Original article

Contents of second peak in the circadian variation of acute myocardial infarction in the Japanese population

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KEYWORDS
Circadian rhythm; Acute myocardial infarction; Gender

Summary
Background: Circadian variation has been accepted as a factor in acute myocardial infarction (AMI). An increased incidence of cardiac events in the morning has been reported for a long time. Recent reports have indicated that the onset of AMI shows two peaks, which occur in the morning and evening. It has also been demonstrated that circadian pattern of AMI may vary with sex and age.

Methods and results: We investigated 522 consecutive patients who underwent primary percutaneous coronary intervention (PCI) for ST segment elevation myocardial infarction (STEMI) between 2000 and 2010. The patients were classified into 3 age groups: younger (<59 years old), intermediate (60–79 years old), and older (≥80 years old). Clinical data were investigated, including the age and sex, angiographic characteristics, and time of onset of STEMI.

There were two peaks in the onset of STEMI throughout the day, which were at 7:00–10:00 and 19:00–21:00 h, among all patients (male and female).

Conclusions: There were two peaks in the onset of STEMI in a Japanese population in Tokyo. The second peak was significantly dominated by the older female group. Age and gender influenced the second peak in the circadian variation of AMI in a Japanese population in Tokyo.
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Introduction

Several epidemiologic studies have demonstrated circadian variation in the onset of acute myocardial infarction (AMI) [1—5], with an increased incidence of cardiac events in the morning. The multicenter investigation of limitation of infarct size revealed that the frequency of chest pain peaks...
between 6 AM and noon, with the incidence of myocardial infarction (MI) being 1.28 times higher during this period \( p < 0.01 \) [1]. The reasons for this circadian rhythm of AMI have been partially illuminated [6–8], and may include the morning blood pressure surge or physiological changes of platelet aggregation and sympathetic activity.

On the other hand, recent reports (especially from Asian countries) have indicated a different circadian pattern with two peaks of AMI [9–13]. These studies have shown that cardiovascular events also increase in the evening.

The aim of the present study was to analyze the circadian pattern of the onset of ST segment elevation myocardial infarction (STEMI) in the Japanese population. We also investigated whether differences in age and gender affected the circadian pattern of STEMI.

**Methods**

**Subjects**

This was a retrospective study that examined a database on emergency patients at our institution. The study population comprised 566 consecutive STEMI patients admitted to our institution from January 2000 to December 2010.

STEMI was defined by typical chest pain lasting for \( \geq 30 \text{min} \) and significant ST segment elevation (\( \geq 0.1 \text{mV} \) or \( \geq 0.2 \text{mV} \) in \( \geq 2 \) adjacent limbs or precordial leads, or new left bundle branch block) and was confirmed by an increase of biomarkers.

To avoid the influence of change of the circulation dynamic state by hemodialysis to circadian variation, we excluded patients on hemodialysis and those with renal insufficiency (stage 5 chronic kidney disease). Estimated glomerular filtration rate (eGFR) was calculated by the simplified equation derived from the Modification of Diet in Renal Disease (MDRD) GFR [14, 15]. We used the modified US National Kidney Foundation classification for chronic kidney disease [16]. Twenty subjects were excluded for the reason of indefinite identification of exact onset time of AMI.

As a result, 522 patients were enrolled in this study.

Ethical review board approval was obtained and all subjects provided written informed consent.

**History and time of onset**

Physical examination was carefully conducted by trained cardiologists at the time of patient arrival at our institution. Congestive heart failure was classified according to the Killip classification. Cardiologists interviewed patients to obtain their history and identified the time of onset of chest pain. We compared the circadian variation of STEMI between subgroups stratified according to age and gender. For age, we classified the patients into 3 groups: younger (\( \leq 59 \text{ years old} \)), intermediate (60–79 years old), and older (\( \geq 80 \text{ years old} \)). The circadian pattern of STEMI was also evaluated for each gender. To assess the circadian variation of STEMI, the day was divided into 24 periods of 1 h each from midnight to midnight and variation in the onset of symptoms was evaluated.

Diabetes mellitus was defined as being present in patients on treatment with oral hypoglycemic agents or insulin and in those with a fasting blood glucose level \( \geq 126 \text{mg/dl} \) irrespective of treatment or a diabetes mellitus pattern determined by the 75-gram oral glucose tolerance test. Hypertension was defined in patients who had a history of medical treatment, a systolic blood pressure \( \geq 140 \text{mmHg} \), or a diastolic blood pressure \( \geq 90 \text{mmHg} \). Hypercholesterolemia was defined as a total cholesterol level \( \geq 220 \text{mg/dl} \).

**Angiography**

All patients underwent emergency coronary angiography (CAG) and angiographic data were obtained from the cardiac catheterization laboratory records. Perfusion was evaluated according to thrombolysis in myocardial infarction (TIMI) criteria [17]. Coronary artery stenosis of \( > 50 \% \) was considered clinically significant.

**Statistical analysis**

Results are expressed as the mean \( \pm \text{SD} \) for continuous variables, while qualitative data are presented as numbers (percentages). Continuous variables were compared by using the chi-square test and categorical variables were compared by using Fisher’s exact test. A \( p \)-value of \( < 0.05 \) was considered to indicate statistical significance. All statistical analyses were carried out with SPSS software (version 19.0, SPSS, Chicago, IL, USA).

**Results**

**Patient characteristics**

The patients were stratified by age and gender and their characteristics are listed in Table 1. There were 75 patients in the younger age group, 145 in the intermediate age group, and 302 in the older age group. Regarding gender, 272 patients were men and the remainder were women. Older patients were more likely to have hypertension and hypercholesterolemia. They also had more severe heart failure at hospitalization. With regard to gender, women were more likely to have hypercholesterolemia, and they also had more severe heart failure at hospitalization. However, current smoking was more common among men.

Laboratory data are summarized in Table 2. Both eGFR and hemoglobin were lower in the older age group, while total cholesterol was higher in this group. Serum creatinine was higher in men and same result was observed for eGFR. Other data were not different between men and women, except for hemoglobin.

**Angiographic characteristics**

Table 3 shows the angiographic characteristics. The locations of the culprit lesions, as well as the preprocedural and postprocedural TIMI flow grades, were similar among the groups. However, women had more multivessel disease.

**Circadian variation**

Fig. 1 shows histograms for the pattern of STEMI in all patients.
Table 1  Baseline characteristics of the subjects.

<table>
<thead>
<tr>
<th></th>
<th>Age groups</th>
<th>Gender groups</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Younger (&lt;59 years) (n=75)</td>
<td>Intermediate (60—79 years) (n=145)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>48 ± 15</td>
<td>72 ± 7</td>
</tr>
<tr>
<td>Men</td>
<td>49 (65)</td>
<td>61 (42)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>36 (48)</td>
<td>86 (59)</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>29 (39)</td>
<td>78 (54)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>28 (37)</td>
<td>52 (36)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>24 (32)</td>
<td>48 (33)</td>
</tr>
<tr>
<td>Killip&gt;2</td>
<td>3 (4)</td>
<td>3 (2)</td>
</tr>
</tbody>
</table>

* Comparison of younger and older groups.

Table 2  Laboratory data.

<table>
<thead>
<tr>
<th></th>
<th>Age groups</th>
<th>Gender groups</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Younger (&lt;59 years) (n=75)</td>
<td>Intermediate (60—79 years) (n=145)</td>
</tr>
<tr>
<td>Serum creatinine, mg/dl</td>
<td>0.89 ± 0.9</td>
<td>1.12 ± 1.0</td>
</tr>
<tr>
<td>Estimated GFR, ml/min/1.73 m²</td>
<td>72.5 ± 32.4</td>
<td>58.8 ± 28.4</td>
</tr>
<tr>
<td>Hemoglobin, g/dl</td>
<td>13.8 ± 3.6</td>
<td>12.8 ± 2.4</td>
</tr>
<tr>
<td>Total cholesterol, mg/dl</td>
<td>176 ± 80</td>
<td>206 ± 68</td>
</tr>
<tr>
<td>LDL-cholesterol, mg/dl</td>
<td>110 ± 96</td>
<td>126 ± 80</td>
</tr>
<tr>
<td>HDL-cholesterol, mg/dl</td>
<td>50 ± 30</td>
<td>48 ± 38</td>
</tr>
<tr>
<td>Triglycerides, mg/dl</td>
<td>162 ± 102</td>
<td>158 ± 126</td>
</tr>
<tr>
<td>Blood glucose, mg/dl</td>
<td>158 ± 160</td>
<td>162 ± 180</td>
</tr>
<tr>
<td>Peak CK, U/L</td>
<td>700 ± 820</td>
<td>660 ± 620</td>
</tr>
</tbody>
</table>

* Comparison of younger and older groups.
Two peaks were observed in the onset of STEMI, with the first peak in the morning (07:00—10:00) and the second peak in the evening (19:00—21:00), among all patients (male and female). Fig. 2 shows STEMI stratified by gender. In men, STEMI showed one dominant peak in the morning, whereas women had two peaks in the morning and evening. Furthermore, the evening peak of STEMI was significantly higher than that of the morning peak among women.

Fig. 3 shows a comparison of the 3 age groups of women. It is clear that the second peak of STEMI is dominated by

### Table 3 Angiographic characteristics.

<table>
<thead>
<tr>
<th>Culprit lesion</th>
<th>Age groups</th>
<th>Gender groups</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Younger (&lt;=59 years)</td>
<td>Intermediate (60–79 years)</td>
</tr>
<tr>
<td>LMCA</td>
<td>n=75 (%)</td>
<td>n=145 (%)</td>
</tr>
<tr>
<td>LAD</td>
<td>29 (37)</td>
<td>52 (36)</td>
</tr>
<tr>
<td>Cx</td>
<td>12 (16)</td>
<td>26 (18)</td>
</tr>
<tr>
<td>RCA</td>
<td>28 (37)</td>
<td>62 (43)</td>
</tr>
<tr>
<td>RCA</td>
<td>28 (37)</td>
<td>62 (43)</td>
</tr>
<tr>
<td>Others</td>
<td>4 (5)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>No. of diseased vessels</td>
<td>1 29 (39)</td>
<td>56 (39)</td>
</tr>
<tr>
<td></td>
<td>2 29 (39)</td>
<td>62 (43)</td>
</tr>
<tr>
<td></td>
<td>3 17 (23)</td>
<td>27 (19)</td>
</tr>
<tr>
<td>Pre TIMI grade</td>
<td>0/1 38 (51)</td>
<td>68 (47)</td>
</tr>
<tr>
<td></td>
<td>2 10 (13)</td>
<td>32 (22)</td>
</tr>
<tr>
<td></td>
<td>3 27 (36)</td>
<td>45 (31)</td>
</tr>
<tr>
<td>Post TIMI grade</td>
<td>0/1 0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td></td>
<td>2 1 (1)</td>
<td>0 (0)</td>
</tr>
<tr>
<td></td>
<td>3 74 (99)</td>
<td>145 (100)</td>
</tr>
</tbody>
</table>

* Comparison of younger and older groups.

![Figure 2](image-url)  
**Figure 2** Histogram for the pattern of ST segment elevation myocardial infarction (STEMI) stratified by gender.
the older group. Fig. 4 is a comparison of the 3 age groups of men. Unlike women, there is no obvious second peak of STEMI.

It was clear from Figs. 3 and 4 that there exists a statistically significant difference in the circadian variation between genders also limited to the elderly.

Discussion

The main finding of this study was that the circadian rhythm of STEMI in a Japanese population in Tokyo shows 2 peaks in the morning and evening. Age and gender are related to differences in the circadian pattern of STEMI.
In 1985, Muller et al. analyzed 1000 patients and demonstrated circadian variation in the onset of AMI [1]. Since then, several studies performed in Western countries have suggested that the circadian rhythm of AMI is characterized by a morning peak [2–4]. On the other hand, a study from Singapore revealed a different circadian pattern of cardiac arrest, with a bimodal distribution through the 24-h period [10]. In that study, the incidence of cardiac arrest in the morning was the same as that in the evening. Recently, Japanese investigators have reported a similar trend regarding the onset of cardiac events [9,13,18,19]. Sumiyoshi et al. found that onset of AMI was more frequent in the evening than in the morning [18]. Fujita et al. [13] also reported that cardiac arrest due to non-traumatic causes was more common in the evening than in the morning. These observations are consistent with the present findings. Thus, the pattern of circadian variation may differ between Asian and Western countries.

Kinjo et al. [20] reported a contradictory result about the evening peak. They reported that younger patients aged less than 65 years who had the habits of cigarette smoking and alcohol intake showed an evening peak. Add to the differences in the regionality of Tokyo and Osaka, perhaps, such a contradictory result was caused by differences in clinical characteristics of patients. Conversely, we might examine purer influence of circadian variation caused by sex difference.

The mechanism of a morning increase in cardiac events seems to be relatively easy to understand. It is well known that blood pressures increase after waking due to the change of basal vascular tone associated with marked sympathetic vasoconstrictor activity [6,21] and sympathetic activity is increased by modulation of the autonomic nerve system [22]. In addition, plasma levels of epinephrine and norepinephrine increase and this results in increased vascular resistance during the morning [23,24]. It is known that β-blocker therapy can reduce these changes in the morning, particularly in patients with myocardial infarction [25]. It has long been speculated that such factors could lead to a morning increase in cardiac events and produce a circadian rhythm of such events.

On the other hand, the mechanism of the second peak in the evening remains unclear. In a recent report from Japan on the circadian variation of cardiac arrest, factors related to the evening peak were examined [19]. They noted that most of the second peak was due to elderly patients (≥80 years old), a finding consistent with our present results.

However, they did not recognize a sex difference in the evening peak. In our study, we observed an evening peak of STEMI and found that this evening peak was caused by STEMI in elderly woman. The difference may have arisen because the other study investigated cardiac arrest, which includes arrhythmia, dissection of the aorta, etc. as well as STEMI. We limited the subjects to patients with STEMI and they all received CAG. This might have increased the certainty of diagnosis and precise identification of the onset time of STEMI.

Why did elderly women show a different circadian pattern of STEMI? For a long time, gender- and age-related differences have been reported in the field of circulatory disease. It has been reported that older women show some physiological differences compared to men.

The Framingham study revealed that ischemic heart disease developed ten years later in women compared with men and had a different clinical picture in females [26]. Mahon et al. [27] reported that the gender difference in AMI mortality is greatest for younger patients.

Our research demonstrated that older women have more severe cardiac failure and multivessel disease at admission.

Estrogen would be a probable candidate for the physiological differences between men and women, since many reports have suggested a protective effect of estrogen on vascular smooth muscle and the heart [28–31].

The influence of sex hormones on cardiac events is also suggested by the report that androgens influence the QT interval [32].

These reports may help to explain why elderly postmenopausal women display a peculiar circadian pattern with two peaks in the onset of STEMI.

Limitations

This study had the well-known limitations of a retrospective design and the results also represent a single-center experience. There is a possibility of reflecting the characteristic of the population of a specific area in Tokyo.

Compared with previous papers, the interest of our study is surely aged patients. In Japan, an aging society is in progress and the average onset age of AMI is going up with the development of optimal medical therapy in these years. We cannot deny that such facts may influence the contents of circadian variation.

Furthermore, we do not have enough information about transport prior to admission (self transport versus transfer from other hospitals without PCI facilities) and behavior at the onset of STEMI.

Conclusion

The present study of Japanese patients showed circadian variation of STEMI with 2 peaks in the morning and evening, and the second peak was dominated by elderly female patients.

References


