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Absence of circadian variation in the onset of acute myocardial infarction in diabetic subjects

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Abstract

***Objectives*—To investigate the circadian pattern of acute myocardial infarction in non-insulin-dependent diabetic patients and to compare it with that of controls.**

***Background*—Previous studies have shown that there is a circadian variation in the incidence of acute myocardial infarction, but there are few data on diabetic subjects.**

***Methods*—A hospital based prospective case-control study.**

***Results*—196 diabetic patients and 196 age and sex matched controls were admitted with a diagnosis of acute myocardial infarction during the study period. In 32 diabetic patients and 38 controls, the time of onset of myocardial infarction was unknown; in 34, 44, 42, and 44 diabetic patients the onset was in the first to fourth quarters respectively ($\chi^2 = 1{\cdot}66$, NS). The corresponding figures for the controls were 30, 56, 45, and 27 ($\chi^2 = 13{\cdot}9$, $P < 0{\cdot}005$). The difference between the two groups was highly significant ($\chi^2 = 10{\cdot}3$, $P < 0{\cdot}025$).**

***Conclusions*—Diabetic subjects do not show a significant circadian variation in the onset of acute myocardial infarction.**

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Keywords: myocardial infarction; circadian variation; diabetes

The time onset of acute myocardial infarction has circadian variation with a significant morning peak.[1–3] A smaller evening peak has been less consistently reported.[4 5] Possible mechanisms for the circadian rhythm in the incidence of acute myocardial infarction include a morning increase in platelet aggregability and activation,[6 7] a morning decline in fibrinolytic activity,[8–10] and a morning rise in blood viscosity[11] and arterial blood pressure.[12 13] Interestingly other cardiovascular events such as sudden death[14 15] and ischaemic stroke[16 17] have also been shown to have a similar circadian rhythm.

The aim of this study was to investigate the circadian pattern of acute myocardial infarction in diabetic patients and to compare it to that of controls.

Methods

One hundred and ninety six consecutive non-insulin-dependent (NIDDM) patients who were admitted to the coronary care unit with a diagnosis of acute myocardial infarction were entered into the study. The diagnosis of NIDDM was based on World Health Organisation criteria. Age and sex matched non-diabetic patients admitted with acute myocardial infarction were randomly selected as controls. Patients with known impaired glucose tolerance or a blood glucose of more than 7·8 mmol/l on admission were excluded from controls. The diagnosis of acute myocardial infarction was established on the basis of a creatine kinase activity of more than twice the upper limit of the reference range and diagnostic electrocardiographic (ECG) changes. The latter consisted of at least one of the following: ST segment elevation of at least 2 mm 0·08 s from the J point in at least two related electrical fields, with typical evolutionary changes; appearance of new pathological Q waves in at least two related electrical fields; appearance of prominent R waves in V_1 and V_2 when compared with previous ECGs.

For both diabetic and control patient the time of onset of symptoms was recorded on admission.

STATISTICAL ANALYSIS

The χ^2 test was used to assess the significance of circadian variation in the diabetic patients and in controls and between the two groups. Student's t test was used to assess the significance between the peak incidence of acute myocardial infarction and the average incidence during the remainder of the day.

Results

The proportion of patients from the diabetic and control groups previously on aspirin (within one week), β adrenergic receptor blockers, and calcium channel blockers is shown in table 1. Table 2 shows the number of diabetic and control patients with onset of acute myocardial infarction in each of six-hour intervals. In 32 diabetic patients and 38 controls the time of infarction could not be determined due to the gradual onset of symp-

Table 1 Previous use of medication

	Diabetic patients (n = 196)	*Controls (n = 196)*	*Statistical significance*
Aspirin	35	25	NS
β Blockers	39	46	NS
Calcium antagonists	31	35	NS
Anticoagulants	1	2	NS

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Table 2 Circadian variation of myocardial infarction

Time of day (0·00–24·00 h)	*0–6 h*	*6–12 h*	*12–18 h*	*18–24 h*	*Total*	*Unknown*
Number of diabetic patients	34	44	42	44	164	32
Number of controls	30	56	45	27	158	38

toms. The mean age of those with a known time of infarction was 66·5 years in the diabetic group (n = 164) and 66·1 years in the controls (n = 158) (NS). Of the diabetic subjects, 57% with a known time of onset of myocardial infarction were male compared to 58·2% of controls (NS). The proportion of patients with a previous acute myocardial infarction was 19·4% in the diabetic group and 20·4% in the control group (NS).

There was no circadian variation in the incidence of acute myocardial infarction in diabetic subjects (χ^2 = 1·66, NS). The circadian variation was significant in the controls (χ^2 = 13·9, P < 0·005). The peak incidence occurred in the second quarter (6 am to 12 noon); this was statistically higher than the average incidence in the remainder of the day (P < 0·02). The difference between the circadian pattern of diabetic patients and controls was highly statistically significant (χ^2 = 10·37, P < 0·025).

The outcome of the diabetic and control groups has already been reported.[18]

Discussion

Our study showed no significant circadian variation in the incidence of acute myocardial infarction in diabetic subjects. Controls showed a monophasic circadian rhythm in the onset of acute myocardial infarction, similar to that reported in the general population. The difference between the diabetic and control groups was statistically highly significant.

The diabetic and control groups were matched for prior use of aspirin, β adrenergic receptor blockers, and calcium channel blockers. These have been reported to affect the circadian pattern of acute myocardial infarction.[2 19–22] Long acting nitrates probably do not affect the circadian pattern.[21] Although there are no data available, anticoagulants might conceivably also alter the circadian rhythm of acute myocardial infarction. Very few of the patients in the present study were on anticoagulants, with no statistically significant difference between the diabetic and control groups.

To our knowledge, the absence of a circadian pattern in the incidence of acute myocardial infarction in diabetic patients has not previously been documented in a case-control prospective study. Our data are consistent with those of the ISIS-2 trial.[22] However, in the latter the time of onset of symptoms was only indirectly estimated. More importantly, patients with a contraindication to streptokinase or aspirin were excluded.[22 23] This may have introduced a bias in favour of those without complications. Furthermore the diabetic and non-diabetic groups were not matched for previous use of medication, and as the authors themselves note, the observed difference between the two groups could have simply been a function of the use of medication.

Hjalmarson *et al*[4] reported equal peaks in the morning and evening of myocardial infarction in diabetic patients, as in those on β blockers. However this was not a case-control study but rather a part of a multiple subgroup analysis; there was no matching for previous use of medication.

The explanation for the more even circadian pattern in the onset of acute myocardial infarction in diabetic subjects is unclear and requires further investigation. However, it could be related to the blunting of diurnal variation in physiological variables. The morning rise in platelet aggregability has been reported to be lost in diabetic patients by some investigators[24] but not by others.[25] Diabetic subjects also show diminished circadian variation in blood pressure[26]; this could be related to autonomic neuropathy.[27 28]

Another possible explanation is that, because of more advanced microvascular and macrovascular disease, there is a smaller thrombotic element of the acute occlusion in diabetic subjects with acute myocardial infarction than in controls. It has been reported that when acute myocardial infarction is preceded by angina pectoris there is an increased likelihood of extensive coronary artery disease (fixed stenosis),[29 30] and that preceding angina is commoner in diabetic patients.[18]

The lack of circadian variation in the onset of acute myocardial infarction may have therapeutic implications. As cardioprotective medication has been shown to exert its effect mainly by diminishing the morning peak in acute myocardial infarction,[21 22] the optimal timing of such medication may differ in diabetic subjects from their non-diabetic counterparts.

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