Effect of gender on circadian variations and outcome in ST-segment elevated anterior wall myocardial infarction patients

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Abstract

Background and Aim: The circadian rhythm is known to influence a number of physiological and pathological cardiovascular processes including the incidence of acute myocardial infarction. Therefore, in the present work the role of gender in anterior wall ST-Segment Elevated Myocardial Infarction (STEMI) patients have been studied.

Methods: In this hospital-based, cross-sectional study, 200 patients were chosen as per the selection criteria from among the acute myocardial infarction (MI) patients admitted in the Department of Cardiology, Medical College Hospital, Kottayam.

Results: Of the 200 subjects, 166 (83%) survived MI while 34 (17%) developed complications; statistical analytic tests applied between the time of onset of symptoms and the clinical outcome of the subjects were nonsignificant. A progressive increase was seen in the incidence of anterior wall myocardial infarction as age advances. There is a statistically significant higher occurrence of systemic hypertension in female subjects compared to the incidence of other comorbid illnesses among males and females.

Conclusion: Occurrence of STEMI shows the first peak between 6 AM and 12 Noon and the second peak was from 12 Noon to 6 PM. There is a statistically significant higher occurrence of systemic hypertension in female subjects compared to the incidence of other comorbid illnesses among males and females. There is no significant correlation between the time of onset of symptoms and complications in any particular gender. Mortality was higher in males and the deaths in each period were proportionate irrespective of the circadian pattern.

Key words: Anterior wall myocardial infarction, circadian rhythm, complications, gender

Received: 25th September, 2015; Revised: 09th January, 2016; Accepted: 10th February, 2016

INTRODUCTION

Circadian patterns of acute myocardial infarction (MI) were first described in 1976 by the World Health Organization Regional Office for Europe with a peak between 8:00 AM and 10:00 AM.11 The Multicenter Investigation of Limitation of Infarct Size study group in 19852 showed a circadian pattern of acute MI with peak incidence in the morning between 6:00 AM and 12:00 Noon. Thereafter, several studies have demonstrated a relationship between acute MI and circadian rhythm with varying patterns.3‑15 Several factors have been found to modify or attenuate the circadian pattern of acute MI including demographic factors,6,6 medications,2,4,6,8,9 comorbidities,6,6,10,11 and lifestyle choices.5‑7

Significant lifestyle changes have occurred in the intervening years, and the role of an individual’s gender in varying the risk for first attack of anterior wall ST-segment elevated myocardial infarction (STEMI) and its complications is the goal of the present study.

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Circadian clocks have been identified and characterized in almost all mammalian cell types, including cardiomyocytes, vascular smooth muscle cells, endothelial cells, and fibroblasts. Studies from multiple investigative teams over the last 25 years have begun to unravel a number of roles of circadian clocks within the cardiovascular system physiologically as well as in pathologic conditions such as acute MI. Most reports indicate an increased onset of the acute MI in the morning with a peak incidence between 6:00 AM and 12:00 Noon although the secondary peak in the late evening has also been reported in some studies. A circadian variation in onset of other manifestations of cardiac ischemia, usually with a late morning peak, has also been reported for sudden death, stable and unstable angina pectoris, and ST-segment changes of silent myocardial ischemia. A multicenter study by the World Health Organization showed only a morning peak in a large number of patients younger than 65 years of age. However, reports are scanty in Indian population, and the influence of gender on circadian variation in MI is underreported.

MATERIALS AND METHODS

Study population
The present study was done on 200 patients with the first attack of anterior wall myocardial infarction (AWMI) (163 males and 37 females) chosen as per the inclusion and exclusion criteria from among the acute MI patients admitted in the Department of Cardiology, Medical College Hospital, Kottayam, from June 2004 to September 2005.

Patients aged 30 years and above with the first attack of acute anterior wall STEMI presenting at the ICCU in the Department of Cardiology, Medical College, Kottayam, were included in the study. Patients with uncontrolled diabetes mellitus or systemic hypertension/patients with any other associated heart disease such as valvular heart disease or cardiomyopathy or blocks/patients admitted in Killip’s Class IV/patients with preceding angina were excluded from the study. After getting the Ethics Committee approval, informed consent was obtained from the study participants before collecting the data. Details of the demographic and clinical variables were recorded in the proforma, and the time of onset of symptoms and occurrence of complications were obtained from the ICCU medical history where this parameter is systematically recorded.

Statistical analysis of data
Data collected from the patients were entered in the proforma. SPSS of Windows version 10, EpiInfo Version 1.1 program developed by Centers for Disease Control and Prevention (CDC) in Atlanta, Georgia (USA), was utilized for data analysis. Student’s t-test was applied to ensure the comparability of data. Association between variables was assessed using Pearson Chi-square test.

Definitions
ST-segment elevated anterior wall myocardial infarction
This was defined by the following current clinical practice guidelines: Typical chest pain of ≥30 min and significant ST-segment elevation (≥0.1 mV or ≥0.2 mV on ≥2 adjacent limb or precordial leads (Minnesota code), respectively, or new left bundle-branch block) and confirmed by a rise in biomarkers more than twice the upper limit of normal.

Time of symptom onset and of complications
Time-of-day of STEMI onset was first divided into four 6-h periods according to the previous studies; Period 1: 12 Midnight – 6:00 AM, Period 2: 6:00 AM–12 Noon (dark-to-light transition); Period 3: 12 Noon–6 PM; Period 4: 6 PM–12 Midnight.

RESULTS

Circadian variations
The occurrence of anterior wall STEMI followed a circadian pattern with the first early morning peak between 6 AM and 12 Noon with 75 (37.5%) cases and the second peak from 12 Noon to 6 PM with 53 (26.5%) arrhythmias being the most frequent complication in all the periods. Of the 200 subjects, 166 (83%) survived MI while 34 (17%) went in for complications. The occurrence of the complications was analyzed further. Arrhythmias were the most frequent complication seen in 7 (35%) out of 20 subjects in the 12 Noon–6 PM quarter. Among the 4 subjects who developed left ventricular failure, the majority 3 (60%) subjects, had symptom onset in the 6 AM–12 Noon period. Mortality was maximum in the period 12 Midnight–6 AM for 4 (40%) out of 10 subjects. Application of statistic analytic tests reveals a nonsignificant Chi-square test, \( P = 0.363 \). These results are shown in Table 1.

Sociodemographic profile
Of the 200 subjects, 163 (81.5%) were males and 37 (18.5%) were females, their age ranging from 30 to 92 years. The mean age was 57.41 years.

The subjects were categorized according to their age and gender into four groups of ≤40 years, 41–50 years, 51–60 years, and ≥61 years. There was a progressive increase in the incidence of AWMI as age advances. This age- and gender-wise distribution are shown in Table 2. Ten percent of the study subjects were young (≤40 years
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Table 1: The time of onset of symptoms and the complications developed during each at time period

<table>
<thead>
<tr>
<th>Time</th>
<th>Survived</th>
<th>Arrhythmia</th>
<th>LVF</th>
<th>Died</th>
<th>Total (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>12 Midnight to 6 AM:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Period 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Count</td>
<td>30</td>
<td>5</td>
<td>1</td>
<td>4</td>
<td>40</td>
</tr>
<tr>
<td>Percentage within time</td>
<td>75.0</td>
<td>12.5</td>
<td>2.5</td>
<td>10.0</td>
<td>100.0</td>
</tr>
<tr>
<td>Percentage within outcome</td>
<td>18.1</td>
<td>25.0</td>
<td>25.0</td>
<td>40.0</td>
<td>20.0</td>
</tr>
<tr>
<td>6 AM to 12 Noon:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Period 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Count</td>
<td>68</td>
<td>4</td>
<td>2</td>
<td>1</td>
<td>75</td>
</tr>
<tr>
<td>Percentage within time</td>
<td>90.7</td>
<td>5.3</td>
<td>2.7</td>
<td>1.3</td>
<td>100.0</td>
</tr>
<tr>
<td>Percentage within outcome</td>
<td>41.0</td>
<td>20.0</td>
<td>50.0</td>
<td>10.0</td>
<td>37.5</td>
</tr>
<tr>
<td>12 Noon to 6 PM:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Period 3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Count</td>
<td>43</td>
<td>7</td>
<td>1</td>
<td>2</td>
<td>53</td>
</tr>
<tr>
<td>Percentage within time</td>
<td>81.1</td>
<td>13.2</td>
<td>1.9</td>
<td>3.8</td>
<td>100.0</td>
</tr>
<tr>
<td>Percentage within outcome</td>
<td>25.9</td>
<td>35.0</td>
<td>25.0</td>
<td>20.0</td>
<td>26.5</td>
</tr>
<tr>
<td>6 PM to 12 Midnight:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Period 4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Count</td>
<td>25</td>
<td>4</td>
<td>0</td>
<td>3</td>
<td>32</td>
</tr>
<tr>
<td>Percentage within time</td>
<td>78.1</td>
<td>12.5</td>
<td>0.0</td>
<td>9.4</td>
<td>100.0</td>
</tr>
<tr>
<td>Percentage within outcome</td>
<td>15.1</td>
<td>20.0</td>
<td>0.0</td>
<td>30.0</td>
<td>16.0</td>
</tr>
<tr>
<td>Total</td>
<td>166</td>
<td>20</td>
<td>4</td>
<td>10</td>
<td>200</td>
</tr>
<tr>
<td>Count</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Percentage within time</td>
<td>83.0</td>
<td>10.0</td>
<td>2.0</td>
<td>5.0</td>
<td>100.0</td>
</tr>
<tr>
<td>Percentage within outcome</td>
<td>100.0</td>
<td>100.0</td>
<td>100.0</td>
<td>100.0</td>
<td>100.0</td>
</tr>
</tbody>
</table>

LVF: Left ventricular function

Table 2: Age-and sex-wise distribution of study subjects

<table>
<thead>
<tr>
<th>Age group (years)</th>
<th>Males (n=163) (%)</th>
<th>Females (n=37) (%)</th>
<th>Total (n=200) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤40</td>
<td>20 (12.3)</td>
<td>0 (0)</td>
<td>20 (10)</td>
</tr>
<tr>
<td>41-50</td>
<td>39 (23.9)</td>
<td>4 (10.8)</td>
<td>43 (21.5)</td>
</tr>
<tr>
<td>51-60</td>
<td>52 (31.9)</td>
<td>8 (21.6)</td>
<td>60 (30)</td>
</tr>
<tr>
<td>≥61</td>
<td>52 (31.9)</td>
<td>25 (67.6)</td>
<td>77 (38.5)</td>
</tr>
</tbody>
</table>

of age) and all of them were males. Males were maximally affected in the age group 51–60 years followed by age groups ≥61 years and 41–50 years. About two-thirds of affected females were above 60 years of age. A maximum number of females with AWMI were in the age group ≥61 years followed by 51–60 years age group (25 [67.6%] and 8 [21.6%]).

On studying the risk factors, 72 (44%) males were smokers which had a highly significant P value (male–female difference: 0.0001). Twenty-four (15%) males were alcoholics. There were no alcoholics/smokers among females. Eighty percent of diabetics and 62.5% of systemic hypertensives were males. About 87.5% of subjects with family history of CAD were also males. In comparison, females constituted 20% of diabetics, 37.5% of systemic hypertensives, and 12.5% of family history of CAD. The presence of diabetes mellitus was found to be more frequent in male AWMI patients >50 years of age [Table 3]. However, the association of age and gender with the occurrence of diabetes mellitus was not significant in any age group. These results are depicted in Figure 1. There is a statistically significant higher occurrence of systemic hypertension in female subjects compared to the incidence of other comorbid illnesses among males and females (P value of male–female difference: 0.0001). These findings are recorded in Table 3. Association of age and gender with comorbid illnesses was studied. Twenty-seven (45%) subjects (both males and females) in the age group 51–60 years and 22 (29%) subjects ≥61 years showed statistically significant occurrence of systemic hypertension with P = 0.018 and 0.001 in the two age groups, respectively. AWMI was more frequent in females of 51–60 years of age with systemic hypertension (75% female vs. 29% male) and in females ≥61 years of age (68% female vs. 29% male). Systemic hypertension was the most frequent comorbid illness more significantly associated with females, 24 (65%) and the P value of male–female difference was 0.0001 [Figure 1].

DISCUSSION

Circadian variation in the levels of cortisol, circulating epinephrine levels, coronary flow, blood viscosity, endogenous thrombolytic activity, and platelet aggregability is a well-known phenomenon. Our study demonstrates the early morning peak in MI from 6 AM to 12 Noon quarter (37.5%) which correlates with western literature and could be due to the increase in physical and mental stress after waking. Sympathetic activity increases after waking and plasma concentrations of catecholamine also increase. Cortisol concentration peaks early in the morning, generally before waking, and it remains high but falls during the period after awakening.
Systemic arterial pressure,[28] coronary vascular tone,[29] and platelet aggregability,[30] also increase in the early morning. Although fibrinolytic activity is low during sleep and still reduced soon after awakening, it rises during this time.[21] The second peak from 12 Noon to 6 PM quarter (26.5%) observed in our study is similar to the recent observations made by Sari et al. and Misiriya et al.[32,33] The exact reason for this phenomenon remains obscure though genetic variations of the study population,[32] and a prothrombotic state during physical inactivity after lunch[34] may be the possible explanations.[32] There is evidence of differing circadian patterns of symptom for the onset in subgroups of patients with acute MI as in patients with a history of congestive heart failure, or with non-Q wave infarction, there was a pronounced peak only in the evening.[35,36]

To study the circadian pattern further, we assessed some sociodemographic parameters such as age, gender, habits, and comorbid illnesses. The mean age at presentation of patients with STEMI was 57.41 years in this study, which is comparable to observations of CREATE Registry (57.5 years).[37] Male preponderance was observed in the patients with STEMI at all age-groups and the sex ratios observed in both the younger and older age-groups were comparable to the sex ratios observed in another series reported from North India.[38]

In our study population, habits such as smoking and alcoholism were adopted only by males. Behavioral influences, such as mental activity and emotional state,[39] and lifestyle factors, such as smoking cigarettes and drinking alcohol, have been shown to affect the natural rhythm of blood pressure (BP).[40] Smoking can result in coronary atherosclerosis leading to increased risk of myocardial infarction. By increasing myocardial oxygen demand and decreasing oxygen supply, myocardial ischemia is aggravated. Smoking also can result in systemic hypertension which if sustained, leads to left ventricular hypertrophy, and is thus a major risk factor for ischemic heart disease. A maximum of one or two alcoholic drinks per day over long periods may decrease the risk of cardiovascular death; perhaps through an increase in high-density lipoprotein cholesterol or changes in clotting mechanism. However, heavy drinking is an important contributor to mild to moderate systemic hypertension that could lead to ischemic heart disease.

Disruption of the circadian clock can cause severe disturbances in our body’s endocrine rhythms and the impact of comorbid endocrine disorders such as diabetes mellitus on the morning peak incidence of acute myocardial infarction (AMI) has been reported.[41] Some authors have reported that the early morning peak incidence of AMI is attenuated in patients with diabetes,[42] while others have observed a similar peak incidence of AMI onset in the sleep-to-wake period.[43] In addition to diabetes, the glucose levels at the time of AMI onset have been associated with poor outcomes in patients with diabetes.[44] Even though the levels of blood glucose are also regulated by the circadian rhythm, the 24-h glucose and insulin secretion rate rhythms are only partially adapted in permanent night workers,[45] and essentially retain their circadian pattern. Increased incidence of large vessel atherosclerosis and myocardial infarction is seen in diabetic patients. Further, their myocardial infarction tends to be larger in size and is more likely to result in complications such as heart failure, shock, and death.

BP rises sharply in the morning in response to the activation of the sympathetic nervous system when one awakens.[40,46] This early morning surge is associated with other important hemodynamic and neurohormonal changes, including increase in heart rate, vascular tone, and blood viscosity and decrease in vagal activity.[46] Early morning BP surge is associated with an increase in the incidence of cardiovascular events such as MI.[2] Our study shows a highly statistically significant (P value of male-female difference was 0.0001) association of AWMI with systemic hypertension in female subjects. AWMI was more frequent in female hypertensives who are >50 years of age.

**Table 3:** Frequency of risk factors among study subjects

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>Total (n=200)</th>
<th>Males (n=163)</th>
<th>Females (n=37)</th>
<th>P value of male-female difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoking</td>
<td>72 (36)</td>
<td>72 (44)</td>
<td>0 (0)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>60 (30)</td>
<td>48 (29)</td>
<td>12 (32)</td>
<td>0.721</td>
</tr>
<tr>
<td>Systemic hypertension</td>
<td>64 (32)</td>
<td>40 (25)</td>
<td>24 (65)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Family history of coronary artery disease</td>
<td>13 (6.5)</td>
<td>11 (7)</td>
<td>2 (5)</td>
<td>0.765</td>
</tr>
</tbody>
</table>
Manfredini et al. have studied that the time of symptom onset could potentially influence mortality in acute MI since little is known about the possible influence of circadian pattern on prognosis in MI. It was seen that not only the frequency but also the mortality in acute MI could be increased in the morning hours. This correlates with our finding of highest mortality of 40% in the period 12 Midnight–6 AM. Gender-wise difference could not be assessed as this complication affected only males (in our study) and 6 (60%) of them were >50 years of age, but the number of deaths in each period was proportionate irrespective of the circadian pattern. However, mortality rate was lesser among our STEMI cases compared to the mortality rate observed among cases from the CREATE Registry 12 (5% vs. 8.6%), which could be due to improved hospital care.

Limitations of the study
The number of females recruited in the study was comparatively less, and hence, the nonsignificant statistical test results may be attributed to this less number of subjects. A higher sample size could increase the power of the study.

CONCLUSION
The occurrence of AWMI showed the first early morning peak between 6 AM and 12 Noon and the second peak from 12 Noon to 6 PM with arrhythmias being the most frequent complication in all the periods. There was a progressive increase in the incidence of AWMI with increasing age, and younger males and elderly females were the most affected. There is a statistically significant higher occurrence of systemic hypertension in female subjects compared to the incidence of other comorbid illnesses among males and females. Our study reports that males, especially those >50 years of age, have higher mortality rates. Diabetic patients with STEMI have greater risk for death. Females, elderly individuals, and those with systemic hypertension and diabetes mellitus should be managed more carefully to reduce the mortality rates.

Acknowledgments
We gratefully acknowledge all the volunteers involved in this study. We also acknowledge the help provided by Dr. V.S. Sumadevi and Dr. K.P. Kalyanikutty, Professor in Physiology Department for all the help provided.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

REFERENCES
20. Beamer AD, Lee TH, Cook EF, Brand DA, Rouan GW,
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