Circadian variation in the frequency of onset of chest pain in acute myocardial infarction

David R Thompson, Terence W Sutton, Nigel I Jowett, Jurgen E F Pohl

Abstract
The time of onset of chest pain was studied prospectively in 1154 consecutive patients admitted to a coronary care unit with myocardial infarction during a five year period. Statistical analysis confirmed a previous finding in a retrospective study of a bimodal frequency distribution with peaks in the time of onset of chest pain between 2330 and 0030 hours and between 0630 and 0830 hours.

Many cardiac disorders1 including sudden death,2 angina,3 and asymptomatic myocardial ischaemia4 are more frequent at the normal waking time. Studies have shown that the onset of acute myocardial infarction also often occurs at this time.4-6 However, in a retrospective study of the time of onset of chest pain in myocardial infarction1 our data also suggested a bimodal distribution, with a secondary peak around midnight. Though several studies found convincing evidence for a second, late evening peak4-11 others have not found such a pronounced midnight peak. We have, therefore, completed a five year prospective study of the time of onset of chest pain in 1154 patients admitted to a coronary care unit with a myocardial infarction.

Patients and methods
PATIENTS
Since the inception of the coronary care unit of Leicester General Hospital in 1976 accurate records of all patients admitted have been kept on a card index. The date and time of onset of chest pain and admission to and discharge from the unit together with electrocardiographic and cardiac enzyme changes, complications, and treatment have been recorded separately from each patient’s hospital notes.

During a five year period (1984–89) 4975 patients were admitted to the coronary care unit. In 1716 (34.5%) of these an acute myocardial infarction was diagnosed on the basis of at least two of the following criteria: (a) myocardial ischaemic pain lasting > 30 minutes, (b) creatine kinase concentration more than twice the upper limit of normal, and (c) electrocardiographic evidence (Minnesota code) of acute infarction. Five hundred and sixty two patients were excluded because they had no pain, were admitted to the coronary care unit > 24 hours after symptoms began or because data could not be collected on arrival because of uncertainty, language difficulties, or collapse. The time of the onset of chest pain was taken to the nearest hour.

STATISTICAL ANALYSIS
When the frequency of chest pain over time was plotted there were two major peaks at 2330–0030 hours and at 0630–0830 hours. The distribution over time was not uniform ($\chi^2 = 116.3$, df = 23, $p < 0.0001$). A harmonic regression analysis gave a statistically significant fit ($p < 0.001$, $R^2 = 64\%$) with the equation: frequency of onset = 48.1 + 0.94 cos (2$t$/24) + 13.1 sin (2$t$/24) + 11.2 cos (6$t$/24) + 0.83 sin (6$t$/24), where $t$ = time of day in hours.

Results
In 1154 patients with proven myocardial infarction we found two significant peak times for the onset of chest pain: 2330–0030 hours and 0630–0830 hours (figure). This five year prospective study confirmed the previously reported bimodal distribution.

Discussion
There is a clear circadian pattern to myocardial ischaemic chest pain. Several studies reported a significant rise in frequency during the early morning hours and some report a smaller secondary increase in frequency during the afternoon and late evening.4-11 As far as we are aware, however, this and our earlier study4 are the only ones to report an increased frequency...
at midnight. Why chest pain is more common at these times is unknown, though recent studies on the circadian rhythm of onset of myocardial infarction have suggested that the morning peak of incidence is related to other known daily rhythms.\textsuperscript{14} An obvious explanation for the early morning peak is the increase in physical and mental stress after waking.\textsuperscript{12} Sympathetic activity increases after waking and plasma concentrations of catecholamine increase. Cortisol concentration peaks early in the morning, generally before waking, and it remains high but falls during the period after awakening.\textsuperscript{13} Systemic arterial pressure,\textsuperscript{14} coronary vascular tone,\textsuperscript{15} and platelet aggregability\textsuperscript{12} also increase. Though fibrinolytic activity is low during sleep and still reduced soon after awakening it rises during this time.\textsuperscript{17}

The reasons for the midnight peak are less clear, though it could be linked to dilatation of the left ventricle at lower heart rates in the supine position with an increase in filling pressure, which has been reported to be associated with nocturnal ischaemia.\textsuperscript{18} Patients with resting angina and severe coronary stenosis often exhibit a nocturnal decline in their ischaemic threshold: the incidence of angina at rest was highest between 2000 and 2300 hours.\textsuperscript{19} There is evidence of differing circadian patterns of symptom onset in subgroups of patients with acute myocardial infarction: in patients with a history of congestive heart failure, or with non-Q wave infarction there was a pronounced peak only in the evening.\textsuperscript{20} The midnight peak may reflect altered circadian rhythms caused by late working hours, or individual behavioural differences. We are now collecting information on these differences and normal waking time and daily activities for another study.

There have been isolated reports of an evening peak, though not all studies have shown it to be significant. It is likely that a meta-analysis of all major studies would show that this peak is statistically significant, but the validity of the present analysis does not depend on it. It is unlikely that the same systematic bias operated for five years. The present data set (n = 1154) is one of the largest reported. The result of circadian analysis completely confirms the findings obtained in a large retrospective data set (n = 1099) obtained from the same location and processed by the same unit.\textsuperscript{1}

Patients are admitted directly to the coronary care unit via the emergency ambulance service. The average delay between reporting onset of symptoms and admission to the unit is about 30 minutes. The two main coronary care units admit on seven days a week from all parts of the city of Leicester and surroundings. The number of patients admitted at Leicester General Hospital is roughly 50% of the total, without any geographical, sex, or age bias.

We considered the possibility that patients presenting with nocturnal chest pain were overrepresented in our study group. But those taken ill at night are less likely to call help immediately and thus more likely to die before reaching the coronary care unit. As in most previous studies, we used subjective reports of onset of chest pain. None the less, the data suggest that, for acute myocardial infarction, subjective reports are consistent with objective measured.

It is unlikely that errors were introduced by patient recall because in most patients the data were carefully checked for accuracy with the spouse.

The observation of a circadian variation in the frequency of onset of chest pain in acute myocardial infarction has obvious therapeutic implications. It seems logical to target pharmacological treatment on the underlying physiological changes responsible for ischaemic events in those patients at risk. Ideally, this treatment should offer protection during the night and early morning hours.