ORIGINAL ARTICLE

INFLUENCE OF CIRCADIAN VARIATIONS ON ONSET AND IN-HOSPITAL OUTCOME OF FIRST ACUTE MYOCARDIAL INFARCTION

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ABSTRACT

Objective: To evaluate the influence of circadian variations on the onset and in-hospital outcome of first acute myocardial infarction (AMI).

Materials And Methods: After fulfilling the inclusion criteria 425 patients presenting with new onset acute myocardial infarction were studied. The study patients were divided into 4 groups according to time of onset of symptoms. Group I consisted of 67(15.8%) patients presenting during 0-6 hours interval, Group II 118(27.7%) patients presenting during 6:01-12 hours, Group III 144(33.9%) patients presenting in 12:01-18 hours and Group IV comprised of 96(22.6%) patients having onset of AMI during 18:01-24 hours. Cardiovascular risk factors and in-hospital outcome were compared between the groups by applying Chi Square test.

Results: Two peaks of onset of symptom were observed, first between 12:01-18 hours 144(33.9%) patients and the second between 6:01-12 hours 118(27.7%) patients. The trough was early morning time 0-6 hours when only 67(15.8%) patients had acute MI. Mean age of the study population was 54.5±12.3 years. There were 337(79.3%) males and 88(20.7%) females. There were 114(26.8%) diabetics, 138(32.5%) hypertensives and 215(50.6%) smokers. Majority of patients 168(39.5%) presented 3-6 hours after the onset of symptoms. Overall 100(23.5%) patients presented to the hospital within 3 hours of onset of symptoms. Overall 173(40.7%) patients had anterior wall myocardial infarction followed by Anterospetal wall myocardial infarction in 147(34.6%) patients. In Group IV patients there was more 9(6.3%) tendency of presenting in advanced Killip class followed by Group II 7(5.9%) and 4(2.8%) in Group III p<0.485. Overall 201(47.3%) patients received streptokinase therapy. Overall in-hospital mortality was 62(14.8%), mortality was higher 22(18.6%) in Group II, followed by 14(14.6% in Group IV, 19(13.2%) in Group III and 8(11.9%) in Group I p<0.113. Left ventricular failure was the common cause 45(10.6%) of in-hospital mortality.

Conclusion: The onset time of AMI has bimodal appearance with an early peak at 12:01-18 hours and a second lesser peak at 6:01-12 hours. In-hospital mortality was higher in patients presenting between 6:01-12 hours because of more frequency of advanced killip class at the time of presentation in this Group.

Key Words: Acute myocardial infarction; Coronary artery disease; Circadian variations; Diabetes Mellitus; Mortality.

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INTRODUCTION

Atherosclerotic coronary artery disease (CAD) is projected to become the leading cause of global morbidity and mortality by 2020; this trend has grave implications for countries in South Asia.[1] Cardiovascular diseases are major causes of morbidity and mortality in the Indian subcontinent causing more than 25% of deaths.[1,2] In the United States nearly 1.5 million patients annually suffer from acute myocardial infarction (AMI).[2] For the last 3 decades there has been great interest in evaluation of underlying pathophysiological triggering

mechanisms responsible for the occurrence of AMI.[3]

The morning peak of the onset of AMI is well-known and has been reported in numerous studies.[4] It has been proposed that, increased sympathetic activity, elevated plasma catecholamine levels, increase in heart rate, blood pressure, platelet reactivity and coronary tone and altered endothelial function were among predisposing factors causing atherosclerotic plaques to rupture in the morning.[5-7]

Studies done in Turkey, Bulgaria, Uruguay have revealed peaks of AMI occurrence other than morning hours.[3,8-12]

Adverse prognosis after AMI has been associated with factors such as advanced age, larger infarcts, left ventricular systolic dysfunction,[13-15] and conditions in which a disproportionate sympathetic activation is known to occur.[15]

Data from randomized clinical trials[16] coupled with parallel angiographic studies have provided unequivocal proof that achievement of myocardial reperfusion is largely responsible for the observed health benefits.[17] In addition, the "time-dependent" impact of fibrinolytic therapy[18] has been demonstrated consistently and provides incontrovertible support for increased patient survival, decreased infarct size, and improved left ventricular performance with early successful reperfusion.[18] In-hospital death rates for patients enrolled in the National Registry of Myocardial Infarction (NRMI) were similar for each reperfusion modality (primary angioplasty 5.2%, fibrinolytics 5.4%).[19]

This study was designed to evaluate the impact of circadian variations on onset and in-hospital outcome of first acute myocardial infarction.

MATERIALS AND METHODS

Four hundred and twenty five consecutive patients of acute myocardial infarction hospitalized in Coronary Care Unit and Cardiology ward of Nishtar Hospital Multan from 1st October 2006 till 30th April 2007, were included in this descriptive study.

Patients were included in the study on the basis of these criteria.

a) Patients presenting with first acute myocardial infarction were included in the study on the basis of any two of the following criteria: 1) Chest pain consistent with acute myocardial infarction. 2) i. Electrocardiographic changes; ST segment elevation >0.2mv in at least two contiguous chest leads or > 0.1 mv in at least two contiguous limb leads or ii. New or presumably new left bundle branch block. 3) Elevated levels of cardiac enzyme CK-MB (more than double of reference value).

Patients having Non ST elevation myocardial Infarction were excluded from the study.

In order to study the impact of various variables on the time of onset of acute myocardial infarction we divided the study population into four groups. The time of day was divided into four equal intervals of 6 hours each. Group I consisted of 67(15.8%) patients presenting during 0-6 hours interval, Group II 118(27.7%) patients presenting during 6:01-12 hours, Group III 144(33.9%) patients presenting in 12:01-18 hours and Group IV comprised of 96(22.6%) patients having onset of AMI during 18:01-24 hours.

A full history was taken, particularly age, sex, occupation, address, history of smoking diabetes mellitus, hypertension, ischemic heart disease and family history of ischemic heart disease. For diabetic patients duration and type of diabetes and treatment taken were noted. Relevant clinical examination of all the patients included in the study was done with emphasis on pulse, blood pressure, precordial examination and signs of congestive cardiac failure. ECG was done once daily in all patients. X-ray chest was done only in those patients having signs of left ventricular failure. Site of myocardial infarction, Killip class and medication used especially streptokinase, were noted for all patients. All patients were treated according to latest recommendations and were given Aspirin, Betablockers and Angiotensin Converting Enzyme Inhibitors except those having contraindications to these drugs. For diabetic patients oral hypoglycemic agents were discontinued and all patients were put on insulin according to fasting and random blood sugar levels. Patients were followed up daily and pulse, blood pressure, ECG changes and complications if any were monitored. The main outcome measure was in-hospital mortality. Cause of death was noted in case of mortality.

STATISTICAL ANALYSIS

All the data were analyzed by SPSS (Statistical Package for Social Sciences release 14.0; SPSS, Inc; Chicago, IL) system for Windows. Categorical variables were expressed as frequencies and percentages and continuous variables as means± Standard deviations (SD). Variables especially risk factors for coronary artery disease like smoking, hypertension, family history of Ischemic heart disease, time from onset of symptoms till arrival to the hospital, Killip class, site of myocardial infarction and use of streptokinase injection and in-hospital mortality were compared between the four groups by applying Chi Square test and p values were calculated. P value less than 0.05 was taken as significant.

RESULTS

After fulfilling the inclusion criteria 425 patients presenting with new onset acute myocardial infarction were studied. Two peaks of onset of symptom were observed, first between 12:01-18 hours 144(33.9%) patients and the second between 6:01-12 hours 118(27.7%) patients. A non-significant association was observed in time of onset of acute myocardial infarction p<0.082. The trough was early morning time 0-6 hours when only 67(15.8%) patients had acute MI. Figure 1. It was observed that patients presented 2.1 times more during 12:01-18 hours as compared to early morning 0-6 hours.

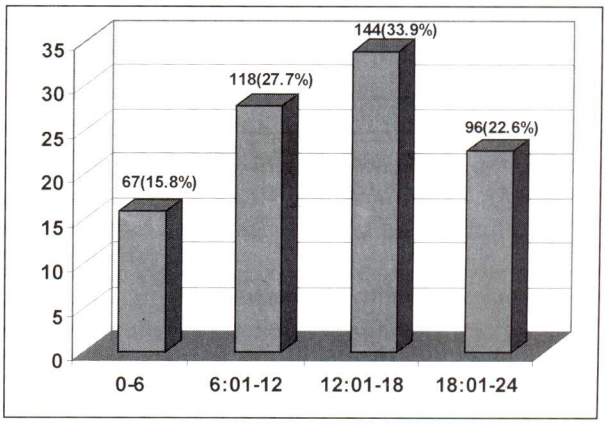
Mean age of the study population was 54.5±12.3 years. Mean age was similar in all the four groups p<0.13. There were 337(79.3%) males and 88(20.7%) females. Male patients were significantly more than females in all the groups. Number of male patients was similar in all the groups p<0.912. There were 114(26.8%) diabetics. Group I consisted of higher number 24(35.8%) of diabetics as compared to other groups. In Group II there were 28(23.7%), Group III 38(26.4%) and Group IV 24(25%) patients with diabetes mellitus p<0.319. There were 138(32.5%) hypertensives. Overall Group I had the maximum number of hypertensive patients 28(41.8%) as compared to other groups. Table 1. There were 215(50.6%) smokers, 84(58.3%) in Group III, 35(52%) in Group I, 48(50%) in Group IV and 48(40.7%) in Group II p<0.042. Family history of IHD was present in 62(14.4%) with similar number of patients in all the groups p<0.121. Dyslipidemia was observed in 73(17.2%) with majority 44(30.5%) in Group III p<0.041. Previous history of ischemic

Table-1 : Epidemiological characteristics

CHARACTERISTICS	Group I 0-6 n=67	Group II 6:01-12 n=118	Group III 12:01-18 n=144	Group IV 18:01-24 n=96	Total n=425	p value
Age mean years	56.9±10	54.2±13	54.1±12.7	53.4±11.8	54.5±12.3	<0.13
Sex						<0.912
Male	55(82.1%)	94(79.7%)	112(77.8%)	76(79.2%)	337(79.3%)	
Female	12(17.9%)	24(20.3%)	32(22.2%)	20(20.8%)	88(20.7%)	
Diabetes Mellitus	24(35.8%)	28(23.7%)	38(26.4%)	24(25%)	114(26.8%)	<0.319
Hypertension	28(41.8%)	33(28%)	43(29.9%)	34(35.4%)	138(32.5%)	<0.206
Smoking	35(52.0%)	48(40.7%)	84(58.3%)	48(50%)	215(50.6%)	<0.042
F/H of IHD	14(20.9%)	15(12.7%)	15(10.4%)	18(18.8%)	62(14.6%)	<0.121
H/O IHD	24(35.8%)	26(22%)	37(25.7%)	20(20.8%)	107(25.2%)	<0.131
Dyslipidemia	10(14.9%)	14(11.9%)	44(30.5%)	5(5.2%)	73(17.2%)	<0.041

F/H= Family history; H/O= History of; IHD= Ischemic heart disease.

Figure-1 : Influence of Circadian variation on onset of acute myocardial infarction



heart disease was observed in 107(25.2%) with majority 24(35.8%) in Group I p<0.131.

Majority of patients 168(39.5%) presented between 3-6 hours after the onset of symptoms, 68(47.2%) in Group III, 38(39.6%) in Group IV, 25(37.3%) in Group I and 37(31.4%) in Group II p<0.015. Overall 100(23.5%) patients presented to the hospital within 3 hours of onset of symptoms with majority 42(35.6%) in Group II. Overall 173(40.7%) patients had anterior wall myocardial infarction followed by Anterospetal wall myocardial infarction in 147(34.6%) patients. Site of MI was similar in all the circadian groups p<0.501.Overall 92(21.6%) patients presented in Killip class I, 26(6.1%) in Killip class II, 17(4%) in Killip class IV and 9(2.1%) in Killip class III. In Group IV and II patients there was a higher tendency of presenting in advanced Killip class as compared to other groups p<0.485. Table 2. Overall 201(47.3%) patients received streptokinase therapy, 50(52.1%) in Group IV followed by 59(49.2%) in Group II, 65(45.1%) in Group III and 28(41.8%) in Group I p<0.546. Door to needle time was >1 hour in 121(28.5%) patients, 30 minutes to 1 hour in 47(11.1%) patients and <30 minutes in 31(7.3%) patients p<0.063 Table 2.

Table-2 : Presentation characteristics

CHARACTERISTICS	Group I 0-6 n=67	Group II 6:01-12 n=118	Group III 12:01-18 n=144	Group IV 18:01-24 n=96	Total n=425	p value
Time from onset of symptoms till arrival						<0.015
<3 hours	19(28.4%)	42(35.6%)	22(15.3%)	17(17.7%)	100(23.5%)	
3-6 hours	25(37.3%)	37(31.4%)	68(47.2%)	38(39.6%)	168(39.5%)	
6-12 hours	15(22.4%)	21(17.8%)	30(20.8%)	21(21.9%)	87(20.5%)	
>12 hours	8(11.9%)	18(15.3%)	24(16.7%)	20(20.8%)	70(16.5%)	
Site of MI						<0.50
Anterior wall MI	29(43.3%)	46(39%)	54(37.5%)	44(45.8%)	173(40.7%)	
Anteroseptal MI	12(17.9%)	23(19.5%)	23(16%)	10(10.4%)	147(34.6%)	
Inferior wall MI	20(29.9%)	42(35.6%)	54(37.5%)	31(32.3%)	68(16%)	
Inferior wall +RV MI	2(3%)	1(0.8%)	3(2.1%)	6(6.3%)	12(2.8%)	
Inferolateral MI	3(4.5%)	2(1.7%)	5(3.5%)	4(4.2%)	14(3.3%)	
LBBB	1(1.5%)	4(3.4%)	5(3.5%)	1(1%)	11(2.6%)	
Killip Class						<0.485
I	17(25.4)	21(17.8%)	30(20.8%)	24(25%)	92(21.6%)	
II	5(7.5%)	8(6.8%)	7(4.9%)	6(6.3%)	26(6.1%)	
III	3(4.5%)	3(2.5%)	2(1.4%)	1(1%)	9(2.1%)	
IV	0	7(5.9%)	4(2.8%)	6(6.3%)	17(4%)	
Streptokinase	28(41.8%)	58(49.2%)	65(45.1%)	50(52.1%)	201(47.3%)	<0.546
Door to needle time						<0.063
<30 Mins	3(4.5%)	2(1.7%)	16(11.1%)	10(10.4%)	31(7.3%)	
30 Mins to 1 hour	6(9%)	16(13.6%)	16(11.1%)	9(9.4%)	47(11.1%)	
>1 hour	18(26.9%)	40(33.9%)	32(22.2%)	31(32.3%)	121(28.5%)	

CPK= Creatinine Phosphokinase; CK-MB= Creatinine Kinase MB fraction

Table-3 : Outcome of study population

CHARACTERISTICS	Group I 0-6 n=67	Group II 6:01-12 n=118	Group III 12:01-18 n=144	Group IV 18:01-24 n=96	Total n=425	p value
In-hospital mortality	8(11.9%)	22(18.6%)	19(13.2%)	14(14.6%)	63(14.8%)	<0.113
Cause of death						<0.331
LV failure	5(7.5%)	17(14.4%)	13(9%)	10(10.4%)	45(10.6%)	
Arrhythmias	1(1.5%)	3(2.5%)	3(2.1%)	1(1%)	8(1.8%)	
Asystole	2(2.9%)	2(1.7%)	3(2.1%)	3(3.1%)	10(2.4%)	

LV=Left ventricle

Overall in-hospital mortality was 62(14.8%), mortality was higher 22(18.6%) in Group II, followed by 14(14.6%) in Group IV, 19(13.2%) in Group III and 8(11.9%) in Group I p<0.113. Table 3. Left ventricular failure was the common cause 45(10.6%) of in-hospital mortality followed by asystole 19(2.4%) and Arrhythmias 8(1.8%). Left ventricular failure was more frequent 19(14.4%) in Group II followed by 10(10.4%) in Group IV, 13(9%) in Group III and 5(7.5%) in Group I.

DISCUSSION

Acute myocardial infarction is a major cause of morbidity and mortality in the developed and developing countries.[1] Various pathophysiological triggering mechanisms are responsible for the occurrence of AMI. Circadian variation in the occurrence of AMI has been demonstrated with a morning peak and a vague evening peak.[14]

In the current study it was observed that maximum episodes were seen during the period between 12:01-18 hours 144(33.9%) and the second between 6:01-12 hours 118(27.7%). A non-significant association was observed in time of onset of acute myocardial infarction p<0.082. The trough was early morning time 0-6 hours when only 67(15.8%) patients had acute MI. In Group IV 18:01-24 there was a higher tendency of presenting in advanced Killip class followed by Group II 12:01-18 and Group III 18:01-24. Streptokinase was given more to patients presenting at night followed by afternoon and morning time. In-hospital mortality was higher in Group II, followed by Group IV, Group III and Group I.

We observed that in our study population, the cardiac events follow the circadian variations but the pattern noted is similar to some studies and different from others.[3,8-12] In majority of the studies a single morning peak has been noted for cardiac events like AMI and unstable angina.

Although morning peak of the onset of MI is very common, some population studies showed different results. Dimitrov et al[10] from Bulgaria reported a maximal peak of onset of MI between 16:00 and 00:00 hours with a second smaller peak between 06:00 and 08:00 hours.[10] A report from China demonstrated a peak between 01:00 and 07:00 hours and a trough between 13:00 and 19:00 hours.[11] The results describing a cohort of 1063 patients recruited from 65 CCU located in Argentina and Uruguay who were admitted to the CCU within 24 h of the onset of symptoms of an acute MI, point out to the existence of two peaks in the incidence of MI, at the morning (between 08:00 and 12:00 h) and at the afternoon (between 16:00 and 20:00 h). A nadir in nocturnal MI incidence (between 03:00 and 07:00 h) and a secondary minimum at early afternoon (between 13:00 and 15:00 h) also occurred.[8] A similar bimodal picture was observed for MI frequencies among different excluding subgroups (older or younger than 70 years; with or without previous symptoms; diabetics or non diabetics; Q wave- or non-Q wave-type MI; anterior or inferior MI location). Older and patients with previous symptoms tended to have more MI at the afternoon, who had MI equally distributed between the morning and the afternoon maxima.[8]

Moreover, in some populations circadian variation of MI differs in subgroups of the populations for example Kinjo et al[12] from Japan reported that female patients aged 65 years or more showed a morning peak and male patients aged < 65 years with an occupation and the habits of cigarette smoking and alcohol intake showed a nighttime peak alone. Lopez et al[9] investigated the influence of ethnicity on the circadian distribution of MI in England and Spain and reported significantly higher number of AMI onsets occurred between midnight and noon in British Caucasians and Indo-Asians, whereas most of the AMI events happened between noon and midnight in Mediterranean Caucasians. Marked circadian periodicity in the time of onset of ST elevation MI, with a peak incidence between 12:01 and 18:00 hours in the present study is discordant with the western populations but is rather similar with the Bulgarian population and Mediterranean Caucasians. In addition, our data is partly compatible with the report from Argentine and Uruguay but just the opposite of the report from China.

Ethnicity and lifestyle may also be responsible in the discrepancy of circadian variation of MI among different populations. Differences in eating habits, light and dark cycle, sleep patterns, smoking, diabetes and other cardiovascular risk factors' prevalence might also contribute this discrepancy. Although controversial, heavy meal is considered as a trigger of

MI.[20,21] There are variations in which the main meal of the day is breakfast in some populations, but lunch or dinner in the others. It has also been reported in a recent paper that siesta effects circadian variation of MI and ingestion of the main daily meal, followed by a period of physical inactivity, with or without sleep was considered as a trigger for AMI which is common in some geographical regions.[22] Finally, some authors claim that ischaemia in the morning hours is mostly because of the increase in the oxygen demand but ischaemia in the evening hours is mostly because of the decrease in coronary blood flow.[23] All these factors might affect the chronobiology of MI among different populations.

The reason for a morning peak has been elucidated in various studies, but the evening peak can not be explained on the basis of physiological changes. The evening peak may be a result of trigger factors like stress, anger or various other such factors that were not clearly identifiable. These external trigger factors are associated with coronary events beyond what is to be expected by chance alone. In one study (these factors played a role in causation of acute coronary syndromes in up to 20% cases.[24]

Unfortunately delays in reperfusion are not unexpected, particularly for patients presenting to the hospital at night. In the NRMI-2, median time to first balloon inflation was 111 min, compared with 42 min for initiation of fibrinolytic treatment (door-to-needle).[25] Data from the same registry identified non-daytime presentation as one of the strongest predictors of door-to-balloon times >2 h.

The study by Henriques et al[26] using data from 1,702 consecutive patients referred to a single center with acute ST-elevation MI, identified a difference in angioplasty success rates based on times of treatment. This was associated with a two-fold increase in 30-day mortality for patients admitted "off hours" (4.2% vs. 1.9%). Interestingly, and reflective of this center's dedication to "round the clock" primary angioplasty, time to first balloon inflation was not significantly different by time of presentation 8:00 AM to 6:00 PM, 64 min vs. 6:00 PM to 8:00 AM, 69 min). These data suggest that the "time of treatment" is independent of "time to treatment" and collectively determines the benefit of mechanical reperfusion.

Andreotti et al[27] reported major circadian fluctuations in fibrinolytic factors, with a marked peak in plasminogen activator inhibitor activity during the early morning hours. Consistent with platelet biology and coagulation protease activity, a "prothrombotic period" exists between 6 AM and 12 PM and is independent of physical activity, work schedule, and/or sleep patterns.

Finally, a diurnal variation in response to fibrinolytic therapy has also been documented. In a study of 244 patients with MI treated with either urokinase or tissue plasminogen activator, resistance to fibrinolytics was observed in the early morning and late evening hours.[32] In our study streptokinase infusion was given in similar proportions in the four groups. The increased mortality in Group II and IV could probably be due to more advanced Killip class at the time of presentation in these groups which was followed by more left ventricular failure leading to death in these patients.

CONCLUSION

The onset time of AMI has bimodal appearance with an early peak at 12:01-18 hours and a second lesser peak at 6:01-12 hours. In-hospital mortality was higher in patients presenting between 6:01-12 hours because of more frequency of advanced killip class at the time of presentation in this Group.

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