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[**Original Article**]

ACUTE MYOCARDIAL INFARCTION IN FUKUSHIMA AREA OF JAPAN

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Abstract: Although acute myocardial infarction (AMI) is the most serious coronary disease, the background of its onset and the mortality are not fully understood, especially in Japan. From June 1999 to May 2005, we mailed an annual questionnaire to eighteen hospitals in which emergency cardiac catheterization and percutaneous coronary intervention (PCI) were available in the Fukushima area of Japan. A total of 1,590 patients were included. The onset time of AMI had two peaks, i.e., from 9:00 AM to 10:00 AM and 9:00 PM to 10:00 PM. As for reperfusion therapy, four groups were analyzed, the non-reperfusion therapy group (Group N, $n=233$), thrombolysis alone group (Group T, $n=80$), PCI without thrombolysis group (Group P, $n=1106$), and PCI with thrombolysis group (Group TP,

三次　実，木島幹博，清野義胤，阿部之彦，藤野彰久，廣坂　朗，比佐新一，久保貴昭，前山忠美，大原直人，小野正博，大和田尊之，斎藤富善，五十嵐盛雄，佐藤雅彦，鈴木重文，玉川和亮，津田達徳，津田晃洋，渡辺正之，油井　満，小松宣夫，中里和彦，丸山幸夫
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$n=151$). The in-hospital mortality rate was significantly reduced in Group P (8.4%) compared with that in Group N (33.0%, $p<0.01$) and Group T (18.8%, $p<0.01$). However, the in-hospital mortality in Group P did not differ from that in Group TP (9.9%). The in-hospital mortality was analyzed by the logistic regression analysis among age, arrival time after onset, peak creatine kinase (CK) values, coronary risk factors, reperfusion therapy, PCI, and thrombolysis. There were significant differences in age ($p<0.01$), peak CK values ($p<0.01$), hypertension ($p<0.05$), and diabetes mellitus ($p<0.01$). These results suggest that the onset of AMI may be partly related to human biorhythms, and that PCI would be effective in reducing the in-hospital mortality.

Key words: acute myocardial infarction, circadian rhythm, reperfusion therapy, percutaneous coronary intervention

INTRODUCTION

Acute myocardial infarction (AMI) is regarded as the most serious coronary disease. There have been reports of circadian, day-of-week, and seasonal variabilities in the occurrence of AMI[1-8]. However, the frequency differences of the onset in terms of different times and seasons are not fully understood, especially in Japan. An assessment of the variability of these factors would be important for the recognition of its underlying mechanisms and the prevention of AMI. Moreover, recently the efficacy of reperfusion therapy has been demonstrated in patients with AMI in Japan[8-13]. However, the difference in mortality between the various methods of reperfusion therapy remains unclear. Thus, we studied the onset and mortality of AMI patients in the Fukushima area of Japan who had either undergone no reperfusion or been treated using different reperfusion methods of percutaneous coronary intervention (PCI) or thrombolysis.

METHODS

From June 1999 to May 2005, we mailed out an annual AMI questionnaire to eighteen hospitals at which emergency cardiac catheterization and PCI were available in the Fukushima area (Fukushima Prefecture and Yonezawa City in Yamagata Prefecture) of Japan. Those hospitals receive over eighty percent of AMI patients in Fukushima Prefecture. The questionnaire items included the onset date and time, method of reperfusion therapy, and in-hospital mortality. As for reperfusion therapy, four groups were analyzed from the standpoint of the in-hospital mortality rate during the hospitalization of 28.2 ± 21.9 days: the patients treated without reperfusion therapy (Group N, $n=233$), the patients treated with thrombolysis alone (Group T, $n=80$), the PCI patients treated without thrombolysis

(Group P, $n=1{,}106$), and the PCI patients treated with thrombolysis (Group TP, $n=151$). Reperfusion therapy was selected as the treatment of choice by all eighteen hospitals. The remaining patients were treated with coronary artery bypass grafting ($n=20$). Coronary risk factors except for obesity were also included in the questionnaire, which were measured during the hospitalization according to the criteria of each institution. Obesity was defined as body mass index (BMI) ≥ 25.0 kg/m^2.

Statistical analysis

Values are expressed as mean±SD. The circadian variation, variation on the day of the week, and seasonal variability were analyzed by the chi-square test. The proportions of male, hypertension, hyperlipidemia, diabetes mellitus, smoking, obesity, and family history were analyzed using Fisher's exact probability test. Statistical evaluation of in-hospital mortality among the four treated groups was done using chi-square test, followed by a post hoc test (Fisher's protected least significant difference). Statistical analyses of age, the arrival time after onset, and peak creatine kinase (CK) values among the four groups were done using one-way analysis of variance, followed by a post hoc test (Fisher's protected least significant difference). In-hospital mortality was assessed by the logistic regression analysis among age, the arrival time after onset, peak CK values, coronary risk factors, reperfusion therapy, PCI, and thrombolysis. Several variables including coronary risk factors were analyzed by odds ratio. The level of significance was $p<0.05$.

RESULTS

All together, 1,590 patients were included in this study. Their average age was 68.2±12.3 years. Figure 1 demonstrates that the onset time of AMI had two peaks, i.e., from 9 : 00 AM to 10 : 00 AM and 9 : 00 PM to 10 : 00 PM, implying a circadian variation as assessed from the onset times ($p<0.01$). Figure 2 shows the onset day of the week, and Figure 3 indicates the monthly frequency of AMI onset. As demonstrated, the onset day of the week and seasonal variability were not significantly different, although the AMI onset seemed to occur more often in January and less often in July and August.

As for reperfusion therapy, 233 patients were included in the non-reperfusion group (Group N), 80 patients in the thrombolysis group (Group T), 1,106 patients with PCI not in the thrombolysis group (Group P), and 151 patients with PCI in the thrombolysis group (Group TP). Twenty patients treated with coronary artery bypass grafting in the acute phase were not included in the present analysis. The characteristics of patients in the three groups are shown in the Table 1. The proportions of male, hyperlipidemia, and smoking were significantly different in Groups T, P and TP compared with those in Group N. The in-hospital mortality was significantly decreased in Group P (8.4%) compared with that in Group N

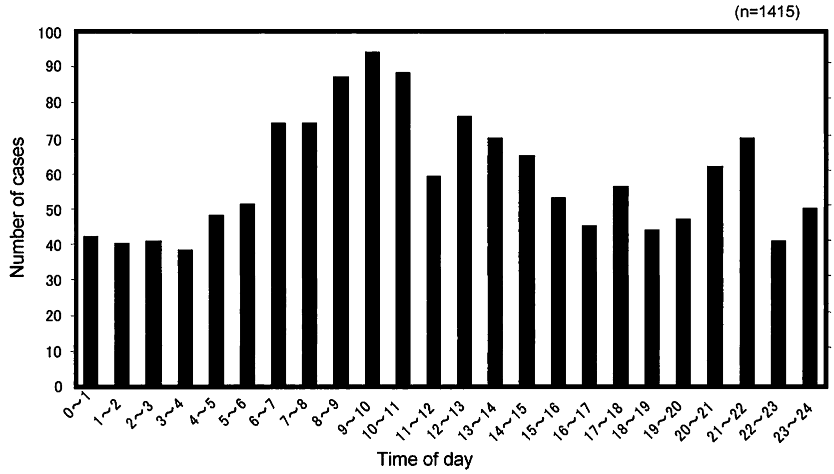

Figure 1. Circadian variations in acute myocardial infarction. Myocardial infarction cases with unclear onset time were not included ($n=175$). The circadian variations differed significantly depending on the onset times ($p<0.01$).

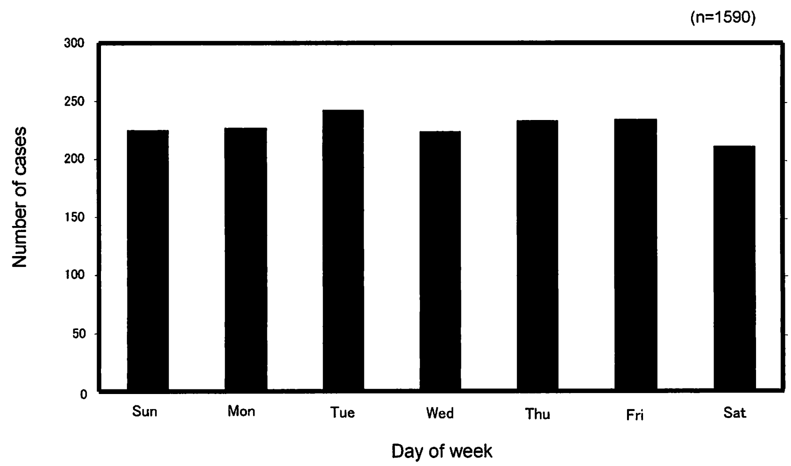

Figure 2. Day-of-week variation during one week in acute myocardial infarction attack.

(33.0%, $p<0.01$) or Group T (18.8%, $p<0.01$, Table 2, Figure 4), whereas in Group P it was not different from that in Group TP (9.9%, Table 2, Figure 4). The age was significantly older in Group N (75.0±12.7 years) compared with that in Group T (70.1±11.9 years, $p<0.01$), Group P (67.1±11.8 years, $p<0.01$), and Group TP (64.8±12.3 years, $p<0.01$, Table 2, Figure 5). Moreover, the arrival time after onset was significantly longer in Group N (17.6±28.2 hours) than in Group T (7.1±10.0 hours, $p<0.01$), Group P (9.1±20.9 hours, $p<0.01$), and Group TP (5.2±9.5 hours, $p<0.01$, Table 2, Figure 6). Peak CK values were significantly lower in Group N (1,902.9±1,450.1 U/L) than in Group T (2,847.8±3,345.8 U/L, $p<0.05$),

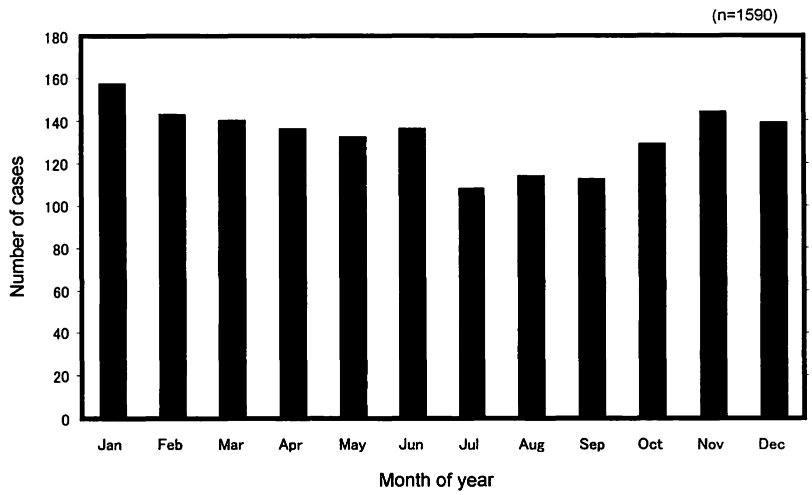

Figure 3. Seasonal variability in the onset of acute myocardial infarction.

Table 1. Patient Characteristics

	Group N (n=233)	Group T (n=80)	Group P (n=1,106)	Group TP (n=151)
Male	57.1%	72.5%**	73.5%**	75.5%**
Hypertension	52.8%	43.8%	51.5%	52.3%
Hyperlipidemia	16.3%	30.0%*	30.0%**	31.1%**
Diabetes mellitus	23.6%	18.8%	28.3%	34.4%*†
Smoking	29.6%	50.0%**	44.2%**	45.7%**
Obesity	25.7%	28.1%	34.6%*	38.8%*
Family history	5.6%	12.5%*	8.0%	9.3%

*$p<0.05$ and **$p<0.01$ vs Group N ; †$p<0.05$ vs Group T.

Table 2. In-hospital mortality, Age, Arrival time after onset, and Peak CK

	Group N (n=233)	Group T (n=80)	Group P (n=1,106)	Group TP(n=151)	p value
In-hospital mortality	33.0%	18.8%	8.4%	9.9%	$p<0.01$[1]
Age (years)	75.0±12.7	70.1±11.9	67.1±11.8	64.8±12.3	$p<0.01$[2]
Arrival time after onset (hours)	17.6±28.2	7.1±10.0	9.1±20.9	5.2±9.5	$p<0.01$[2]
Peak CK (U/L)	1,902.9 ±1,450.1	2,847.8 ±3,345.8	2,919.3 ±2,536.0	2,943.7 ±1,964.6	$p<0.01$[2]

mean±SD, [1]: chi-square test, [2]: one-way analysis of variance.
CK, creatine kinase.

Group P (2,919.3±2,536.0 U/L, $p<0.01$), and Group TP (2,943.7±1,964.6 U/L, $p<0.01$, Table 2, Figure 7).

Although patients in Group T were significantly older than those in Group P

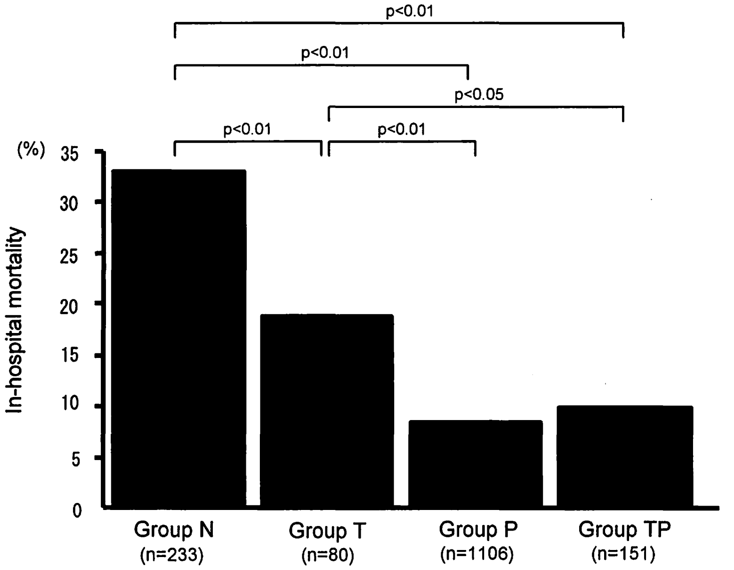

Figure 4. In-hospital mortality depending on different reperfusion methods. Patients who underwent coronary aortic bypass graft in acute phase were not included ($n=20$).

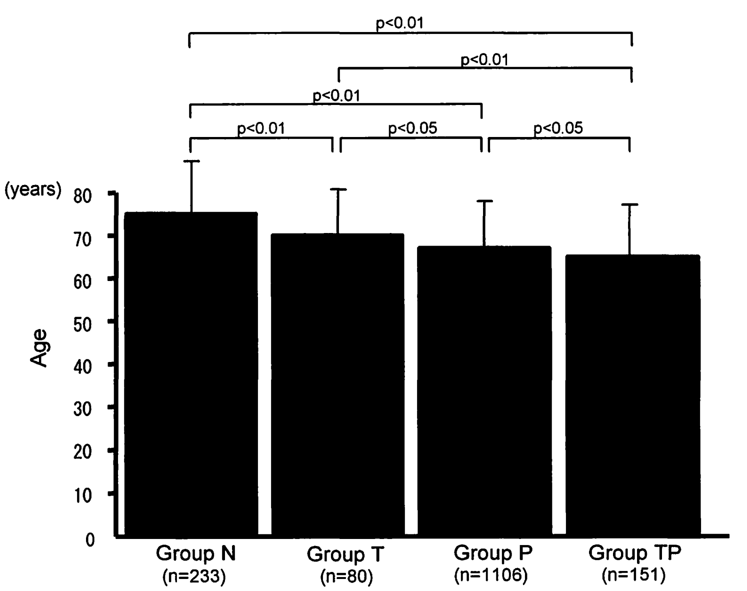

Figure 5. Age (mean±SD) is shown in relation to three kinds of reperfusion methods.

($p<0.05$, Figure 5), differences in the arrival time after onset and in peak CK values were not significant (Figure 6, 7). Patients in Group P were significantly older than those in Group TP ($p<0.05$, Figure 5), and their arrival time after onset in Group P

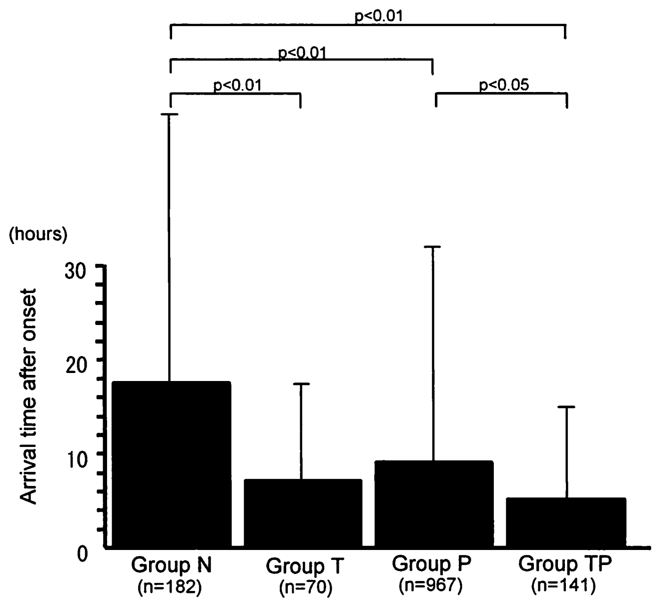

Figure 6. Arrival time after onset of acute myocardial infarction is shown in relation to three reperfusion methods. Cases with unclear arrival times were not included (n=210).

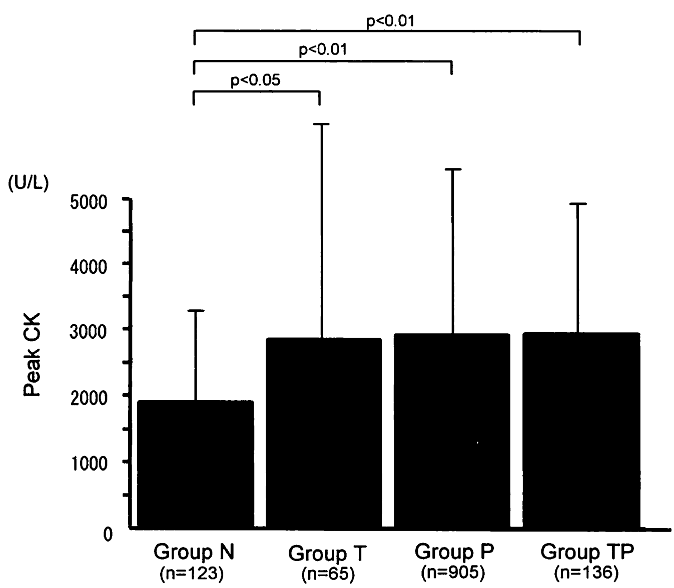

Figure 7. Mean±SD values of peak creatine kinase are shown for three reperfusion methods. Unclear peak creatine kinase value cases and peak-out cases of creatine kinase were not included (n=341). CK, creatine kinase.

Table 3. Logistic Regression Analysis

	Coefficient	SE	chi-square	p value	Exp (Coefficient)
Constant	8.76	1.00	76.51	<0.01	6,378.94
Age	−0.08	0.01	42.01	<0.01	0.92
Male	−0.04	0.24	0.02	0.88	0.97
Obesity	−0.24	0.3	0.64	0.42	0.79
Hypertension	0.46	0.23	4.03	<0.05	1.58
Hyperlipidemia	−0.23	0.28	0.70	0.40	0.79
Diabetes mellitus	0.76	0.24	10.31	<0.01	2.14
Smoking	−0.37	0.26	2.01	0.16	0.69
Family history	0.07	0.43	0.02	0.88	1.07
Arrival time after onset	−0.01	0.10	0.49	0.49	0.99
Peak CK	−2.73E-04	3.92E-05	48.44	<0.01	1.00
Reperfusion therapy	−1.06	0.56	3.58	0.06	0.35
PCI	−0.49	0.48	1.05	0.31	0.61
Thrombolysis	0.57	0.34	2.75	0.10	1.76

SE, standard error; Exp, exponent; CK, creatine kinase; PCI, percutaneous coronary intervention.

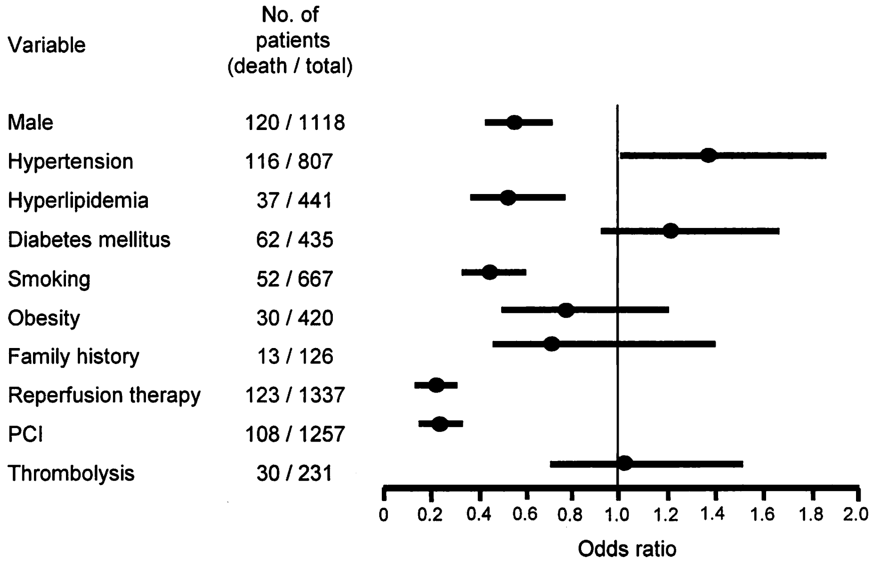

Figure 8. Odds ratios for several variables. Horizontal bars represent 95% confidence interval. PCI, percutaneous coronary intervention.

was longer than in Group TP ($p<0.05$, Figure 6), although peak CK values were not significantly different between the groups (Figure 7).

The in-hospital mortality was analyzed by the logistic regression analysis among age, arrival time, peak CK values, coronary risk factors, reperfusion therapy, PCI, and thrombolysis. There were significant differences in age ($p<0.01$, Table 3), peak CK values ($p<0.01$, Table 3), hypertension ($p<0.05$, Table 3), and diabetes mellitus ($p<0.01$, Table 3). Thus, age, peak CK values, hypertension, and diabetes mellitus were the important factors determining the in-hospital mortality.

Several variables including coronary risk factors were analyzed by odds ratio (Figure 8). The in-hospital mortality was significantly decreased in male, hyperlipidemia, smoking, reperfusion therapy, and PCI ($p<0.05$), but significantly increased in hypertension ($p<0.05$).

DISCUSSION

This study demonstrated that circadian, the day-of-week, and seasonal variabilities in the occurrence of AMI and the in-hospital mortality rate were related to the different methods used for reperfusion therapy. Many studies have been conducted on the onset of AMI[1-8]. Spielberg *et al.* reported that the onset of AMI was most frequent at 10 : 00 AM[7]. They found that the suggested reason for the high occurrence in the morning may be related to morning increases in catecholamine concentrations, blood pressure, serum cortisol, and platelet aggregability. Our data also demonstrated peak occurrences from 9 : 00 AM to 10 : 00 AM (Figure 1). Muller *et al.* reported the secondary peak at 8 : 00 PM, and the maximum frequency at 9 : 00 AM[1]. They indicated that the late evening peak could reflect a different process from what caused AMI in the morning. In Japanese patients, we also found the secondary peak from 9 : 00 PM to 10 : 00 PM (Figure 1). These results suggest that human biorhythms may be involved in the onset of AMI.

The highest incidence of AMI reportedly occurred on Monday[5-7]. Willich *et al.* reported that the occurrence of AMI demonstrated a peak on Monday, especially in the working population[6]. They assumed an increase in physical and mental burden from leisurely weekend activities to stressful work on Monday in the majority of working patients. However, the occurrence of AMI throughout one week was not notably different in our study (Figure 2). The reason may be the many elderly patients most of who were non-working. Thus, the day of onset is likely to be largely dependent on the patient or lifestyle.

As for seasonal variability in the occurrence of AMI, Spielberg *et al.* reported the peak occurrence in March[7]. They suspected that the cold air and solar hours per day would affect the occurrence of AMI. Our study showed the peak occurrence of AMI was in January (Figure 3), but the difference was not significant. Although our results would partly reflect the fact that January is the coldest month in the Fukushima area, no strong trend in seasonal variability could be detected.

PCI is widely accepted as the effective reperfusion treatment of choice for AMI[8-20]. Our study also demonstrated that in-hospital mortality was significantly decreased in Group P compared with Group N (Figure 4). In this analysis, however, it should be noted that it took longer for Group N patients to reach the hospital after AMI onset, leading to lower peak CK values and no recommendation for PCI or thrombolysis. Moreover, Group N patients were older. It is also unclear why the ischemic area at AMI onset was large in patients with non-reperfusion therapy, compared with that of Group P patients. Accordingly, the highest mortality rate in Group N does not necessarily reflect non-reperfusion induced myocardial damage alone.

Upon comparison, the adverse aggregate outcome occurred significantly less often in the PCI group ($p=0.033$) than in the thrombolysis group at day 30 in the GUSTO IIb trial[14]. Le May *et al.* reported that thrombolysis followed by PCI reduced the risk of recurrent ischemic events compared with thrombolysis alone, and that it was not associated with an increase in major bleeding complications[16]. Gershlick *et al.* found that event-free survival after failed thrombolytic therapy was significantly higher in patients with rescue PCI than those with repeated thrombolysis or conservative treatment[18].

In a comparison between PCI with and without thrombolysis, Ross *et al.* reported that since early recanalization before catheter laboratory arrival preserved left ventricular function, thrombolysis plus PCI was more effective than PCI alone[15]. Moreover, Brodie *et al.* reported that door-to-balloon time was a key factor in in-hospital and late cardiac mortality[19]. They considered that the optimum reperfusion strategy may be a local thrombolysis followed by PCI, i.e., facilitated PCI. However, Keeley *et al.* reported that facilitated PCI was associated with increased rates of short-term death, non-fatal reinfarction, and target vessel revascularization, compared with PCI alone, and was associated with higher rates of major bleeding than PCI alone[20]. A controversy exists between the two strategies in the modern era.

In our study, the in-hospital mortality in Group P was not different from that in Group TP (Figure 4). Although the arrival time after onset was significantly earlier in Group TP than in Group P, peak CK values did not significantly differ between Groups P and TP (Figure 6, 7), suggesting no difference in infarct size between the two groups. Further study is needed in this issue.

Multiple variables were analyzed by the logistic regression analysis and odds ratio. There were significant differences in age, peak CK values, hypertension, and diabetes mellitus (Table 3). Hypertension and diabetes mellitus are widely accepted with coronary risk factors[8,12,13]. Age and peak CK values affected the in-hospital mortality, but not arrival time after onset (Table 3). It is likely that arrival after onset in severe myocardial infarction cases was not always delayed, whereas there were mild myocardial infarction cases with delayed arrival after onset. In our analysis by odds ratio, in-hospital mortality was significantly decreased in male, hyperlipidemia, smoking, reperfusion therapy, and PCI and significantly increased in hypertension (Figure 8). Reperfusion therapy and PCI would be effective against in-hospital mortality. It seems that the mortality rate is higher although morbidity rate is lower in female (Table 1, Figure 8). Actually, Milcent *et al.* reported that female with AMI had a higher in-hospital mortality rate than male[21]. However, it is unclear why patients with hyperlipidemia or smoking showed lower risk in in-hospital mortality in this study during the short observation period. One of the reasons of the results might be caused by the various criteria of each institution. Concerned with the hyperlipidemia, a paradoxical decrease in mortality with increasing BMI was shown in patients undergoing PCI (the obesity paradox)[22-24]. Compared with normal weight patients, obese patients less frequently developed in-hospital hemorrhagic complications and less commonly required blood product transfusions[24]. In these reports, obese patients more frequently had hyperlipidemia than normal weight patients[22-24]. Therefore, obesity and hyerlipidemia could be protective against the mortality in patients undergoing PCI in our study, because patients with PCI were about four times compared with patients without PCI. Further study is needed concerned with coronary risk factors.

Study limitations

Not all patients with AMI in the Fukushima area were included in this study. Moreover, this study was a retrospective cohort. There was no randomization with regard to reperfusion therapy. In comparing the three groups given reperfusion therapy, the myocardial infarction area, culprit lesion, the number of diseased vessels, and collateral flow were not evaluated in the present study. Therefore, it is difficult to directly determine what kind of reperfusion therapy is superior. Moreover, the choice of therapy was entrusted to the judgment of the institutions. Thus, the results may not be unfair. Further studies are needed concerned with these issues. However, the results of this study would be useful for understanding the efficacy of the reperfusion therapy, because the doctors themselves would select the method of reperfusion therapy in actual clinical situations according to on a case-by-case basis. Furthermore, coronary risk factors were expressed by the criteria of each institution. Therefore, the severity of each coronary risk factor is unclear. Further study is needed in this issue, too.

In conclusion, the onset of AMI seemed closely related to circadian rhythms, variations in days of the week, and seasonal variability, suggesting human biorhythm involvement. Although the intervention of coronary reperfusion, especially by PCI, was likely to be effective in reducing in-hospital mortality after the onset of AMI, no precise analysis of PCI effectiveness was made in the present study. Although further study is recommended to clarify these issues, the present epidemiological investigation may help to establish the protection or treatment for AMI in Japan.

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REFERENCES

1. Muller JE, Stone PH, Turi ZG, Rutherford JD, Czeisler CA, Parker C, Poole WK, Passamani E, Roberts R, Robertson T, Sobel BE, Willerson JT, Braunwald E. Circadian variation in the frequency of onset of acute myocardial infarction. N Engl J Med, **313**: 1315-1322, 1985.
2. Hjalmarson Å, Gilpin EA, Nicod P, Dittrich H, Henning H, Engler R, Blacky R, Smith Jr. SC, Ricou F, Ross Jr. J. Differing circadian patterns of symptom onset in subgroups of patients with acute myocardial infarction. Circulation, **80**: 267-275, 1989.
3. Willich SN, Linderer T, Wegscheider K, Leizorovicz A, Alamercery I, Schröder R. Increased morning incidence of myocardial infarction in the ISAM study: absence with prior β-adrenergic blockade. Circulation, **80**: 853-858, 1989.
4. Goldberg RJ, Brady P, Muller JE, Chen Z, de Groot M, Zonneveld P, Dalen JE. Time of onset of symptoms of acute myocardial infarction. Am J Cardiol, **66**: 140-144, 1990.
5. Thompson DR, Pohl JEF, Sutton TW. Acute myocardial infarction and day of the week. Am J Cardiol, **69**: 266-267, 1992.
6. Willich SN, Löwel H, Lewis M, Hörmann A, Arntz H, Keil U. Weekly variation of acute myocardial infarction. Increased Monday risk in the working population. Circulation, **90**: 87-93, 1994.
7. Spielberg C, Falkenhahn D, Willich SN, Wegscheider K, Völler H. Circadian, day-of-week, and seasonal variability in myocardial infarction: comparison between working and retired patients. Am Heart J, **132**: 579-585, 1996.
8. Kinoshita N, Imai K, Kinjo K, Naka M. Longitudinal study of acute myocardial infarction in the southeast Osaka district from 1988 to 2002. Circ J, **69**: 1170-1175, 2005.
9. Shibata J, Tanazawa S, Hirasawa K, Tateda K, Kanda M. Deaths in early phase of acute myocardial infarction and approaches for reducing the in-hospital and out-hospital case-fatality rates of the disease. Jpn Circ J, **51**: 325-331, 1987.
10. Nishigaki K, Yamazaki T, Fujiwara H. Assessment of coronary intervention in Japan from the Japanese Coronary Intervention Study (JCIS) Group. Comparison between 1997 and 2000. Circ J, **68**: 181-185, 2004.
11. Nishigaki K, Yamazaki T, Fukunishi M, Tanihata S, Fujiwara H. Assessment of acute myocardial infarction in Japan from the Japanese Coronary Intervention Study (JCIS) Group. Circ J, **68**: 515-519, 2004.
12. Tsuchihashi M, Tsutsui H, Tada H, Shihara M, Takeshita A, Kono S. Volume-outcome relation for hospitals performing angioplasty for acute myocardial infarction. Results from the nationwide Japanese registry. Circ J, **68**: 887-891, 2004.
13. Kinjo K, Sato H, Sakata Y, Nakatani D, Mizuno H, Shimizu M, Nishino M, Matsu-ura Y, Koretsune Y, Nanto S, Mishima M, Hori M. Identification of uncomplicated patients with acute myocardial infarction undergoing percutaneous coronary intervention. Are these patients suitable for early discharge? Circ J, **69**: 1163-1169, 2005.
14. The global use of strategies to open occluded coronary arteries in acute coronary syndromes (GUSTO IIb). Angioplasty substudy investigators. A clinical trial comparing primary coronary angioplasty with tissue plasminogen activator for acute myocardial infarction. N Engl J Med, **336**: 1621-1628, 1997.
15. Ross AM, Coyne KS, Reiner JS, Greenhouse SW, Fink C, Frey A, Moreyra E, Traboulsi M, Racine N, Riba AL, Thompson MA, Rohrbeck S, Lundergan CF. A randomized trial comparing primary angioplasty with a strategy of short-acting thrombolysis and immediate planned rescue angioplasty in acute myocardial infarction: The PACT trial. J Am Coll Cardiol, **34**: 1954-1962, 1999.
16. Le May MR, Wells GA, Labinaz M, Davies RF, Turek M, Leddy D, Maloney J, McKibbin T, Quinn B, Beanlands RS, Glover C, Marquis J, O'Brien ER, Williams WL, Higginson LA. Combined angioplasty and pharmacological intervention versus thrombolysis alone in acute

myocardial infarction (CAPITAL AMI Study). J Am Coll Cardiol, **46** : 417-424, 2005.
17. Schömig A, Mehilli J, Antoniucci D, Ndrepepa G, Markwardt C, Di Pede F, Nekolla SG, Schlotterbeck K, Schühlen H, Pache J, Seyfarth M, Martinoff S, Benzer W, Schmitt C, Dirschinger J, Schwaiger M, Kastrati A. Mechanical reperfusion in patients with acute myocardial infarction presenting more than 12 hours from symptom onset. A randomized controlled trial. JAMA, **293** : 2865-2872, 2005.
18. Gershlick AH, Stephens-Lloyd A, Hughes S, Abrams KR, Stevens SE, Uren NG, de Belder A, Davis J, Pitt M, Banning A, Baumbach A, Shiu MF, Schofield P, Dawkins KD, Henderson RA, Oldroyd KG, Wilcox R. Rescue angioplasty after failed thrombolytic therapy for acute myocardial infarction. N Engl J Med, **353** : 2758-2768, 2005.
19. Brodie BR, Hansen C, Stuckey TD, Richter S, VerSteeg DS, Gupta N, Downey WE, Pulsipher M. Door-to-balloon time with primary percutaneous coronary intervention for acute myocardial infarction impacts late cardiac mortality in high-risk patients and patients presenting early after the onset of symptoms. J Am Coll Cardiol, **47** : 289-295, 2006.
20. Keeley EC, Boura JA, Grines CL. Comparison of primary and facilitated percutaneous coronary interventions for ST-elevation myocardial infarction : quantitative review of randomized trials. Lancet, **367** : 579-588, 2006.
21. Milcent C, Dormont B, Durand-Zaleski I, Steg PG. Gender differences in hospital mortality and use of percutaneous coronary intervention in acute myocardial infarction. Microsimulation analysis of the 1999 nationwide French hospitals database. Circulation, **115** : 833-839, 2007.
22. Gruberg L, Weissman NJ, Waksman R, Fuchs S, Deible R, Pinnow EE, Ahmed LM, Kent KM, Pichard AD, Suddath WO, Satler LF, Lindsay Jr. J. The impact of obesity on the short-term and long-term outcomes after percutaneous coronary intervention : the obesity paradox ? J Am Coll Cardiol, **39** : 578-584, 2002.
23. Gurm HS, Brennan DM, Booth J, Tcheng JE, Lincoff M, Topol EJ. Impact of body mass index on outcome after percutaneous coronary intervention (the obesity paradox). Am J Cardiol, **90** : 42-45, 2002.
24. Nikolsky E, Stone GW, Grines CL, Cox DA, Garcia E, Tcheng JE, Griffin JJ, Guagliumi G, Stuckey T, Turco M, Negoita M, Lansky AJ, Mehran R. Impact of body mass index on outcomes after primary angioplasty in acute myocardial infarction. Am Heart J, **151** : 168-175, 2006.