Ageing and circadian variation in cardiovascular events

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ABSTRACT

Introduction: Circadian variation in cardiovascular events is well recognised in vascular events. This study aims to observe any significant difference in circadian variability in geriatric patients when compared to their younger counterparts.

Methods: This prospective study was conducted at medical emergency at the Government Medical College and Hospital, Chandigarh, India. All the patients attending medical emergency with symptoms suggestive of coronary artery disease were included. The time of occurrence of first symptom and subsequent symptoms was noted. Electrocardiography, cardiac enzymes and echocardiography were performed to establish the diagnosis of acute coronary syndrome. The 24-hour day was divided into 12 equal parts of two hours each. For the final analysis, the two-hour periods were grouped into six equal periods of four hours each and four quarters of six hours each.

Results: We studied 559 patients, out of whom 459 were 65 years old or younger, and 100 patients were older than 65 years old. 459 patients had 498 episodes in all. 100 patients above the age of 65 years had 104 episodes. Both the groups had peaking of acute myocardial infarction in the early morning hours with patients older than 65 years of age having a slightly early peak. However, there was considerable variability for peaking of unstable angina and non-Q myocardial infarction. In patients older than 65 years, early morning peaking of events was noted whereas in 65 years or younger, the peaking of events was noted in the evening hours.

Conclusion: Circadian variability exists in occurrence of acute coronary events and is variable in geriatric patients when compared to their younger counterparts.

Keywords: acute myocardial infarction, ageing, cardiovascular events, circadian variation, geriatric patients, unstable angina

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INTRODUCTION

Pell and D'Alanzo first described the presence of circadian variation in occurrence of myocardial infarction in 1963[1]. Since than, many studies have consistently shown that there is an increase in cardiovascular events during the early morning hours. There is enough evidence to suggest the presence of circadian variation in blood pressure, ventricular tachycardia, refractoriness of the ventricle, anginal attacks and sudden cardiac death[2,3]. The rise in these events is more marked during the early morning hours[2-5]. There is a complex interplay between the protective and trigger factors which is considered to be responsible for this variation. The coronary events do take place at other times during the day but at a relatively lesser frequency than morning hours[2,5-7].

Various physiological changes occurring during the early morning hours can be grouped into haemodynamic, vascular and haematological changes[5,8]. The most important haemodynamic change is the rise in heart rate and blood pressure. This, along with decreased vagal tone, rise in catecholamine level and activation of renin angiotensin system make the atherosclerotic plaque more liable to fissuring, rupture and resultant thrombosis[5,8,9]. Vascular changes like increased vascular receptor sensitivity, increased vascular tone also contribute to the damage[2,8]. Haematological changes like increased platelet aggregability on assuming upright posture, increased blood viscosity and a fall in the fibrinolytic activity add fuel to the fire[2,6,8,10,11].

These factors alone may not be capable of resulting in adverse coronary events. Various

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trigger factors act in conjunction with physiological changes in the early morning hours[4,5,7,9]. These factors are start of physical activity, bursts of anger, sexual activity and heavy physical exertion[4,5], and they can precipitate an acute attack at any time of the day. Some other recognised external trigger factors are earthquakes, war, riots, and climatic factors like extremes of temperatures, especially winters[4]. Increased event rate has been demonstrated in winter months, on Mondays and least event rate on Sundays[12,13]. Decreased incidence of these events has been correlated with relaxation and decreased level of stress. A shift in the time of awakening in the morning or getting up late and starting an activity at a later hour does not negate the physiological effect of these factors but shifts it to a later hour[14].

Blunting of various cardiovascular responses and reflexes is a hallmark of ageing. This blunting may result in increasing the deleterious effects of trigger factors as the body loses its ability to mount adequate response. This study was undertaken to compare the circadian variation in cardiovascular events in younger patients with the variation observed in elderly patients to look for differences.

METHODS

With the aim to study the existence of circadian variation in coronary events in the urban population in and around Chandigarh, this prospective observational study was conducted at the medical emergency department of the Government Medical College and Hospital, Chandigarh, India. All the patients attending emergency services with complaints suggestive of coronary artery disease (chest pain, dyspnoea, chest discomfort with or without sweating, palpitation, fainting spells) were included in the study. The patients were asked about the time of occurrence of first symptom, and time of subsequent episodes was also noted. A resting 12-lead electrocardiogram (ECG), cardiac enzymes and echocardiography was carried out to establish the diagnosis of acute myocardial infarction.

A diagnosis of myocardial infarction was considered in patients having anginal pain lasting more than 15 minutes, associated with/without dyspnoea or sweating, established/evolving ST-T wave changes on serial ECGs, and raised cardiac enzymes. The patients having anginal pain, persisting ST-T wave changes without the development of Q waves on serial ECGs, and raised enzymes were labelled as non-Q wave myocardial infarctions. The patients with typical anginal pain lasting less than 10 minutes, having reversible ST-T wave changes on serial ECGs, normal cardiac enzymes and no evidence of fresh regional wall motion abnormality on echocardiography were grouped as unstable angina.

Patients with non-anginal chest pain or those in whom an alternative diagnosis could be established, were excluded from the study. The patients with congestive cardiac failure were also not included in the study analysis, as the number of these patients was very small. The 24-hour day was divided into 12 equal parts of two hours each, and the data was input into the computer. For the final analysis, the patients were divided into two groups, those ≤65 years and those >65 years. Further, these two-hour periods were grouped into six equal periods of four hours each and to four quarters of six hours each. The data was analysed by using the EPI 6 statistical package.

RESULTS

We studied 559 patients, out of whom 459 were 65 years old or younger. The mean age was 57 (±5.4) years. These 459 patients (64.2% males and 35.8% females) had a total of 498 episodes of unstable angina (51.4%), acute myocardial infarction (AMI) (42%), and non-Q wave myocardial infarction (non-Q MI) (7.6%). When we divided 24 hours into four equal quarters each, we observed that maximum episodes (all coronary events) were seen between six pm and 12 midnight (148/498, 29.71%) and a second comparable peak was seen between six am and 12 noon where 146/498 (29.31%) events were recorded. The events observed during these two peaks were comparable. The least number of episodes were seen during the period between 12 midnight and six am (92/498, 18.47%).

In patients with AMI, two peaks were observed. The first peak was seen between six am and 12 noon when 68/206 (335) events were noted, and a second peak was noted between six pm and 12 midnight. The minimum number of events (40/206, 19.8%) were noted were between 12 midnight and six am. Patients with non-Q MI had maximum number of events (14/28, 50%) between six pm and 12 midnight. In patients with unstable angina, the peaking of events followed the pattern of all coronary events. First peak was seen between six pm and 12 midnight (82/264 events, 31%) and a second peak was noted between six am and 12 noon (74/264 events, 28%). The minimal events here were again noted between 12 midnight and six am (48/264, 18.2%).

When we divided 24 hours into six equal parts

of four hours interval each, we observed that maximum episodes were seen during the period between eight pm and 12 midnight (106/498, 21.28%), and a second peak was seen between eight am and 12 noon when 104/498 (20.88%) events were recorded. The least number of episodes were seen during the period between 12 midnight and four am (64/498, 12.85%). In patients with AMI, the two comparable peaks were noted between eight pm and 12 midnight (44/206 events, 21.1%) and between four am and eight am (40/206 events, 19.5%). In unstable angina, two equal peaks were noted between eight pm and 12 midnight, and between eight am and 12 noon, when 58/ 264 events (21.96%) were noted. Patients with non-Q MI had maximum events between four pm and 8 pm (10/28 events, 35.7%), followed by 6/28 events (21.4%) between eight pm and 12 midnight.

In our study group, 100 patients were older than 65 years and they had 104 episodes. 57% were male and 43% female patients with a mean age of 69 (±4) years. 51.2% had AMI, 36.4% had unstable angina and 12.4% had non-Q MI. When we divided 24 hours into four equal quarters each, we observed that maximum episodes were seen during the period between six am and 12 noon (38/104, 36.71%), and a second peak was seen between six pm and 12 midnight when 26/104 (25.31%) events were recorded. The least number of episodes were seen during the period between 12 midnight and six am (15/104, 15.6%). Peaking of events was noted for AMI with maximum events occurring between six am and 12 noon, and a second peak between six pm and 12 midnight. Only one peak was seen in unstable angina patients with one-third of events occurring between six am and 12 noon.

However, when we divided 24 hours into four-hourly intervals, the maximum events noted were 22/104 (21.2%) between eight am and 12 noon, followed by 20/104 (19.2%) between four am and eight am. The minimum events (9/104, 8.7%) were noted between 12 midnight and four am. Maximum numbers of AMI were noted between four am and eight am, followed by a second peak between eight am and 12 noon. The patients with unstable angina had the first peak between eight am and 12 noon, followed by a second peak between eight pm and 12 midnight.

Table I. Circadian variation in patients ≤65 years vs >65 years (six-hourly intervals).

	1st peak		2nd peak	
Events	≤65 years	>65 years	≤65 years	>65 years
AMI	6am-12 noon	6am-12 noon	6pm-12 MN	6pm-12MN
Unstable angina	6pm-12MN	6am-12 noon	6am-12 noon	
Non-Q MI	6pm-12 MN	6am-12 noon		

Table II. Circadian variation in patients ≤65 years vs >65 years (four-hourly intervals).

	1st peak		2nd peak	
Events	<65 years	>65 years	<65 years	>65 years
AMI	8pm-12 MN	4am-8am	4am-8am	8am-12noon
Unstable angina	8pm-12MN	8am-12 noon	8am-12 noon	8pm-12 MN
Non-Q MI	4pm-8pm	8pm-12 MN		

DISCUSSION

Our study population showed the presence of circadian variation in adverse cardiac events in patients both below and above 65 years of age. The peaking of these events was noted in the early morning and late evening hours in both the patient groups. The events during these hours were significantly more than the other times, however, there was no statistically significant difference between the events occurring during these two periods. 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[4], these factors played a role in causation of acute coronary syndromes in up to 20% cases.

In majority of the studies, a single morning peak has been noted for cardiac events like acute myocardial infarction and unstable angina[12,13,15-17]. Very few studies have addressed the point of circadian variation and its correlation with age. In a large study, Arntz et al reported the incidence of cardiac events in 24,061 patients, and found a morning peaking of events between six am and 12 noon, on Mondays in winter months. They also noted that these variations are more pronounced in patients ≤65 years old and less pronounced those >65 years old[12]. Similar results were reported in other studies as well[13,15].

This finding is in contrast to our study in which two very similar peaks were noted in AMI patients in both the groups. Our patients with non-Q MI

had shown only a single peak; however the number of the patients in both the groups was too small to draw any meaningful conclusion. A few recent studies have reported similar findings of two distinct peaks between eight am and 12 noon, along with another peak between eight pm and 12 midnight[10,18]. In another study, the morning peak was noticed to be absent in women, diabetics, hypertensive patients and patients with a previous-documented coronary event but they had not studied older patients as a separate group[15].

In a study by the OACIS group in Japan, only the morning peak was noticed in female patients aged 65 years or more. Male patients less than 65 years showed a night time peaking[18]. In contrast, in a study by Yamasaki et al, a significantly higher incidence of AMI in the morning was observed only in the elderly group (65-74 years), with 33% events occurring between six am and 12 noon[16]. In this study, our young and elderly patients not only showed a morning peak but also an evening peak, a finding which differed from the other two studies.

In the ESCVA study, where 3,453 patients of angina were studied, a morning peak at 9 am-12 noon and a secondary peak at 1500-1800 hours were observed. 74% of these patients noted external triggers like stress, physical activity and anger as precipitating factors[19]. In another study on unstable angina patients, 39 patients were monitored for 48 hours using Holter monitoring and were observed to have maximum ischaemic events between 11am and 3 pm[20]. For our patients with unstable angina, both groups showed two equal peaks between eight am and 12 noon and between eight pm and 12 midnight. However, when the events were studied in four quarters, the geriatric patients had only one peak between six am and 12noon. The events recorded at these times were almost twice that of the minimal events noted during all the intervals.

We found that in our study population, the cardiac events follow the circadian variation but the pattern noted is similar to some studies and different from others. The elderly patients in our study group had morning peaking for all the events studied, whereas their younger counterparts had a morning peak of AMI but exhibited evening peaking of unstable anginal episodes. The difference may be explained by the fact that the morning peaking results from intrinsic physiological changes whereas evening peak may be a result of an external trigger. Since we have not gone into the details of various factors responsible for the peaking of events at a particular time, it may not be possible for us to comment on them, based on present study. The practical importance of knowing these variations may lie in planning preventive strategies and planning dosing schedules for the patients, so as to give maximum cover to prevent adverse cardiac events peaking at these times.

In conclusion, in both groups of our study, we observed that circadian variability in coronary events was distinctly seen but with a slight variation of timing. The elderly patients in our study group had morning peaking for all the events studied whereas the patients ≤65 years old had a morning peak of AMI but exhibited evening peaking of unstable angina and non-Q myocardial infarction episodes.

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