Attenuation or absence of circadian and seasonal rhythms of acute myocardial infarction

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Abstract

Objectives—To examine the circadian, seasonal, and weekly rhythms of acute myocardial infarction, and to identify subgroups in whom the rhythms are attenuated or absent to provide further information about the mechanisms of the rhythms and the processes responsible for triggering plaque events.

Design and setting—Prospective, observational study in a general hospital.

Patients and methods—1225 consecutive patients admitted to a coronary care unit with acute myocardial infarction were studied. Admission rates were calculated according to the hour of the day (circadian rhythm), day of the week (weekly rhythm), and month of year (seasonal rhythm). The data were analysed for variations within the whole group and within subgroups.

Results—A weekly rhythm of acute myocardial infarction could not be demonstrated but there was a trend towards higher admission rates at the beginning of the week. However, the time of onset of symptoms showed significant circadian variation for the group as a whole, peaking in the morning (P = 0·006), against an otherwise fairly constant background rate. Subgroup analysis showed complete absence of the circadian rhythm in patients who were diabetic, South Asian, or taking β blockers or aspirin on admission. Significant seasonal variation in admission rates was also demonstrated for the group as a whole with a winter peak and a summer trough (P = 0·009). Again, no seasonal rhythm could be demonstrated in patients who were diabetic, South Asian, or taking β blockers or aspirin on admission.

Conclusions—The absence of circadian and seasonal rhythms of acute myocardial infarction in almost identical subgroups suggests that common mechanisms are involved in driving these rhythms. The autonomic nervous system is a likely candidate because the rhythms were absent in patients taking β blockers as well as in patients in whom derangement of autonomic function commonly occurs.

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Coronary syndromes often show circadian variability with a peak in the second quarter of the day. This applies to acute myocardial infarction,[1-6] sudden death,[7] stable angina,[8] and silent ischaemia.[9 10] We have previously confirmed a circadian rhythm for acute myocardial infarction within our own patient population and have also demonstrated a seasonal rhythm determined largely by environmental temperature.[11] In addition to these circadian and seasonal rhythms, the onset of acute myocardial infarction may be influenced by the day of the week, a number of investigators reporting a peak on Monday mornings.[12-15]

It is now clear that the circadian rhythm of acute myocardial infarction may be attenuated or absent in certain subgroups, particularly patients who are diabetic or taking β blockers.[4 6 16 17] Modified circadian rhythms have also been reported in women and smokers.[4] These findings have prompted speculation about the mechanisms that may be responsible for the circadian rhythm of acute myocardial infarction and have contributed to current concepts of the provocation of plaque events. Less is known about seasonal rhythm, and it is not known whether it shares common mechanisms with the diurnal rhythm or operates independently. The question is important because if the mechanisms that drive these rhythms can be identified, it will not only increase our understanding of the pathogenesis of infarction but may also permit application of treatment to protect patients during periods of heightened risk.

The present study examined the circadian, seasonal, and weekly rhythms of acute myocardial infarction. We tried to identify

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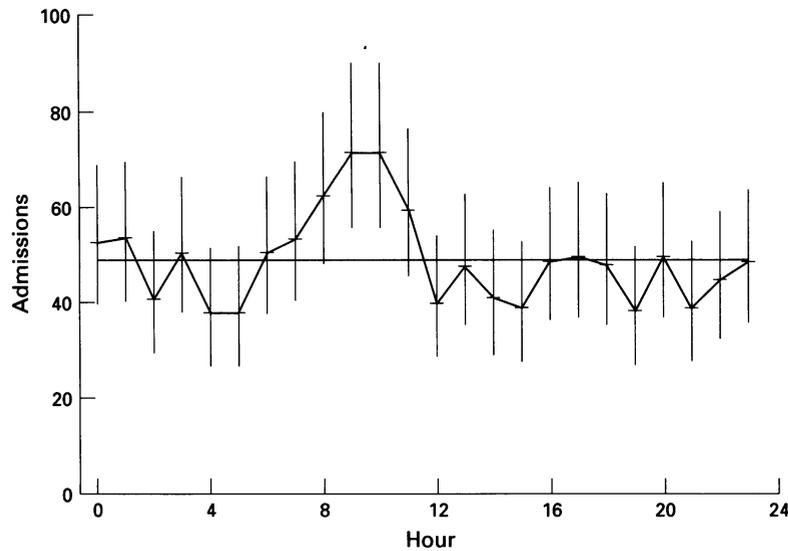Accepted for publication 27 November 1996

Table 1 Patient characteristics. Figures in parentheses indicate the number of patients for whom data were available

	Number (%)
Age (1225)	
< 65 years	695 (57)
≥ 65 years	325 (43)
Sex (1225)	
Men	900 (74)
Women	325 (26)
Smoking (1201)	
Non-smoker	566 (47)
Current smoker	635 (53)
Diabetes (1222)	252 (21)
Racial group (1225)	
White	916 (74)
South Asian	284 (23)
Other	25 (3)
Admitted on β blockers (1125)	166 (15)
Admitted on aspirin (1129)	146 (13)
Previous myocardial infarction (1223)	309 (25)

Figure 1   Admission rates by hour of day for 1182 patients. Test for heterogeneity, χ^2 = 43·5 on 23 degrees of freedom, P = 0·006. Error bars are 95% confidence intervals.
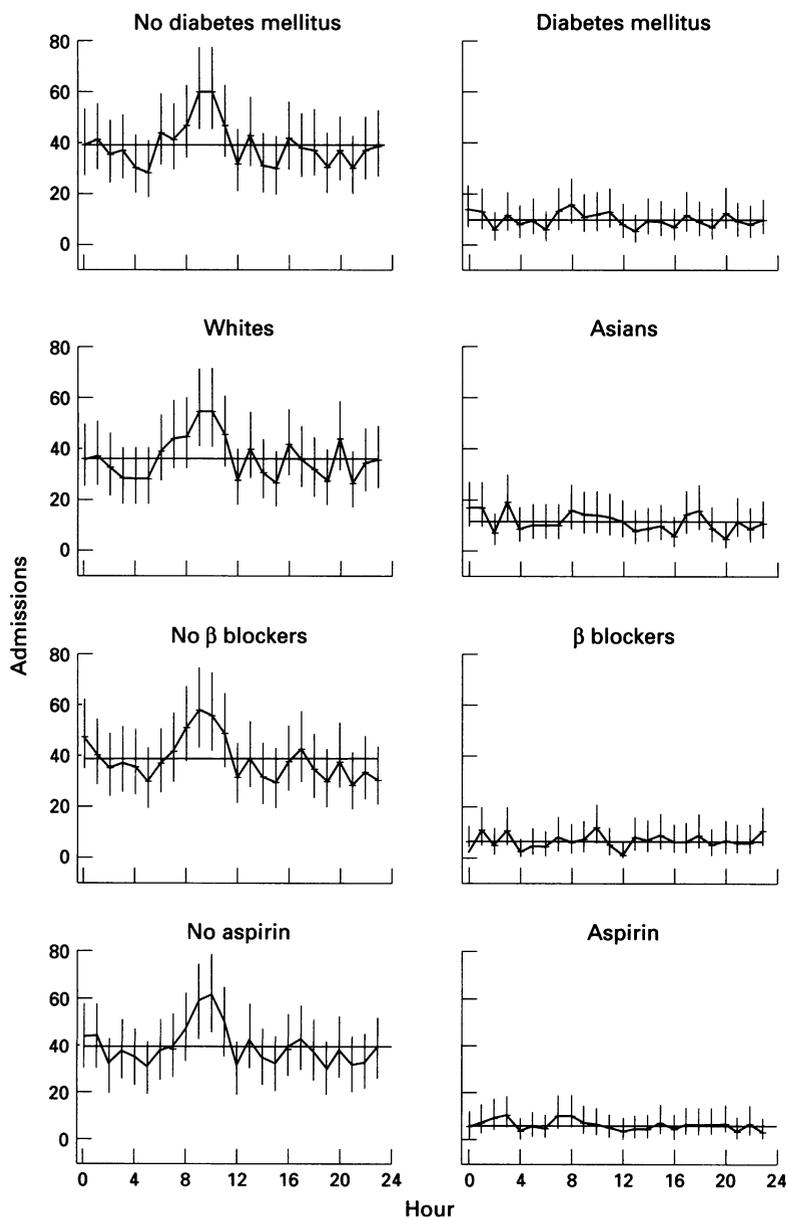

Figure 2   Admission rates by hour of day according to subgroups. Error bars are 95% confidence intervals.

subgroups in whom the rhythms are attenuated or absent, and to determine a link between the subgroups to provide further information about the mechanisms of the rhythms and, by inference, the mechanisms responsible for initiating the process of infarction.

Patients and methods

STUDY POPULATION

The study population comprised 1225 consecutive patients with acute myocardial infarction admitted to the coronary care unit of Newham General Hospital in London from 1 January 1988 to 31 December 1994. The diagnosis of acute myocardial infarction was based on any two of the following three criteria: (a) cardiac chest pain lasting at least 30 minutes; (b) electrocardiographic changes of myocardial infarction with ≥ 0·1 mV ST elevation in at least one standard lead or ≥ 0·2 mV ST elevation in two or more contiguous chest leads; (c) a diagnostic rise in creatine kinase to ≥ 400 IU/l (upper limit of reference range 200 IU/l).

DATA COLLECTION

Baseline data, including the date and time of onset of chest pain, details of treatment on admission, diabetic status, racial group, and smoking habit were collected prospectively at the time of admission by a clinician and entered on a customised database. Racial group was recorded in all patients by direct inquiry; South Asian was defined as Indian, Pakistani or Bangladeshi. A diagnosis of diabetes was recorded if the patient required insulin, oral hypoglycaemic drugs, or dietary sugar restriction. Smoking habit was classified into non-smokers (those who had never smoked or stopped prior to admission) or current smokers.

DATA ANALYSIS

Circadian rhythm was calculated according to the number of patients per hour admitted each day. Admission rates were also calculated according to the day of the week (weekly rhythm) and month of year (seasonal rhythm). Data were analysed for variations within the whole group and according to sex, racial group (excluding the 25 patients of Afro-Caribbean origin), diabetic status, smoking habit, history of myocardial infarction, and drugs being taken on admission (aspirin, β blockers). Tests of heterogeneity were applied.[18] Confidence intervals (95% CIs) were derived from tabulations of the Poisson distribution.

Results

The average (SD) age of the 1225 patients was 62·1 (11·9) years. Other baseline characteristics are summarised in table 1.

CIRCADIAN RHYTHM

The time of onset of symptoms, available in 1182 patients (97%), showed significant circadian variation with a morning peak centred around 0900 against an otherwise
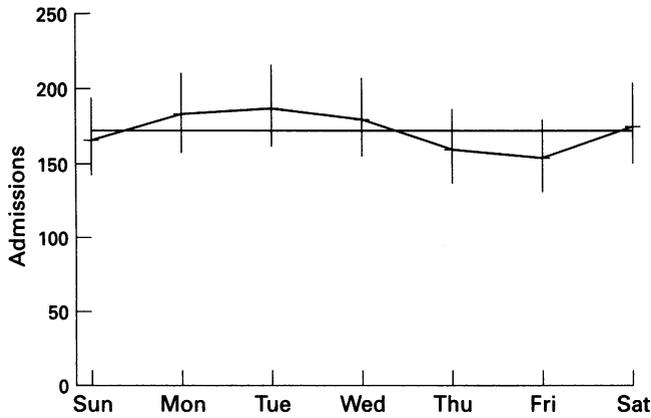
Figure 3 Admission rates by day of the week for 1225 patients. Test for heterogeneity: $\chi^2 = 5\cdot3$ on 6 degrees of freedom, $P = 0\cdot51$. Error bars are 95% confidence intervals.
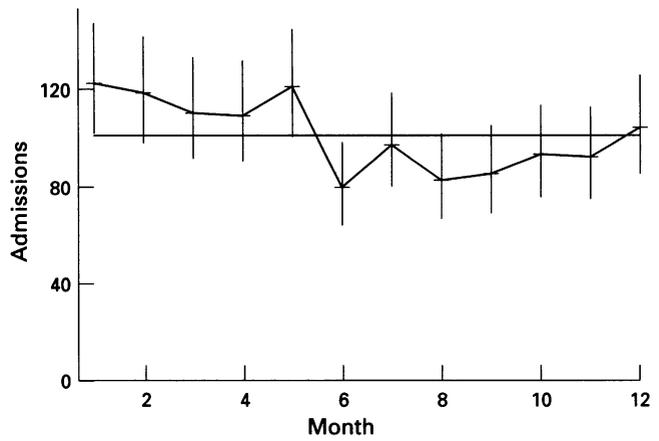

Figure 4 Admission rates by month of year for 1225 patients. Test for heterogeneity: $\chi^2 = 25\cdot2$ on 11 degrees of freedom, $P = 0\cdot009$. Error bars are 95% confidence intervals.
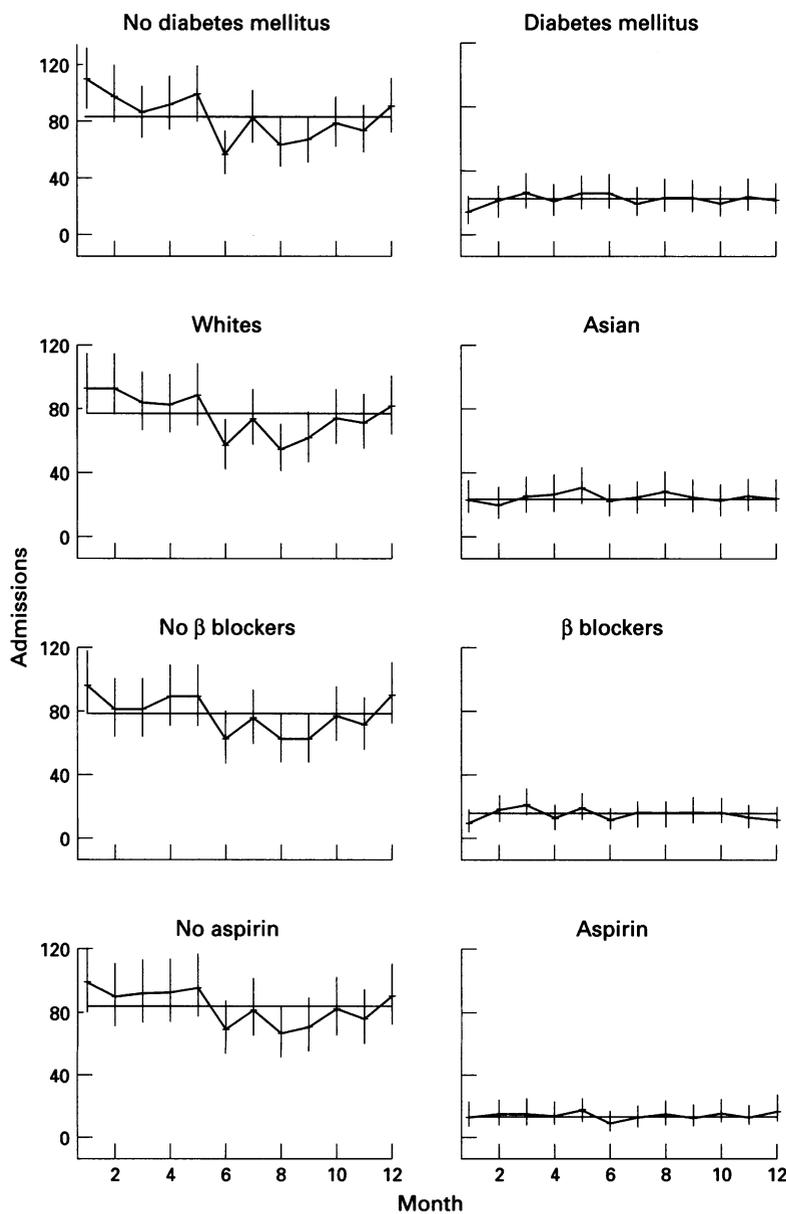

Figure 5 Admission rates by month of year according to subgroups. Error bars are 95% confidence intervals.

fairly constant background rate ($P = 0\cdot006$) (fig 1).

SUBGROUP ANALYSIS
In contrast to the group as a whole, the circadian pattern of symptom onset was either lost or attenuated in patients who were diabetic, South Asian, or taking β blockers or aspirin on admission, females, smokers or patients with a history of previous myocardial infarction (fig 2, table 2).

WEEKLY RHYTHM
Although there was a trend towards higher admission rates at the beginning of the week this was not significant ($P = 0\cdot51$); similarly, no significant variation could be demonstrated within subgroups (fig 3).

SEASONAL RHYTHM
Admission rates for the entire cohort were significantly higher during the winter than the summer months ($P = 0\cdot009$) (fig 4).

SUBGROUP ANALYSIS
In patients who were diabetic, South Asian, taking β blockers or aspirin on admission, and smokers, trends were strikingly similar to those of circadian variation, in that no seasonal variation could be demonstrated (fig 5, table 2).

Discussion

The circadian and seasonal rhythms of acute myocardial infarction are well documented. Previous investigators have reported an absence of circadian rhythm in diabetics and patients taking β blockers, an observation confirmed by the present study.[4 6 16 17] We have extended this observation by demonstrating absence of circadian rhythm not only in diabetics and patients taking β blockers but also in South Asians and patients taking aspirin. Moreover, we have shown for the first time that the seasonal variability of acute myocardial infarction is absent in almost identical subgroups, suggesting that common mechanisms may be involved in driving these rhythms.

Table 2 Subgroup analyses of admission rates by hour of day and month of year. Results are derived from tests for heterogeneity

	Admission by hour of day			Admission by month of year		
	Number	χ^2	P	Number	χ^2	P
Sex						
Men	873	36·7	0·03	900	21·2	0·03
Women	309	26·6	0·20	325	18·3	0·07
Racial group						
White	881	42·6	0·005	917	28·9	0·002
South Asian	276	28·8	0·15	283	4·0	0·97
Diabetes						
Non-diabetic	939	39·8	0·02	972	36·5	0·0001
Diabetic	241	19·4	0·68	250	6·5	0·84
Smoking status						
Non-smokers	548	47·6	0·001	566	18·4	0·07
Smokers	616	20·4	0·56	635	16·0	0·14
Infarct history						
First infarct	881	43·3	0·004	914	22·3	0·02
Previous infarct	301	29·5	0·13	309	18·9	0·06
Admission drugs						
No β blockers	931	35·2	0·04	959	22·1	0·02
β blockers	159	25·6	0·27	166	10·2	0·51
No aspirin	954	39·7	0·01	983	18·2	0·08
Aspirin	140	19·6	0·61	146	5·75	0·89

The hour of pain onset and the month of admission were available in 1182 and 1225 patients, respectively.

If common mechanisms are involved in the circadian and seasonal rhythms of acute myocardial infarction, the autonomic nervous system is a likely candidate and several studies have pointed to a link between sympathetic activation and ischaemic events in patients with coronary artery disease. Deedwania and Nelson[19] showed that in patients with angina the morning peak of ischaemic episodes was associated with a simultaneous peak of heart rate and blood pressure and, since the minute by minute control of these haemodynamic variables is predominantly a function of the autonomic nervous system, they suggested that surges in sympathetic activity might be responsible for their findings. More recently we confirmed approximately simultaneous morning peaks of sympathovagal balance and ischaemic ST change in patients with angina undergoing Holter monitoring.[20] These findings are consistent with the known circadian rhythm of blood catecholamine concentrations[21] and with current concepts of ambulatory ischaemia, which view it as the combined response to increases in myocardial oxygen demand and reductions in supply, both of which are amenable to influence by sympathetic activation. Blood catecholamine concentrations also rise with exposure to cold and lead to exaggeration of the blood pressure response to exercise in patients with coronary artery disease who frequently report symptomatic deterioration in the winter.[22]

A major haemodynamic determinant of plaque vulnerability is circumferential wall stress and this in turn is largely determined by systolic blood pressure.[23] It is possible to speculate, therefore, that the same sympathetic activation that causes the morning peak in myocardial ischaemia and the deterioration of angina in winter might also drive the circadian and seasonal rhythms of myocardial infarction by provoking plaque events through rises in blood pressure. Certainly, modification of sympathetic activity is likely to account for the observation that neither of these rhythms could be demonstrated in patients taking β

blockers. It may also account, at least in part, for the absence of these rhythms in diabetic patients, a group in whom autonomic dysfunction is common and associated with impairment of normal circadian patterns of sympathovagal activity.[24-26] Over 40% of the South Asians included in the present study were diabetic (compared with 14% of the white patients) and this is probably sufficient to explain the absence of circadian and seasonal variability in this ethnic group, although whether the insulin resistance syndrome, which appears to predispose them to coronary artery disease, itself affects autonomic function is not known. Our data also showed severe attenuation of circadian rhythm in patients with previous myocardial infarction, a group in whom ischaemic and sympathovagal rhythms are diminished or lost altogether in the early post-infarction period with continuing impairment for up to 12 months.[20 27-29] Add to this the fact that 26% of these patients were taking β blockers at the time of admission (compared with 11% of patients with first infarcts), the attenuation of circadian variability might well be related to deranged autonomic function.

Thus, across a range of subgroups it is possible to associate pharmacological or pathological derangement of autonomic function with attenuation of circadian and seasonal rhythms of myocardial infarction. If this association is correct, it lends weight to the hypothesis that both rhythms are driven by the autonomic nervous system, increased sympathetic activity in the morning and the winter, predisposing to plaque events at these times. The risk attributable to heightened sympathetic activity may not be limited to its haemodynamic effects. Thus, sympathetic stimulation may enhance platelet aggregation through increases in β-thromboglobulin and platelet factor 4,[30] with cyclical variations in plasminogen activator inhibitor and other haemostatic variables making a further potential contribution to the increased risk of myocardial infarction in the mornings and the winter.[31 32] Our finding that aspirin therapy effectively abolished both the circadian and seasonal rhythms of infarction would, therefore, be consistent with its antiplatelet effects providing protection against coronary thrombosis at these times of heightened risk.

Not all the findings in the present study are readily explained in terms of altered autonomic or haemostatic function. The absence of circadian variability in women is hard to account for although it has been commented upon by other investigators.[4] Similarly, there is no clear explanation for the absence of circadian and seasonal variability in smokers although it is possible that nicotine induced sympathetic stimulation and the prothrombotic effects of smoking (mediated largely by increased circulating fibrinogen concentrations) might together be sufficient to obscure these rhythms.[33] It is also possible that in some of the smaller subgroup analyses the rhythms were obscured by background noise, although the striking parallels between subgroups in

whom both circadian and seasonal rhythms were absent makes this unlikely.

Previous authors have reported an increased risk of myocardial infarction on Mondays and have speculated that this too reflects heightened sympathetic activity on the first day back to work.[12-15] We were unable to confirm this, although there was a tendency for myocardial infarction to occur more commonly in the first part of the week. It should be recognised, however, that 50% of the patients included in our study were over the retirement age (60 for women, 65 for men) and although the employment status of the remainder was unknown it was likely to be low in this socially deprived part of east London. The increased risk of myocardial infarction on Mondays reported by previous investigators appeared to be confined to the working population[15] and the absence of a weekly rhythm in the present study was, therefore, not surprising.

In conclusion, this study has demonstrated attenuation or absence of both circadian and seasonal rhythms of acute myocardial infarction in almost identical subgroups. This suggests that common mechanisms may be involved in driving these rhythms, the autonomic nervous system being a likely candidate. Thus, the rhythms were absent in patients taking β blockers and in patients in whom derangement of autonomic function commonly occurs. The absence of circadian and seasonal rhythms in diabetics, South Asians, smokers and patients with previous myocardial infarction suggests differences in the mechanisms of infarction in these high risk subgroups which may have important implications for prophylactic care.

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