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Periodic Variation and Its Effect on Management and Prognosis of Korean Patients With Acute Myocardial Infarction

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Background: The characteristics of the periodic variation in acute myocardial infarction (AMI) and the subsequent effect on management and prognosis have not been fully investigated in a large number of Asian populations.

Methods and Results: From a prospective, observational multicenter online registry, 4,573 patients diagnosed as AMI in Korea from January to December 2006 were included. The highest incidence of AMI was between 8 a.m. and noon. The number of cases was highest in the winter and lowest in the autumn (13.6 vs 11.4 patients per day, P<0.001). Patients with symptom onset during working hours had a shorter time to first medical contact (203±288 min) compared with out-of-hours onset (230±288 min, P=0.003). In patients who underwent primary angioplasty, out-of hours symptom onset was associated with a greater time delay in both the patient's and the medical facility's response (door-to-balloon time out-of hours vs working hours: 101±54 min vs 84±44 min, P<0.001). In patients with ST-segment elevation myocardial infarction, symptoms to first medical contact showed a significant relationship to in-hospital mortality (for every 10 min of symptoms to first medical contact, odds ratio 1.006, 95% confidence interval 1.001–1.012, P=0.018)

Conclusions: Circadian and periodic variation in AMI exists in Korean patients, which resulted in different patient behavior, hospital management and outcomes. (*Circ J* 2010; **74:** 970–976)

Key Words: Acute myocardial infarction; Circadian variation; Periodic variation

After Pell and d'Alonzo first identified the association of circadian variation and acute myocardial infarction (AMI),[1] many studies have shown similar patterns, with the peak onset in the morning,[2] on Monday and in the winter.[3–5] The physiological changes in hemodynamics,[6–8] vascular status and hematological changes,[9–12] as well as environmental factors, contribute to this variation.[2–4,13] These circadian variations are also associated with the patient's response, medical management and prognosis.[14]

Some reports have suggested that there may be ethnic differences in circadian variation and its association with AMI. Lopez et al reported a difference in the onset of AMI among British Caucasians, Indo-Asians and Mediterranean Caucasians.[15] However, there has not been a large-scale study in

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Table 1. Baseline Characteristics of the Patients

	All	Working hours	Out-of-hours	P value*
Total no. of patients	4,573	1,265	3,308	
Age (years)	62.9±12.7	63.1±12.7	62.8±12.7	0.443
Male	3,281 (71.7%)	893 (70.6%)	2,388 (72.2%)	0.284
Previous IHD	778 (17.0%)	213 (16.8%)	565 (17.1%)	0.846
Anterior MI	2,049 (44.8%)	542 (42.8%)	1,507 (45.6%)	0.076
STEMI	2,912 (63.7%)	836 (66.1%)	2,076 (62.8%)	0.036
Primary PCI	1,410 (48.4%)	472 (56.5%)	938 (45.2%)	<0.001
Thrombolysis	400 (13.7%)	70 (8.4%)	330 (15.9%)	<0.001
Risk factors				
Diabetes mellitus	1,246 (27.2%)	330 (26.1%)	916 (27.7%)	0.276
Hyperlipidemia	325 (7.1%)	98 (7.7%)	227 (6.9%)	0.298
HTN	2,186 (47.8%)	595 (47.0%)	1,591 (48.1%)	0.521
Time to first medical contact (min)	223±288	203±288	230±288	0.003
CK-MB (maximum, ng/ml)	155.2±232.6	156.3±242.0	154.7±229.0	0.837
Cardiogenic shock	229 (5.0%)	61 (4.8%)	168 (5.1%)	0.722

*Working hour vs out-of-hours onset of symptom.
IHD, ischemic heart disease; MI, myocardial infarction; STEMI, ST-segment elevation MI; PCI, percutaneous coronary intervention; HTN, hypertension.

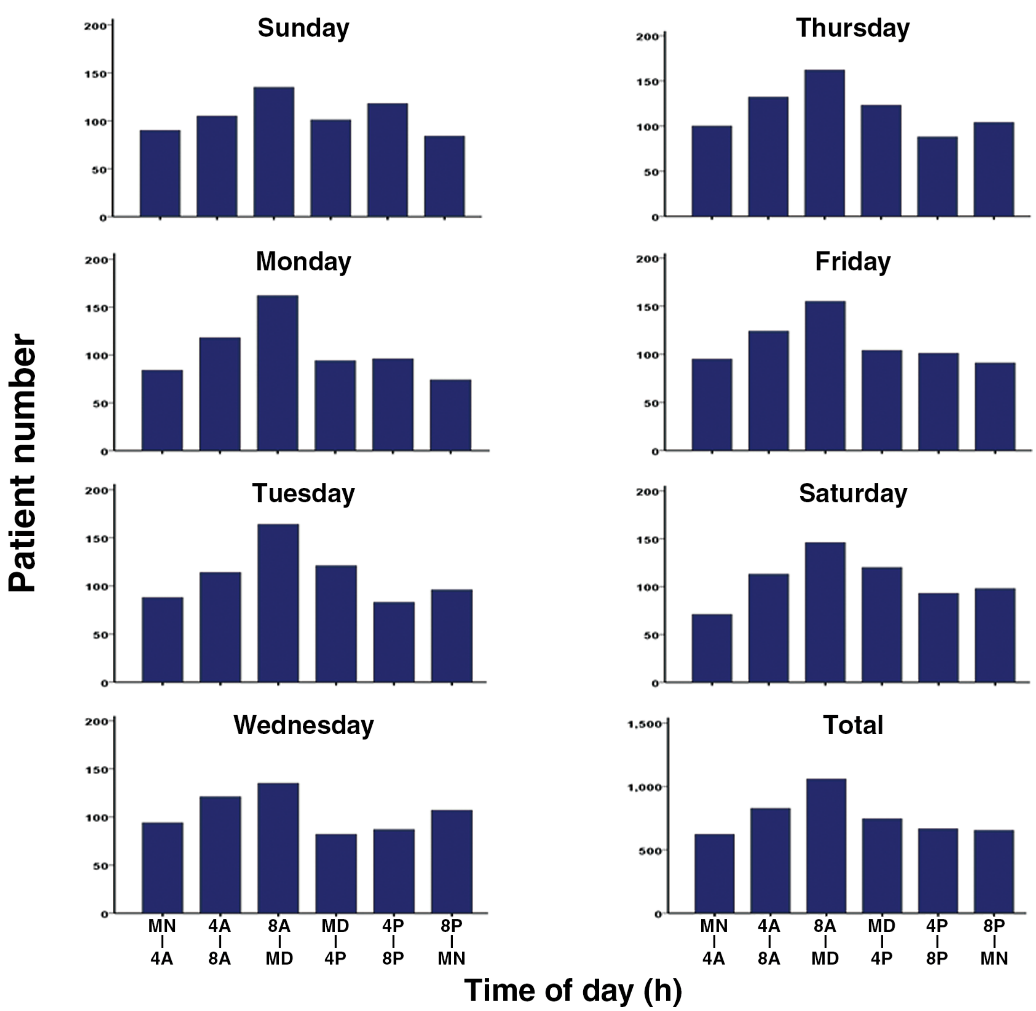
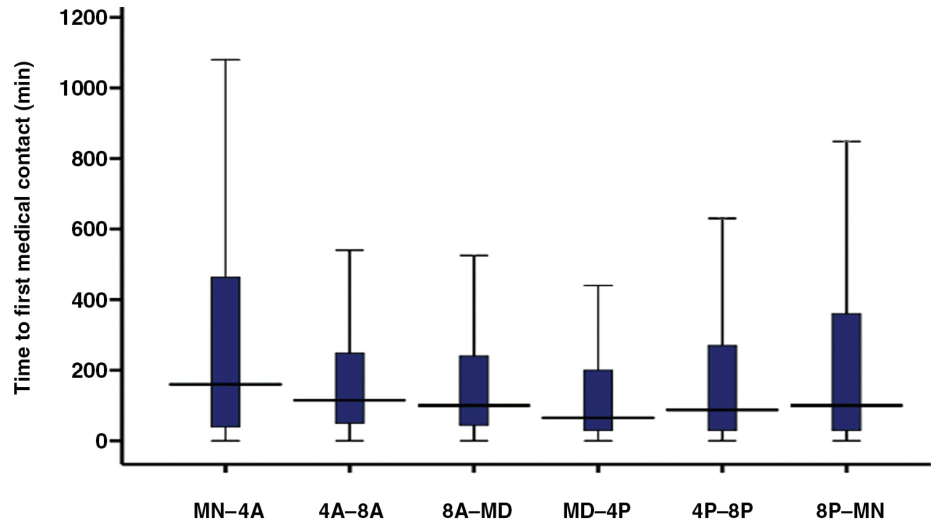


Figure 1. Histograms of circadian variation in the incidence of acute myocardial infarction by 6 4-h periods according to weekday. MD, midday; MN, midnight; A, AM; P, PM.



Time of day	MN–4A	4A–8A	8A–MD	MD–4P	4P–8P	8P–MN
Number of patients	622	827	1,059	745	666	654
Time to first medical contact (min)	281±290	182±196	188±239	201±310	256±353	264±335

Figure 2. Box plots of time to first medical contact according to the time of symptom onset in all patients with acute myocardial infarction. The time of onset of symptom was divided into 6 equal parts of 4 h each and each box plot shows minimum, first quartile, median, third quartile, and maximum value in minutes during each time period. The table represents time to first medical contact in mean ± standard deviations. MD, midday; MN, midnight; A, AM; P, PM.

Asians with regard to the circadian variation of AMI and the effect on medical management and prognosis.

Methods

The Korea Acute Myocardial Infarction Registry (KAMIR) is a prospective, observational multicenter online registry that has been investigating the risk factors associated with mortality in patients with AMI since November 2005. The registry receives data from 41 primary percutaneous coronary intervention (PCI) centers in Korea.[16,17] Between January and December of 2006, 5,421 patients were included and after exclusion of 848 patients who were younger than 20 years, who had visited the hospital more than 24 h after the onset of symptoms, or whose time of symptom onset or time of arrival to the first hospital was unclear, 4,573 patients were finally included in this study.

The diagnosis of AMI was based on the clinical presentation, ECG findings and levels of cardiac enzymes.[18] Patients who presented with acute ST-segment elevation MI (STEMI) within 12 h of symptom onset were considered eligible for primary angioplasty. The time to first medical contact was defined as the time interval between the first recognition of pain to the first visit to a medical facility. In the case of referral to a study hospital, the time interval from symptom onset to the visit to the first hospital was used as the time to the first medical contact. In patients who underwent primary PCI, treatment delay was defined as the time taken from symptom onset to first ballooning, which is the sum of the time to first medical contact, transfer to a PCI center and the door to balloon time. Working hours were defined as Monday to Friday between 8 a.m. and 6 p.m. Weekends were considered as out-of-hours. The patients were classified into working hours or out-of-hours onset according to the time of symptom onset. The frequency of AMI was defined as the number of patients per day. The in-hospital mortality included all-cause mortality during hospitalization.

Data are presented as the mean ± standard deviation for continuous variables and as frequencies for categorical variables. Comparisons of the continuous variables were performed using Student's t-test or ANOVA. Analyses of discrete variables were performed using the chi-square test. The weekly, monthly and seasonal variations were evaluated by comparing the mean number of AMI events per day using ANOVA. Regression analyses were performed to determine the factors associated with the time to medical contact and in-hospital mortality. A value of $P<0.05$ was considered significant. All statistical analyses were carried out with SPSS version 17.0 (Chicago, IL, USA).

Results

Baseline characteristics of the patients are shown in Table 1. Depending on the time of symptom onset, patients showed different patterns of presentation. Among 4,573 patients, 1,265 presented with symptom during working hours and 3,308 patients during out-of-hours. Compared with patients with out-of-hours onset, patients with onset during working hour presented more frequently with STEMI, presented to the hospital earlier and underwent primary PCI more frequently. More patients received thrombolysis out-of-hours.

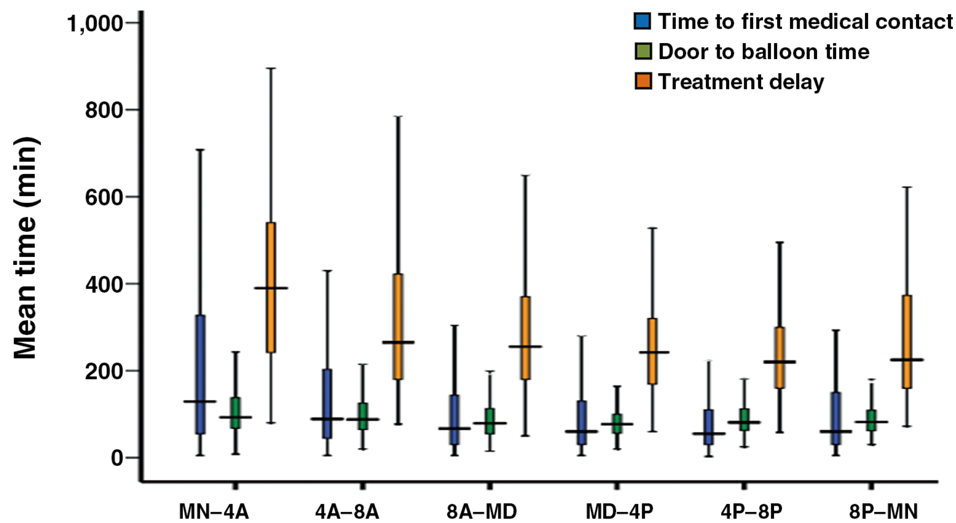
Periodic Variation in the Onset of AMI

To examine the periodic variation in AMI, we analyzed its

Table 2. Determinants of the Time to First Medical Contact in Patients With Myocardial Infarction

	β	95% confidence interval		P value
		Lower bound	Upper bound	
Age (years)	2.017	1.36	2.68	<0.001
Female	15.26	–4.56	35.09	0.13
Diabetes mellitus	25.71	6.85	44.57	0.008
Non-STEMI	73.38	55.97	90.79	<0.001
IHD	–20.67	–42.92	1.59	0.069
HTN	15.73	–1.32	32.77	0.07
Out-of-hours symptom onset (min)	25.55	7.16	43.94	0.006
Cardiogenic shock	–22.48	–60.43	15.47	0.25

Abbreviations see in Table 1.



Time of day	MN–4A	4A–8A	8A–MD	MD–4P	4P–8P	8P–MN
Number of patients	141	318	359	282	169	141
Time to first medical contact (min)	204±183	143±139	112±110	99±99	94±116	123±149
Door to balloon time (min)	115±68	100±52	93±55	84±43	92±40	94±46
Treatment delay (min)	397±196	314±166	290±145	258±120	250±137	288±183

Figure 3. Box plots of time to first medical contact (■), door to balloon time (■) and treatment delay (■) according to the 6 4-h periods in patients with acute ST-segment elevation myocardial infarction who underwent primary angioplasty. Treatment delay is the sum of time to first medical contact, transfer time to the PCI center and door to balloon time. Each box plot shows minimum, first quartile, median, third quartile, and maximum value during each time period, and the values in the table are mean ± standard deviations. MD, midday; MN, midnight; A, AM; P, PM.

incidence according to the time of the day, weekday, each season and month. The 24-h day was divided into 6 equal parts of 4 h each to evaluate the diurnal variation. AMI developed most frequently between 8 a.m. and noon. When analyzed according to weekday, all weekdays had the same tendency of a primary peak between 8 a.m. and noon, but the secondary peak showed variability depending on the weekday (**Figure 1**).

The total frequency for AMI did not differ among the weekdays, but there were significant seasonal and monthly variations. The 12 months were divided into 4 seasons, with each season consisting of 3 consecutive months. The seasonal variation showed a peak incidence of 13.6 patients per day in winter, and decreased to the lowest frequency of 11.4 patients per day in the fall (P<0.001). The monthly variation showed the highest incidence in January with 16.0 patients per day and lowest in November with 10.6 patients per day (P<0.001).

Effect of the Time of Symptom Onset on Patient Behavior and Subsequent Medical Management

The mean time to first medical contact was 223±288 min. The time to the first medical contact was affected by the time of symptom onset (**Figure 2**). Patients with symptom onset during working hours had a shorter time to their first medical contact (203±288 min) than those with out-of hours symptom onset (230±288 min, P=0.003). The multivariate analysis showed that the time to first medical contact was delayed in patients with advanced age, who had diabetes mellitus, non-STEMI (NSTEMI), and onset of symptoms out-of-hours (**Table 2**).

The door-to-balloon time in patients with a STEMI who underwent a primary PCI differed according to the time of symptom onset (**Figure 3**). It was longer for presentation out-of-hours than for presentation during working hours (101±54 min vs 84±44 min, P<0.001). The time to first medical contact and treatment delay were also longer out-of-hours (out-of-hours vs working hours: 135±144 min vs 104±104 min, P<0.001 for time to first medical contact, 309±170 min vs 266±132 min, P<0.001 for treatment delay). However, when only the patients who presented to the hospital within 3 h of symptom onset were analyzed, the mean time to first medical contact and the treatment delay did not differ between out-of-hours and working hours onset (65±45 min vs 64±46 min, P=0.788, 241±111 min vs 231±105 min, P=0.122, respectively). The weekday, month and season were not associated with the door-to-balloon time.

Effect of the Time of Symptom Onset on Prognosis

During hospitalization, 50 patients (4.0%) among those with working hours onset and 159 patients (4.8%) with out-of-hours onset died. A multivariate analysis was performed to determine the factors associated with in-hospital mortality, including the variables of age, sex, previous history of ischemic heart disease, hypertension or diabetes mellitus, final diagnosis of STEMI, time to first medical contact, and cardiogenic shock at initial presentation. The determinants of in-hospital mortality were advanced age (odds ratio (OR) 1.052, 95% confidence interval (CI) 1.037–1.067), diabetes mellitus (OR 1.472, 95%CI 1.079–2.009), STEMI (OR 1.632, 95%CI 1.171–2.274), and cardiogenic shock (OR 11.688, 95%CI 8.305–16.450) among all patients, and advanced age (OR 1.056, 95%CI 1.028–1.086), diabetes mellitus (OR 2.080, 95%CI 1.134–3.813) and cardiogenic shock (OR 11.055, 95%CI 5.800–21.071) among patients who were eligible for primary PCI. In either case, the time to first medical contact, the time of symptom onset to the first ballooning or symptom onset during working hours/out-of-hours did not affect in-hospital mortality.

We then evaluated patients according to the final diagnosis. In patients who presented as NSTEMI, time to the first medical contact did not show a significant relationship to the in-hospital mortality (P=0.165). However, in patients with STEMI, time to first medical contact showed a significant relationship with in-hospital mortality (for every 10 min of symptom to first medical contact, OR 1.006, 95%CI 1.001–1.012, P=0.018). When patients with reperfusion therapy were compared with those without reperfusion therapy, there was no significant relationship between time to first medical contact and in-hospital mortality in either group (P=0.413 in reperfusion group, P=0.529 in no reperfusion group).

Discussion

This is the largest study analyzing periodic variation and AMI in Asian patients.[13,19–22] In general, our study showed similar patterns of periodic variation as in Western populations. However, the weekly and seasonal patterns showed some differences. We have also found that the time of symptom onset affected patient behavior and hospital management.

In this study, the periodic variation in the frequency of AMI in Korean patients showed similar diurnal, monthly and seasonal patterns to patients in Western cultures: peak incidence in the early morning,[2,3] during January and in winter.[3–5,23] However, the frequency of AMI in Korean patients was lowest in the autumn, whereas in most of the previous studies it has been reported to be lowest during the summer.[3–5,23] The difference in regional climate may have contributed to the different seasonal patterns observed in Korean AMI patients, because the occurrence of AMI is affected by climate, with a higher incidence in climates with extreme temperatures.[3,24–27] A similar finding with an autumn nadir was also reported in a Japanese study.[22]

In this study, we found no weekday variation of AMI in Korean patients, which was different from other previous reports. Kinjo et al reported a gender difference in the weekday variation in the Japanese population, with women showing a Saturday peak.[28] Our Korean patient population did not show such sex differences in weekday variation. The monthly and seasonal variations also did not show a sex difference.

The diurnal variation of AMI showed a variable second peak based on the weekday. Kinjo et al suggested socioeconomic factors related to work and lifestyle as an explanation for the secondary peak, especially in young male workers.[19] Because our data did not include such information, we could not analyze the effect of socioeconomic factors.

In addition to diurnal and seasonal variations we compared patients with working hours vs out-of-hours onset to find differences in patient behavior, management and prognosis. Previous reports by Magid et al[14] and Nakayama et al[29] observed a longer door to balloon time out-of-hours than during regular hours, which we have also noted. We found differences in patient behavior and hospital management according to the time of symptom onset. When symptom onset occurred during working hours, there was earlier hospital presentation and a shorter door-to-balloon time, whereas out-of-hours both hospital presentation and door to balloon time were significantly longer. The treatment delay out-of-hours may be caused by delayed visiting by the patients after symptom onset and also a delay in the time taken to activate the catheterization laboratory. The time to first medical contact can be shortened by educating patients and the general population, and the door to balloon time can be shortened by improving the activation system of the catheterization laboratory out-of-hours. Also, improving the referral system between hospitals will shorten the total treatment delay. Other factors that affected the time to the first medical contact were advanced age, diabetes mellitus and the diagnosis of NSTEMI. Delayed hospital visit by elderly patients may have been due to atypical symptoms or reduced perception of pain.[30,31] Autonomic dysfunction and decreased perception of pain in diabetic patients may contribute to a higher incidence of silent MI and subsequent delay in presentation to the hospital.[32–34] Therefore, a more cautious approach is required when evaluating the elderly or diabetic MI patient.

Higher in-hospital mortality occurred in patients of advanced age, with diabetes mellitus, initial cardiogenic shock, and a diagnosis of STEMI in our study. However, presentation out-of hours was not associated with higher in-hospital mortality despite the longer symptom to first medical contact and door-to-balloon time. It is well known that time-to-reperfusion is an important determinant of the short- and long-term outcomes in patients with AMI.[35–38] Previous reports have shown that shorter time-to-reperfusion is an independent predictor of in-hospital mortality, especially with a cut-off value of 3 h.[35] To understand the discrepancy between previous reports[14,39] and our findings, we divided patients according to the time to first medical contact and compared the time variation. Among the patients who were eligible for primary angioplasty, 77% of patients visited hospital within 3h of symptom onset and there was no difference in either symptom to first medical contact time or treatment delay according to the time of symptom onset in this group.

Another possible explanation of our result is the different study population. Magid et al evaluated 68,439 patients with STEMI and reported increased in-hospital mortality and longer time to treatment for PCI with symptom onset occurring out-of-hours,[14] whereas Jneid et al found no measurable differences in the in-hospital mortality of 62,814 patients with AMI according to time of symptom onset, despite slightly fewer primary PCI and overall revascularizations and significantly longer door-to-balloon times for those with out-of hours onset.[40] The difference in study cohorts may have lead to different results: in the study by Magid et al[14] only the patients with STEMI were included, whereas Jneid et al[40] included both STEMI and NSTEMI. We had similar findings to those earlier reports. When all AMI patients were included in the analysis, we could not find a significant relationship between symptom to first medical contact and in-hospital mortality, but when patients with STEMI were analyzed separately, there was significant relationship between symptom to first medical contact and in-hospital mortality.

When patients were grouped according to the presence or absence of reperfusion therapy, we could not find a significant relationship between time to the first medical contact and in-hospital mortality in either group (P=0.413 in reperfusion group, P=0.529 in no reperfusion group). There may have been a survivor-cohort effect, wherein those who present to the hospital after 6–12h have already survived the high-risk period of death. Also, we do not have information on patients in the catchment areas who had an out-of-hospital MI and died prior to hospital arrival, which may have also affected the result.

Study Limitations

First, there is the possibility of selection bias, as this study includes patients who visited 41 collaborating hospitals in Korea. Second, detailed data on infarct size, socioeconomic status and procedural outcomes were not included in the analysis. These data might have added additional insight to the findings. Third, the results of the current study are based on the analysis of patients during only 1 year, and for better understanding, long-term follow up may be needed. Fourth, the severity of symptoms in each patient was not recorded on an objective scale, such as the VAS scale. The behavior of patients may have been affected by the severity of the symptoms, but could not be evaluated because of the lack of objective or comparable data.

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Disclosures

None.

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