ORIGINAL
PROF-1736

MYOCARDIAL INFARCTION IN DIABETICS; CIRCADIAN PERIODICITY IN THE ONSET OF ACUTE ST SEGMENT ELEVATION

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ABSTRACT... Objective: To analyze the influence of diabetes mellitus on circadian rhythm affecting the onset of acute ST elevation myocardial infarction. **Design:** Observational study. **Period:** February to August 2010. **Setting:** Faisalabad Institute of Cardiology, Faisalabad. **Materials and methods:** Three hundred and seven consecutive patients who fulfilled the inclusion and exclusion criteria and presented with first MI were studied. All patients were divided into four groups according to the 6:00 hours interval of the day (Circadian rhythm). Group I comprised of patients presenting with onset of symptoms between 0-6 hours, Group II 6:01 to 12:00 hours, Group III 12:01 to 18:00 hours and Group IV 18:01 to 24:00 hours. Data was analyzed for variations within groups. **Results:** Two peaks of onset of symptoms were observed, first between 0-6 hours 144 (33.9%) patients and the second between 6:01 to 12:00 hours 87 (28.3%) and a non significant association was observed in time of onset of acute myocardial infarction P = 0.082. The trough was evening time 12:01 to 18:00 hours where only 63 (20.5%) patients had acute myocardial infarction. Mean age of study population was 56 ± 12.7 years. Mean age was similar in all the four groups P = 0.155. There were 228 (74.3%) males, 79 (25.5%) females. The circadian morning peak of MI symptom onset was attenuated in patients with diabetes as Group IV consisted of higher number 24 (37.5%) of diabetics followed by group I 23 (34.7%). Overall group II had the maximum number of hypertensive patients 41 (47.1%) as compared to other groups. Obesity was observed in 55 (18%) with similar number of patients in all groups P = 0.492. Majority of patients 117 (38.1%) presented between 4-8 hours after the onset of symptoms. Overall 170 (55.4%) patients had anterior wall myocardial infarction followed by inferior wall myocardial infarction in 82 (26.7%) patients. **Conclusions:** Our study demonstrates that the circadian morning peak of MI symptom onset was attenuated in patients with diabetes, suggesting a role of autonomic dysfunction. Inconsistency in observation of such an effect in patients with diabetes in the past may well have been due to differences in the duration of diabetes.

Key words: Ischemic heart disease; Myocardial Infarction; Diabetes Mellitus; Circadian Variation.

.INTRODUCTION

Atherosclerotic coronary artery disease (CAD) is among the leading cause of death throughout the World[1]. In 1999 cardiovascular diseases claimed 14 million lives, 2/3rd of which were in the developing countries[2]. 25% of deaths in Indo-Pak are caused by cardiovascular diseases[3]. Atherosclerotic disease is projected to become the leading cause of global morbidity and mortality by 2020, this trend has implications for countries in South Asia[4]. Research has identified a circadian rhythm for several acute thrombotic cardiovascular and cerebrovascular diseases[5] and due to this, great interest has developed in evaluating the facts which trigger mechanisms responsible for acute myocardial infarction[6]. The demonstration of a circadian variation in frequency of onset of myocardial infarction, sudden cardiac death and stroke provides an opportunity to gain in sight into the mechanism of transformation from chronic stable to acute unstable manifestation of cardiovascular disease[7]. It is well known that the time of onset of ST elevation myocardial infarction has a pronounced circadian periodicity with peak incidence of events between 6 AM and noon[8]. Contributing physiologic changes that exhibit in morning peak include arterial pressure, heart rate and vascular tone, which promote plaque rupture, together with increased platelets activity and reduced fibrinolytics activity[7]. This along with decreased vagal tone, rise in catecholamine level and activation of renin-angiotensin system, make the atherosclerotic plaque liable to fissuring, rupture and resultant thrombosis[9]. Investigators have revealed a circadian rhythm also in platelets function like increased in platelets aggregability

on assuming up right posture, increased blood viscosity and fall in fibrinolytic activity[10,11].

MATERIALS AND METHODS

This observational study was conducted at the Faisalabad Institute of Cardiology, Faisalabad. Three hundred and seven consecutive patients with first ST elevation acute myocardial infarction hospitalized between February 2010 and August 2010 were included and met the following inclusion and exclusion criteria.

Inclusion Criteria

1. Age> 20
2. Diagnosis of acute ST elevation myocardial infarction if two of the following criteria were present.

i The presence of Ischemic pain and other symptoms lasting 30 minutes.

ii ST segment elevation 2 mm in at least two contagious precordial leads or ST elevation of 1 mm in at least two limb leads , or new left bundle branch block.

iii And increase in serum MB isoenzyme of creatine kinase (CKMB) to more than twice the upper limit of normal.

Exclusion Criteria

1. MI occurring after invasive coronary artery procedure such as PCI or coronary artery bypass grafting (CABG) History of previous MI.
2. Patients with previous history of valvular heart disease and primary pericardial disease.

We divided the day into four 6 hours intervals from 12:01 to 6:00, 6:00 to 12:00, 12:01 to 18:00 and 18:00 to 24:00 and calculated no. of patients in each interval.

For each patient enrolled, structured data form was completed. Clinical features were obtained from patients who were in stable condition and can provide proper history.

Baseline data age, gender, systolic and diastolic blood pressure, heart rate, smoking, history of diseases (Diabetes, hypertension, cerebrovascular disease) was recorded. Duration from onset of chest pain to emergency was calculated. For diabetic patients type of diabetes and treatment taken was noted. Site of myocardial infarction and medication used were noted for all patients. All patients were treated according to latest recommendations and were given Aspirin, Beta blockers, ACEI / ARB, statins etc. except those having some contraindications to these drugs.

Statistical Analysis

All data was transferred from data sheets to a computed database for analysis using SPSS (Statistical Package for Social Sciences) Version 14 for Windows. Categorical variables were expressed as frequencies and percentages. While continuous variables were expressed as means and standard deviations. Chi Square test was applied to compare risk factors of ischemic heart disease and presenting variables of acute myocardial infarction in the four groups and p values were calculated. A p value of $\leq$ 0.05 was taken as significant.

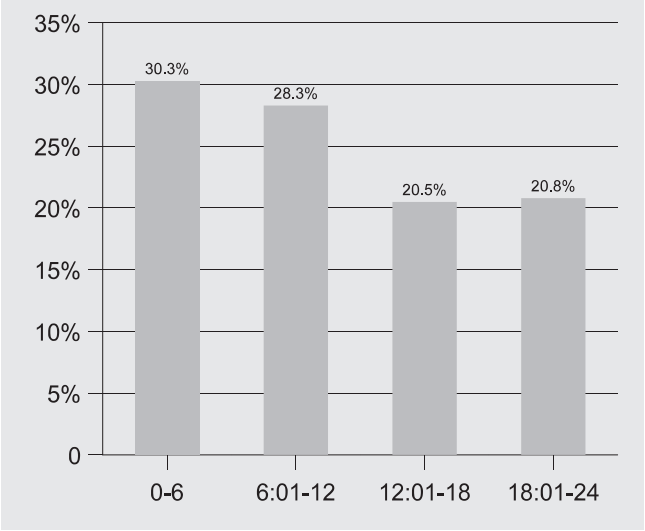
RESULTS

After fulfilling the inclusion criteria, 307 patients presenting with new onset acute myocardial infarction were studied. Two peaks of onset of symptom were observed, first between 0-6 hours 144(33.9%) patients and the second between 6:01-12 hours 87(28.3%) patients. A non-significant association was observed in time of onset of acute myocardial infarction p=0.082. The trough was evening time 12:01-18 hours when only 63(20.5%) patients had acute MI. Figure 1. It was observed that patients presented 1.5 times more during 0-6 hours as compared to evening 12:01-18 hours.

Mean age of the study population was 56.2±12.7 years. Mean age was similar in all the four groups p=0.155. There were 228(74.3%) males and 79(25.7%) females. Male patients were significantly more than females in all the groups. Number of male patients was similar in all the groups p=0.198. There were 92(30%) diabetics.

It was observed that the circadian morning peak of MI symptom onset was attenuated in patients with diabetes as Group IV consisted of higher number 24(37.5%) of diabetics as compared to other groups. In Group I there

Fig-1. Influence of circadian variation on onset of acute myocardial infarction



were 23 (34.7%), Group II 27(31%) and Group III 18(28.6%) patients with diabetes mellitus p=0.384. There were 126(41%) hypertensives. Overall Group II had the maximum number of hypertensive patients 41(47.1%) as compared to other groups. Table I. There were 153(49.8%) smokers, 49(52.7%) in Group I, 33(52.4%) in Group III, 44(50.6%) in Group II and 27(42.2%) in Group IV p=0.479. Family history of IHD was present in 32(10.4%) with more number of patients in the group III and IV as compared to Group I and II p=0.121. Obesity was observed in 55(18%) with similar number of patients in all groups p=0.492. Dyslipidemia was observed in 39(12.7%) with majority 12(19%) in Group III p=0.329.

Majority of patients 117(38.1%) presented between 4-8 hours after the onset of symptoms, 41(47.1%) in Group II, 24(38.1%) in Group III, 32(34.4%) in Group I and 20(31.3%) in Group IV p=0.34. Overall 62(20.2%) patients presented to the hospital within 4 hours of onset of symptoms with majority 19(30.2%) in Group III. Overall 170(55.4%) patients had anterior wall myocardial infarction followed by Inferior wall myocardial infarction 82(26.7%) patients. Site of MI was similar in all the circadian groups p=0.2001. Table II.

DISCUSSION

Acute myocardial infarction continuous to be a major public health problem in the developed and developing World[12] and more than one million people have acute myocardial infarction each year in USA. Circadian variation has been demonstrated in several types of

Table-I. Epidemiological characteristics.

Characteristics	Group I 0-6 (n=93)	Group II 6:01-12 (n=87)	Group III 12:01-18 (n=63)	Group IV 18:01-24 (n=64)	Total (n=307)	p-value
Age mean years	58.2 ± 12.5	56.2 ± 11.5	56.3 ± 14.1	53.2 ± 12.6	56.2 ± 12.7	0.155
Sex Male Female	 71 (76.3%) 22 (23.7%)	 66 (75.9%) 21 (24.1%)	 50 (79.4%) 13 (20.6%)	 41 (64.1%) 23 (35.9%)	 228 (74.3%) 79 (25.7%)	0.198
Diabetes Mellitus	23 (34.7%)	27 (31%)	18 (28.6%)	24 (37.5%)	92 (30%)	0.384
Type of DM Type I Type II	 8 (8.6%) 15 (16.1%)	 10 (11.5%) 17 (19.4%)	 7 (11.1%) 11 (17.5%)	 11 (17.2%) 13 (20.3%)	 36 (11.7%) 56 (18.2%)	0.357
Hypertension	40 (43%)	41 (47.1%)	17 (27%)	28 (43.8%)	126 (41%)	0.078
Smoking	49 (52.7%)	44 (50.6%)	33 (52.4%)	27 (42.2%)	153 (49.8%)	0.479
F/H of IHD	5 (5.4%)	4 (4.6%)	11 (17.5%)	12 (18.8%)	32 (10.4%)	0.003
Obesity	18 (19.4%)	11 (12.6%)	13 (21%)	13 (20.3%)	55 (18%)	0.492
Dyslipidemia	12 (12.9%)	8 (9.2%)	12 (19%)	7 (10.9%)	39 (12.7%)	0.329

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

Table-II. Presentation characteristics

Characteristics	Group I 0-6 (n=93)	Group II 6:01-12 (n=87)	Group III 12:01-18 (n=63)	Group IV 18:01-24 (n=64)	Total (n=307)	p-value
Time from onset of symptoms till arrival						
<4 hours	15 (16.1%)	15 (17.2%)	19 (30.2%)	13 (20.3%)	62 (20.2%)	
4-8 hours	32 (34.4%)	41 (47.1%)	24 (38.1%)	20 (31.3%)	117 (38.1%)	
8-12 hours	19 (20.4%)	9 (10.3%)	8 (12.7%)	9 (14.1%)	45 (14.7%)	0.34
12-16 hours	14 (15.1%)	10 (11.5%)	3 (4.8%)	12 (18.8%)	42 (13.7%)	
16-20 hours	9 (9.7%)	9 (6.9%)	6 (9.5%)	7 (10.9%)	28 (9.1%)	
>20 hours	4 (4.3%)	3 (3.4%)	3 (4.8%)	3 (4.7%)	13 (4.2%)	
Site of MI						
Anterior wall MI	59 (63.7%)	41 (47.1%)	35 (55.6%)	35 (54.7%)	170 (55.4%)	
Inferior wall MI	20 (21.5%)	24 (27.6%)	20 (31.7%)	18 (28.1%)	82 (26.7%)	
Inferior wall + RV MI	3 (3.2%)	8 (9.2%)	3 (4.8%)	1 (1.6%)	15 (4.9%)	0.211
Inferior wall + Post MI	2 (2.2%)	5 (5.7%)	2 (3.2%)	6 (9.4%)	15 (4.9%)	
Lateral MI	9 (9.7%)	9 (10.3%)	3 (4.8%)	4 (6.3%)	25 (8.1%)	

acute cardiovascular diseases, including, acute MI, sudden cardiac death, silent ambulatory Ischemia and thrombotic stroke.

In present study it was observed that maximum episodes were seen during the period between 0:00 to 6:00 hours 144 (33.9%) patients and a second peak was seen between 6:01 to 12:00 hours, 87 (28.31%) patients. The trough was evening time 12:01 to 18:00 hours where only 63 (20.5%) patients had acute MI. Hypertensive patients had peak occurrence of acute myocardial infarction between 6:01 to 12:00 hours. Smokers follow the same circadian periodicity between 0:00 to 6:00 hours 49 (52.7%) patients. Obese patients had peak occurrence of acute myocardial infarction between 12:01 to 18:00 hours 12 (19%). The morning peak of incidence of acute MI is related to some known daily rhythms. It is well known that a surge in sympathetic activity and a vagal withdrawal occurs after wakening accompanied by increased level of catecholamine, renin and cortisol (morning peak approximately 6:00 am, decreasing but still high until noon). As a result high level of heart rate, blood pressure, coronary vascular tone, platelets aggregability and a lower level of fibrinolytic activity are observed during the early morning hours. These changes may increase shear forces in the coronary arterial bed, thus promoting plaque disruption and causing unstable angina and acute MI. Also, a morning increase in platelet reactivity may make a thrombus more likely to grow and cause symptoms. In our study the cardiac events follow the circadian variation but the pattern is similar to some studies and different from other[6,13-15]. In majority of studies a single morning peak has been noted for cardiac events like acute MI and unstable angina. A study[16] including 4796 patients firstly showed that circadian variation of the onset of acute MI, altered in specific clinical characteristic such as diabetes, smoking, heart failure, non Q wave MI, taking beta blocking drugs. One study has confirmed this finding but another study showed conflicting reports. They failed to demonstrate such a variation in the circadian pattern in the onset of acute MI[17] among patients with diabetes. Our study showed that mostly diabetic patients presented between 18:01 to 24 hours 24 (37.5%) and they fall in group IV. The exact mechanism of change of circadian variation in diabetics is not clear but it is suggested that in patients with diabetes, abnormalities in the circadian rhythm of autonomic tone may be responsible for the altered temporal onset of cardiovascular events[18,19]. In diabetics, platelets aggregability and plasminogen activation inhibitor I show no circadian variation[20]. Persistent elevation of factor VII antigen and von Willebrand factor antigen,[20] increased platelet activation[21] may be responsible for loss of normal circadian rhythm in diabetics. Diabetics subjects also show diminished circadian variation in blood pressure[22].

All of these factors predispose patients with long standing diabetes to trigger cardiovascular events throughout the day with the absence of a morning peak, accounting for attenuation of circadian variation of MI in these patients. However there were also conflicted reports. Behar showed the preponderance of the morning peak persisted in patients with diabetes[23]. Jamal reported circadian morning peak of acute MI symptoms onset existed in patients with history of type II diabetes less than five years but it was attenuated with diabetes more than five years[24]. In some studies it was observed that autonomic dysfunction in diabetics may occur even after 1-2 years diagnosis of diabetes and may suggest that this dysfunction present after brief delivery to hyperglycemia or perhaps even in the clinical normal range of glucose[25].

Lopes Messa et al[14] reported that diabetic showed a circadian rhythm with bimodal pattern involving one morning and one nocturnal peak which differ from our study.

CONCLUSIONS

Our study demonstrates that the circadian morning peak of MI symptom onset was attenuated in patients with diabetes, suggesting a role of autonomic dysfunction. Inconsistency in observation of such an effect in patients with diabetes in the past may well have been due to differences in the duration of diabetics.

Limitation of the study:

A possible limitation of our study is inaccuracy in the identification of diabetes. We relied on the clinical diagnosis of diabetes made by the treating clinicians in the medical record and by patient self report. This approach may have misclassified patients with unrecognized diabetes. Such misclassification would tend to minimize the effect of diabetes, so the relative risks reported here might be overly conservative.

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Article received on: 10/01/2011 Accepted for Publication: 11/03/2011 Received after proof reading: 16/05/2011

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Article Citation:
Ali L, Abid AR, Ahmed I, Niaz N, Rehman TA, Azhar M. Myocardial infarction in diabetics; circadian periodicity in the onset of acute ST segment evaluation. Professional Med J Apr-Jun 2011;18(2): 269-274.

"Liberty means responsibility. That is why most men dread it."

(George Bernard Shaw)