Circadian pattern of symptom onset in patients with ST-segment elevation myocardial infarction in western Iran

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Original Article

Abstract

BACKGROUND: Circadian variation is known as an important factor in acute myocardial infarction (AMI). Moreover, the circadian pattern may help in disease prevention and better medication prescription. Therefore, the aim of our study was to investigate the circadian pattern of symptom onset in patients with ST-segment elevation myocardial infarction (STEMI).

METHODS: This cross-sectional study was conducted on 777 patients admitted to the Imam Ali Cardiovascular Center, Kermanshah, Iran, with a diagnosis of STEMI from March 2018 to February 2019. Data were collected using a checklist developed based on the study's objectives. Differences between subgroups were assessed using one-way analysis of variance (ANOVA) with post-hoc testing and chi-square test (or Fisher's exact test).

RESULTS: Out of the 777 patients, 616 (79.3%) were men. The mean and standard deviation (SD) of age of the patients was 60.93 ± 12.86 years. 380 patients (48.9%) were current smoker, 40.3% were hypertensive, 21.1% had hypercholesterolemia, 18.3% had diabetes mellitus (DM), 25.2% had history of angina, and about 15.0% had history of myocardial infarction (MI). The occurrence of STEMI was most common during hours between 06:01-12:00 (27.7%), followed by 12:01-18:00 (27.3%), 00:00-06:00 (24.3%), and 18:01-24:00 (20.7%), respectively. Gender was significantly associated with circadian pattern of STEMI. Women showed a double peak of symptom onset in 06:01-12:00 and 12:01-18:00.

CONCLUSION: The present study of Iranian patients displayed circadian pattern of STEMI with 2 peaks in the morning and afternoon, and the both peaks were dominated by women.

Keywords: Circadian Rhythm; Myocardial Infarction; Iran

Introduction

Acute myocardial infarction (AMI) is a leading cause of cardiovascular death and disability across the world.[1] ST-segment elevation myocardial infarction (STEMI), a classic heart attack, is the most deadly sub-class of myocardial infarction (MI), accounting for more than 35% of MI cases. Some physiological factors may trigger MI, and a number of these factors are known to fluctuate with circadian pattern.[2] In turn, circadian patterns affect cardiovascular physiology by varying in multiple biologic functions such as heart rate, blood pressure (BP), cardiac output, endothelial function, and hormone production and release.[3]

Circadian rhythms of MI were first explained by the World Health Organization-Regional Office for Europe (WHO-Europe) in 1976, which reported a peak incidence in the symptom onset between 8:00 am and 10:00 am (on waking and when resuming activity).[4] Furthermore, epidemiological studies have well documented that the onset of MI significantly changes through the day, with a morning peak (06:00-12:00) in the MI symptoms onset and a secondary peak incidence at night-time.[5,6]

The reasons for morning peak in the MI symptoms onset have been partially illuminated and may be due to the morning BP, platelet agreeability,

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releasing asymmetric dimethylarginine (ADMA), coagulation parameters, lipoprotein levels, decreasing the fibrinolytic activity, and sympathetic neurotransmission.[2,7,8] Although, exogenous factors like sleep deprivation, emotional stress, activity levels, geographic location, and etc. may also modulate these variations.[9]

As MI is the leading cause of mortality in the developed and developing countries, primary prevention of MI is a basic healthcare issue worldwide.[1] Also, new therapeutic approaches based on circadian rhythms have led to the better timing of drugs and treatments to optimize outcomes and minimize adverse effects.[10] Accordingly, identifying the circadian patterns of symptom onset in patients with MI may help in the clinical management of patients to prevent the onset of MI.

Despite a morning peak in the MI symptoms onset, most researchers have reported a relationship between MI symptoms onset and circadian rhythm with varying patterns.[11,12] Moreover, differences in the circadian rhythms of MI in different regions of the world and in different ethnic groups have also been reported.[13] Therefore, the aim of our study was to investigate the circadian pattern of symptoms onset in patients with STEMI.

Materials and Methods

This cross-sectional study was conducted in Imam Ali Cardiovascular Center, Kermanshah University of Medical Sciences, Kermanshah, Iran. The mega general hospital, Imam Ali, with 280 active beds is the main cardiovascular center in western Iran, covering about two millions population mostly Kurdish with Caucasian race.

With the aim of one-year evaluation of patients, one-year data of the patients admitted to the center with a diagnosis of STEMI were assessed. Between March 1, 2018, and February 30, 2019, we evaluated all patients (convenience sampling) who were admitted to the center with a diagnosis of STEMI. In fact, we included all patients based on inclusion criteria. One criterion for inclusion in the study was age ≥ 18 years old. Criteria for the diagnosis of STEMI were based on third universal definition of MI defined by the European Society of Cardiology/American College of Cardiology (ACC)/American Heart Association (AHA)/World Heart Federation (WHF) Task Force for the Universal Definition of Myocardial Infarction.[14] The diagnosis of STEMI was accompanied by the following elements: 1) characteristic chest pain or discomfort 2) electrocardiographic (ECG) changes

consistent with new ST-segment elevations or left bundle branch block (LBBB), and 3) elevated markers of MI [creatine kinase-myocardial band (CK-MB), troponins, and etc.]. Those with incomplete personal or medical information were excluded. Although, response rate was 100%.

The Research Ethics Committee of Kermanshah University of Medical Sciences approved the study protocol. In addition, individual personal information has been kept confidentially.

Data were collected by a research assistant who was well trained in data gathering, and using a checklist developed based on the study goals. The checklist was evaluated and verified by expert opinions compromising a statistician and two cardiologists. The checklist comprised five following parts: demographic characteristics (e.g., age), clinical histories (e.g., previous MI), medication (e.g., aspirin), cardiac enzyme (e.g., CK-MB), and the time of onset of MI.

We collected the data from both paperwork records and electronic medical records to move bias from abstracting records. Furthermore, the results were tested through checking hospital managerial information.

Data analysis was performed using SPSS statistical software (version 23.0, IBM Corporation, Armonk, NY, USA). Quantitative variables [e.g., body mass index (BMI) or age] were described using mean ± standard deviation (SD) and qualitative/categorical variables were expressed as frequencies and percentages. Differences between subgroups were assessed using one-way analysis of variance (ANOVA) for continuous and normally-distributed variables and chi-square test (or Fisher's exact test) for categorical variables. A probability value (P-value) of less than 0.05 was considered statistically significant.

Results

During 12 months, a total of 777 patients, 616 (79.3%) men and 161 (20.7%) women, met the inclusion criteria for this study. The mean age of the patients was 60.93 ± 12.86 years, ranging from 19 to 95 years. 380 patients (48.9%) were current smoker, 40.3% were hypertensive, 21.1% had hypercholesterolemia, 18.3% had diabetes mellitus (DM), 25.2% had history of angina, and about 15.0% had history of MI. All of the patients' demographic and clinical characteristics are shown in table 1.

We classified the day into the four six-hour intervals from 00:00 to 06:00, 6:01 to 12:00, 12:01 to 18:00, and 18:01 to 24:00.

Table 1. The demographic and clinical characteristics of patients (n = 777)

| Value	Variable
Age (year)*	60.93 ± 12.86
BMI (kg/m^2)*	25.95 ± 0.87
Sex (male)	616 (79.3)
Prior MI	116 (14.9)
Prior angina	196 (25.2)
Prior CHF	28 (3.6)
Prior stroke	47 (6.0)
Prior AF	16 (2.1)
Prior PCI	67 (8.6)
Prior CABG	31 (4.0)
Current smoker	380 (48.9)
Diabetes	142 (18.3)
HTN	313 (40.3)
Hypercholesterolemia	164 (21.1)
Cancer	7 (0.9)
Aspirin user	215 (27.7)
Clopidogrel user	34 (4.4)
ARB user	86 (11.1)
β-blocker user	165 (21.2)
ACE inhibitors user	149 (19.2)
Statin user	106 (13.6)
CK-MB (U/l)	140.29 ± 116.58
CPK (U/l)	1656.87 ± 1215.35
Troponin (ng/ml)	13.34 ± 63.50
LDH (U/l)	337.69 ± 153.73
EF (%)	37.18 ± 10.65

* Continuous variables are expressed as mean ± standard deviation (SD), others as number (%)
BMI: Body mass index; MI: Myocardial infraction; CHF: Congestive heart failure; AF: Atrial fibrillation; PCI: Percutaneous coronary intervention; CABG: Coronary artery bypass grafting; HTN: Hypertension; ARB: Angiotensin receptor blockers; ACE: Angiotensin converting enzyme; CK-MB: Creatine kinase myocardial band; CPK: Creatine phosphokinase; LDH: Lactic acid dehydrogenase; EF: Ejection fraction

The frequency of symptom onset by a 24-hour period was shown in figure 1A. The occurrence of STEMI was most common during 06:01-12:00 (27.7%), followed by 12:01-18:00 (27.3%), 00:00-06:00 (24.3%), and 18:01-24:00 (20.7%), respectively (Figure 1B).
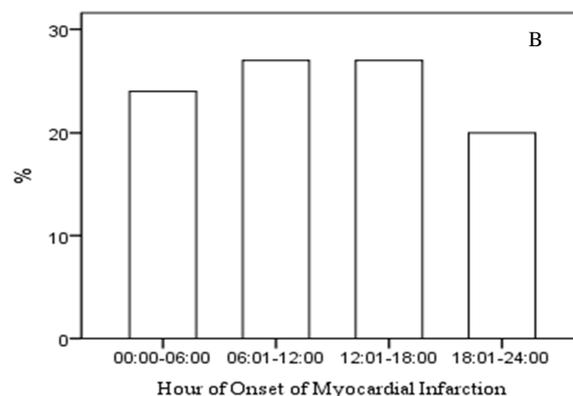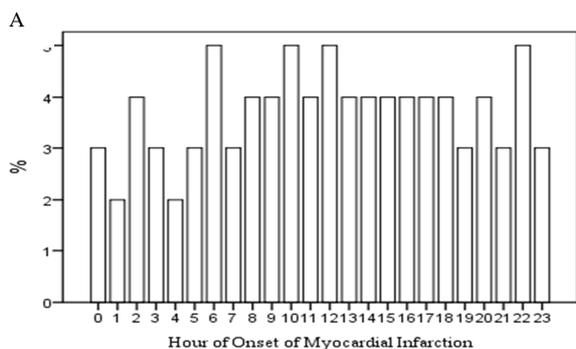
Figure 1. Distribution of symptom onset of ST-segment elevation myocardial infarction (STEMI) by a 24-hour period (A) and by the four six-hour intervals (B)

Sex was significantly associated with circadian pattern of STEMI (P = 0.022) (Table 2). A Bar graph was drawn to show the pattern of symptom onset of STEMI based on gender. Accordingly, women showed a double peak of symptom onset in 06:01-12:00 and 12:01-18:00 (Figure 2).
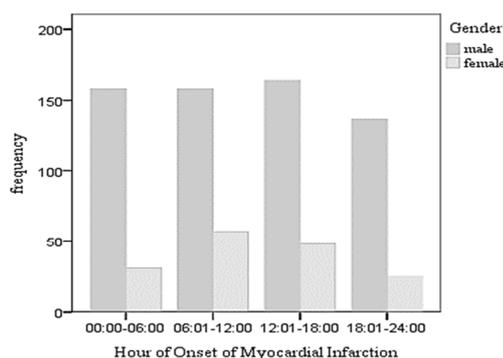
Figure 2. The pattern of symptom onset of ST-segment elevation myocardial infarction (STEMI) stratified by gender

Discussion

This cross-sectional study aimed to evaluate the circadian pattern of symptom onset in patients admitted with a diagnosis of STEMI in Imam Ali Cardiovascular Center at Kermanshah University of Medical Sciences between March 2018 to February 2019. The results of this study illustrated that Iranian patients showed circadian pattern of STEMI with two peaks, the first peak in the morning and the second peak in the afternoon.

Our results concur with the findings of previous studies. Itaya et al. reported two peaks in the onset of STEMI in Japanese population, with the first peak in the morning and the second peak in the evening.[10]

Table 2. Association of various characteristics and circadian patterns of ST-segment elevation myocardial infarction (STEMI) (n = 777)

Characteristic	00:00-06:00 (n = 189)	06:01-12:00 (n = 215)	12:01-18:00 (n = 212)	18:01-24:00 (n = 161)	P
Age ≥ 60 years	91 (50.8)	116 (55.8)	103 (50.5)	68 (44.4)	0.209[**]
BMI ≥ 25 kg/m^2	108 (57.1)	113 (52.6)	123 (58.0)	100 (62.1)	0.216[**]
Sex (female)	31 (16.4)	57 (26.5)	48 (22.6)	25 (15.5)	0.022[**]
Current smoker	97 (51.3)	93 (43.3)	102 (48.1)	88 (54.7)	0.196[**]
Diabetes	38 (20.1)	45 (20.9)	29 (13.7)	30 (18.6)	0.328[**]
HTN	79 (41.8)	88 (40.9)	79 (37.7)	67 (41.6)	0.888[**]
Hypercholesterolemia	41 (21.7)	45 (20.9)	50 (23.6)	28 (17.4)	0.477[**]
Prior CHF	7 (3.7)	9 (4.2)	6 (2.8)	6 (3.7)	0.522[***]
Prior MI	29 (15.3)	33 (15.3)	30 (14.2)	24 (14.9)	0.393[**]
Prior angina	44 (23.3)	62 (58.8)	53 (25.0)	37 (23.0)	0.512[**]
Prior stroke	14 (7.4)	16 (6.0)	8 (3.8)	12 (7.5)	0.376[**]
Prior AF	3 (1.6)	4 (1.9)	7 (3.3)	2 (1.2)	0.492[***]
Aspirin user	39 (20.6)	68 (31.6)	62 (29.2)	46 (28.6)	0.082[**]
Clopidogrel user	2 (1.1)	13 (6.0)	11 (5.2)	8 (5.0)	0.076[**]
β-blocker user	29 (15.3)	54 (25.1)	46 (21.7)	36 (22.4)	0.111[**]
ARB user	16 (8.5)	28 (13.0)	25 (11.8)	17 (10.6)	0.514[**]
ACE inhibitors user	40 (21.2)	42 (19.5)	34 (16.0)	33 (20.5)	0.567[**]
Statin user	20 (10.6)	29 (13.5)	37 (17.5)	20 (10.4)	0.449[**]
CK-MB (U/l)	145.30 ± 131.12	138.75 ± 108.22	142.09 ± 115.12	134.26 ± 112.66	0.844[*]
CPK (U/l)	1648.98 ± 1234.90	1671.29 ± 1194.06	1674.94 ± 1216.70	1621.67 ± 1232.21	0.978[*]
Troponin (ng/ml)	15.86 ± 79.41	13.24 ± 49.12	14.94 ± 82.03	8.48 ± 7.30	0.730[*]
LDH (U/l)	340.00 ± 158.62	239.75 ± 90.01	325.50 ± 79.04	427.00 ± 228.64	0.359[*]

Continuous variables are expressed as mean ± standard deviation (SD), others as number (%)
[*] Analysis of variance (ANOVA); [**] Chi-square test; [***] Fisher's exact test
BMI: Body mass index; HTN: Hypertension; CHF: Congestive heart failure; MI: Myocardial infraction; AF: Atrial fibrillation; ARB: Angiotensin receptor blockers; ACE: Angiotensin converting enzyme; CK-MB: Creatine kinase myocardial band; CPK: Creatine phosphokinase; LDH: Lactic acid dehydrogenase

Rallidis et al. reported that the onset of STEMI was higher during 06:01-12:00 and 12:01-18:00;[15] this observation is consistent with the present findings. In agreement with our study, Gallerani et al.[16] and Park et al.[17] showed that the risk of experiencing MI was increased during the morning. Moreover, Sari et al. reported that incidence of MI between 12:01 and 18:00 was higher than other three 6-hour periods, demonstrating afternoon peak.[13]

Nevertheless, some researchers have reported contradictory results. A report from China demonstrated a peak of symptom onset between 01:00 and 07:00.[18] In contrast, Sumiyoshi et al. reported that onset of AMI was more common in the evening than in the morning.[19] Conversely, a peak from 00:01 to 06:00 for MI onset in the Chinese patients has been reported by Chan et al. in 2012.[12]

For a long time, studies have demonstrated that the onset of MI mostly occurs in the morning hours.[5,20,21] In addition to the morning peak, a secondary peak of MI onset in the evening hours has been reported in some earlier studies.[22,23] This peak was absent in our study as well as in two studies conducted by Leiza et al.[24] and Holmes et al.[25] Actually, although the circadian pattern with a secondary peak of MI onset between 12:01 and 18:00 in the present study is discordant with the western populations, it is similar with the Bulgarian populations.[26] Furthermore, our data are partly similar with the report from Argentine and Uruguay.[27]

The mechanism of a morning peak in AMI onset is well known. In the morning, sympathetic activity and platelets aggregation increase while fibrinolytic activity decreases.[23,28] These changes lead to altered hemostasis and an unbalance between myocardial oxygen store and demand, possibly resulting in thrombotic events in patients. It has long been speculated that the BP increases in morning due to the basal vascular tone changes related to α-sympathetic vasoconstrictor activity.[29] Other changes include renin activity, increased heart rate, and plasma concentrations of cortisol, adrenaline, epinephrine, norepinephrine, and angiotensin II.[30,31] Cortisol may further enhance sensitivity of the coronary vessels to the vasoconstrictor effects of catecholamines, and also, increased plasma levels of epinephrine and norepinephrine may increase vascular resistance in the morning.[32,33] Moreover, hemostatic changes, external triggers, and variations in gene expression

may make a shear stress resulting in atherosclerotic plaque disruption and thrombosis in the morning.[34]

We found that women had two dominant peaks of symptom onset in the morning and afternoon. Itaya et al. reported that men had a dominant peak of symptom onset in the morning (06:01-12:00) and women had two peaks of symptom onset in morning and evening, respectively.[10] Kinjo et al. from Japan reported that women aged 65 years or more showed a morning peak.[35] Gilpin et al. observed a unique pattern of occurrence in female patients with two peaks in the morning and evening,[36] while Leiza et al.[24] and Hansen et al.[37] observed no effect of sex.

For a long time, a sex-based difference has been reported in the field of cardiovascular diseases. In fact, women present some physiological differences compared to men. The effect of sex hormones on cardiac events is obviously reported.[38] This report may help to illustrate why women show a different circadian pattern compared to men in the onset of STEMI.

Conclusion

The present study of Iranian patients displayed circadian pattern of STEMI with 2 peaks in the morning and afternoon, and the both peaks were dominated by women. The results of the current study make clear that circadian pattern of AMI onset with morning and evening peaks may not be applicable worldwide; rather, we can mention 'population pattern' which needs to be illuminated for every population. The factors that are known to affect circadian pattern of MI onset may not be equally effective in all populations.

Limitations: This study had the well-known limitations of a cross-sectional design and our data were derived from a single center. Hence, our participants may not be the representative of the whole STEMI population. However, findings are almost consistent with those in the literature.

Acknowledgments

Conflict of Interests

Authors have no conflict of interests.

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