacy of intravenous tissue-type plasminogen activator (t-PA) in patients with acute myocardial infarction, with resistance to thrombolysis during the morning hours (25,26). This morning

resistance to thrombolysis was speculated to be the result of elevations of plasminogen activator inhibitor-1 in the morning (25–27). A morning increase in resistance to thrombolysis was also shown in treatment with intracoronary urokinase (28), suggesting that this circadian pattern may be independent of the type of thrombolytic agent. However, it is not known whether the resistance to thrombolysis is also present in the late evening in patients who showed a secondary peak incidence in the late evening.

The purpose of the present study was to investigate retrospectively whether the onset of acute myocardial infarction and the resistance to thrombolysis had similar circadian variations.

Methods

Study patients. We studied 608 Japanese patients with acute myocardial infarction, who were admitted to the Osaka Mishima Critical Care Medical Center between November 1985 and June 1995. Acute myocardial infarction was diagnosed by the presence of chest pain suggestive of myocardial ischemia lasting more than 30 min and at least 0.1 mV ST segment elevation in at least two contiguous leads despite treatment with nitrates. The diagnosis was confirmed by the elevation of cardiac enzymes. The time of onset of symptoms was ascertained as precisely as possible.

Two hundred forty-four patients among these 608 patients

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 thrombolytic therapy. 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 to compare the nominal data. The circadian distributions of the frequency of onset of acute myocardial infarction in the overall cohort and resistance to thrombolysis in patients treated with thrombolytic agents were tested for uniformity by a chi-square test for goodness of fit (31). Uniformity was evaluated by 2-h intervals of the day. The similarity of the circadian variations between the onset of acute myocardial infarction and the resistance to thrombolysis was evaluated using a Spearman's rank correlation analysis (32). One-way analysis of variance (ANOVA) was used to evaluate differences in doses of urokinase or t-PA and differences in time to thrombolytic therapy at different times within 24 h. When the result was significant, Bonferroni's multiple comparison test was performed; p < 0.05 was considered significant.

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

	Total Cohort (n = 608)	Patients With Thrombolysis (n = 244)
Age (yr) (mean ± SD)	61 ± 11	59 ± 10
Men/women (no.)	465/143	198/46
Location of AMI		
Anterior	329 (54.1)	139 (57.0)
Inferior	235 (38.7)	95 (38.9)
Lateral	44 (7.2)	10 (4.1)
History of angina	147 (24.2)	52 (21.3)
History of AMI	66 (10.9)	23 (9.4)
Coronary risk factors		
Smoking	324 (53.3)	150 (61.5)
Hypertension	269 (44.2)	95 (38.9)
DM	109 (17.9)	40 (16.4)
Hyperlipidemia	78 (12.8)	40 (16.4)

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.
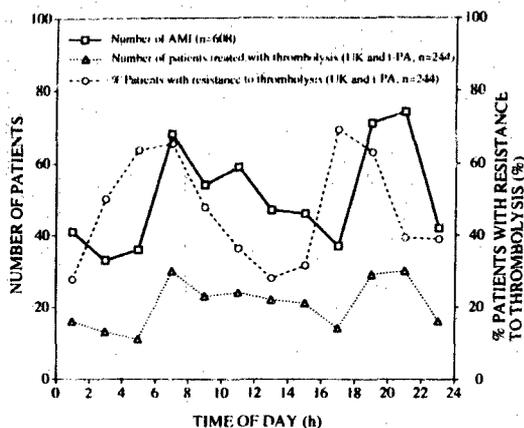
Figure 1. Temporal distribution of onset of acute myocardial infarction and resistance to thrombolysis showed significant circadian variations with early morning and late evening peaks ($p < 0.001$ and $p < 0.05$, respectively). These circadian variations were similar ($r = 0.70$, $p < 0.05$), although 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.
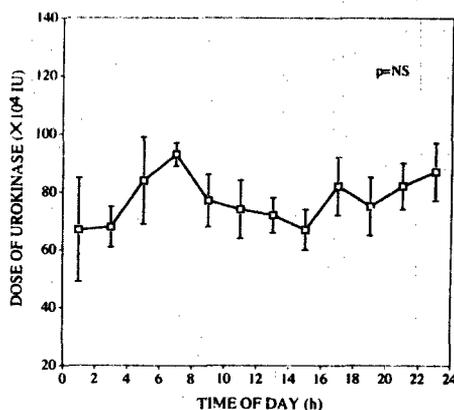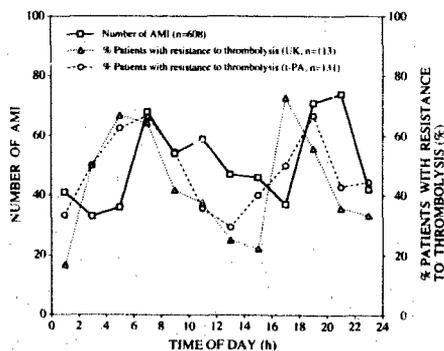

Figure 3. Doses of urokinase used at different times of the day showed no significant variation. Data are expressed as mean value ± SE.

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 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.
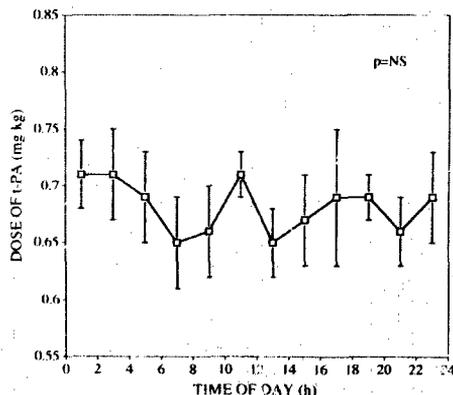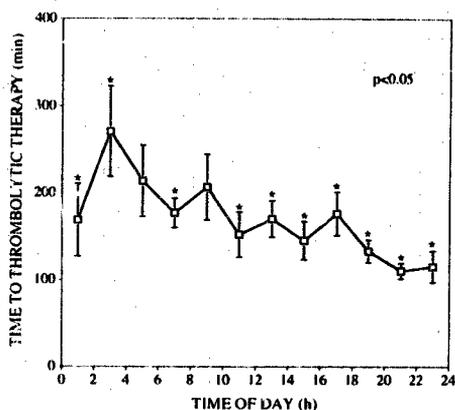
Figure 5. Tim: from onset of symptoms to thrombolytic therapy was longer at 2 to 4 AM than at other times of the day (*p < 0.05), and there was no relatio 1 to either dosing of thrombolytic therapy or thrombolytic efficacy. Data are expressed as mean value ± SE.

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 intraco, anary urokirase (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 revascularization 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 that adjustment of the treatment based on the time of onset of symptoms may be warranted for the patients with acute myocardial infarction.

References

1. Pedoe HT, Clayton D, Morris JN, Brigden W, McDonald L. Coronary heart-attacks in East London. Lancet 1975;2:833-8.

2. WHO International Study Group. Myocardial infarction community registers: public health in Europe. Copenhagen. 1976;5:1–232.

3. Beamer AD, Lee TA, Cook EF, et al, and the Chest Pain Study Group. Diagnostic implications for myocardial ischemia of the circadian variation in the onset of chest pain. Am J Cardiol 1987;60:998–1002.

4. Tofler GH, Muller JE, Stone PH, et al. Modifiers of timing and possible triggers of acute myocardial infarction in the Thrombolysis in Myocardial Infarction Phase II (TIMI II) Study Group. J Am Coll Cardiol 1992;20: 1049–55.

5. Peli S, D'Alonzo CA. Acute myocardial infarction in a large industrial population: report of a 6-year study of 1,356 cases. JAMA 1963;185:831–8.

6. Johansson BW. Myocardial infarction in Malmo 1960–1968. Acta Med Scand 1972;191:505–15.

7. Kaufmann MW, Gottlieb G, Kahaner K. et al. Circadian rhythm and myocardial infarct: a preliminary study. IRCS Med Sci (Biochem) 1981;9: 557.

8. Thompson DR, Blandford RL, Sutton TW, Marchant PR. Time of onset of chest pain in acute myocardial infarction. Int J Cardiol 1985;7:139–46.

9. Muller JE, Stone PH, Turi ZG, et al, the MILIS Study Group. Circadian variation in the frequency of onset of acute myocardial infarction. N Engl J Med 1985;313:1315–22.

10. Hjalmarson A, Gilpin EA, Nicod P, et al. Differing circadian patterns of symptom onset in subgroups of patients with acute myocardial infarction. Circulation 1989;80:267–75.

11. Tsuda M, Hayashi H, Kanematsu K, Yoshikane M, Saito H. Comparison between diurnal distribution of onset of infarction in patients with acute myocardial infarction and circadian variation of blood pressure in patients with coronary artery disease. Clin Cardiol 1993;16:543–7.

12. Turton MB, Deegan T. Circadian variations of plasma cathecolamine, cortisol and immunoreactive insulin concentrations in supine subjects. Clin Chim Acta 1974;55:389–97.

13. Millar-Craig MW, Bishop CN, Raftery EB. Circadian variation of blood pressure. Lancet 1978;1:795–7.

14. Yasue H, Omote S, Takizawa A, Nagao M, Miwa K, Tanaka S. Circadian variation of exercise capacity in patients with Prinzmentals variant angina: role of exercise-induced coronary artery spasm. Circulation 1979;59:938–48.

15. Fujita M, Franklin D. Diurnal changes in coronary blood flow in conscious dogs. Circulation 1987;76:488–91.

16. Petralito A, Mangiafico RA, Gibiino S, Cuffari MA, Miano MF, Fiore CE. Daily modifications of plasma fibrinogen, platelet aggregation, Howells time, PTT, TT, and antithrombin III in normal subjects and in patients with vascular disease. Chronbiologia 1982;9:195–201.

17. Tofler GH, Brezinski D, Schafer AI, et al. Concurrent morning increase in platelet aggregability and the risk of myocardial infarction and sudden cardiac death. N Engl J Med 1987;316:1514–8.

18. Rosing DR, Brakman P, Redwood DR, et al. Diurnal variation and the response to varying intensities of exercise. Circ Res 1970;27:171–84.

19. Andreotti F, Davies GJ, Hackett DR, et al. Major circadian fluctuations in fibrinolytic factors and possible relevance to time of onset of myocardial infarction, sudden cardiac death and stroke. Am J Cardiol 1988;62:635–7.

20. Grimaudo V, Hauert J, Bachmann F, Kruithof EKO. Diurnal variation of the fibrinolytic system. Thromb Haemostas 1988;59:495–9.

21. Angleton P, Chandler WL, Schmer G. Diurnal variation of tissue-type plasminogen activator and its rapid inhibitor (PA-1). Circulation 1989;79: 101–6.

22. Masuda T, Ogawa H, Miyao Y, et al. Circadian variation in fibrinolytic activity in patients with variant angina. Br Heart J 1994;71:156–61.

23. Huber K, Rose D, Resch I, et al. Circadian fluctuations of plasminogen activator inhibitor and tissue plasminogen activator levels in plasma of patients with unstable coronary artery disease and acute myocardial infarction. Thromb Haemostas 1988;60:372–6.

24. Bridges AB, McLaren M, Scott NA, Pringle TH, McNeill GP, Belch JJF. Circadian variation of tissue plasminogen activator and its inhibitor, von Willebrand factor antigen, and prostacyclin stimulating factor in men with ischaemic heart disease. Br Heart J 1993;69:121–4.

25. Kurnik PB. Circadian variation in the efficacy of tissue-type plasminogen activator. Circulation 1995;91:1341–6.

26. Becker RC, Corrao JM, Baker SP, Gore JM, Alpert JS. Circadian variation in thrombolytic response to recombinant tissue-type plasminogen activator in acute myocardial infarction. J Appl Cardiol 1988;3:213–21.

27. Barbash GI, Hod H, Roth A, et al. Correlation of baseline plasminogen activator inhibitor activity with patency of the infarct artery after thrombolytic therapy in acute myocardial infarction. Am J Cardiol 1989;64:1231–5.

28. Fujita M, Araie E, Yamanishi K, Miwa K, Kida M, Nakajima H. Circadian variation in the success rate of intracoronary thrombolysis for acute myocardial infarction. Am J Cardiol 1993;71:1369–71.

29. The TIMI Study Group. The thrombolysis in myocardial infarction (TIMI) trial. N Engl J Med 1985;312:932–6.

30. Cheseboro JH, Knatterud G, Roberts R, et al. Thrombolysis in Myocardial Infarction (TIMI) Trial, Phase I: a comparison between intravenous tissue plasminogen activator and intravenous streptokinase. Circulation 1987;76: 142–54.

31. Snedecor GW, Cochran WG. Statistical Methods. Ames, IA: Iowa State University Press, 1978:236–8.

32. Glantz SA. Primer of Biostatistics. 2nd ed. New York: McGraw-Hill, 1987:230–2.