Circadian Variation in the Onset of Myocardial Infarction

Effect of Duration of Diabetes

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There are conflicting reports regarding circadian variation in the onset of acute myocardial infarction (MI) among patients with diabetes. We therefore, studied the circadian pattern of the incidence of acute MI in patients (n = 3,882) who were enrolled in the Onset Study stratified by the presence, type, and duration of diabetes. The Onset Study was conducted at 64 U.S. medical centers between August 1989 and September 1996. We used harmonic regression model to evaluate the circadian variation of MI symptom onset in patients with and without diabetes. Subgroup analysis was performed according to the presence, type, and duration of diabetes by the χ^2 test (dividing the day into four 6-h intervals). Patients without diabetes exhibited a prominent morning peak in the incidence of acute MI symptom onset ($P < 0.001$). In contrast, patients with type 1 diabetes and type 2 diabetes ≥5 years had a marked attenuation of the morning peak. Patients who had type 2 diabetes diagnosed within the previous 5 years had a pattern of onset of acute MI similar to patients without diabetes. Patients with type 1 diabetes and those with type 2 diabetes ≥5 years have an attenuation of the morning peak in acute MI. Inconsistency in observation of such an effect in patients with diabetes in the past may well have been due to difference in the duration of diabetes and thus the variable extent of underlying autonomic dysfunction. *Diabetes* 52:1464–1468, 2003

The onset of acute myocardial infarction (MI) varies throughout the day, with a peak in the morning hours and a trough at night (1–3). However, there are conflicting reports regarding circadian variation in the onset of acute MI among patients with diabetes (4–6). Possible reasons for the inconsistency in the literature might be due to difference in the duration of diabetes and thus the extent of underlying autonomic dysfunction.

Diabetes is associated with an abnormal circadian pattern of several physiologic processes, including concentrations of glucose (7) and circulating glucocorticoids (8,9). Furthermore, diabetic neuropathy associated with a longer duration of diabetes may lead to loss of the normal circadian pattern of autonomic nervous system activity (10,11) and altered normal circadian variation in blood pressure with a loss of the nocturnal dip (12,13). Only recently, Liao et al. (14) showed that a lower heart rate variability, a reflection of impaired cardiac autonomic control, was also associated with development of coronary heart disease among individuals with diabetes. Zarich et al. (15) performed autonomic nervous system testing on patients with ambulatory ischemia and showed that patients with moderate to severe autonomic nervous system dysfunction did not experience a morning peak of ischemia. To determine whether duration of diabetes has an impact on the circadian variation of MI onset, we studied the circadian pattern of acute MI symptom onset in patients with diabetes from among patients enrolled in the Determinants of Myocardial Infarction Onset Study (16).

RESEARCH DESIGN AND METHODS

The Onset Study was conducted in 64 medical centers in the United States. Between August 1989 and September 1996, 3,882 patients (1,258 women and 2,624 men) were interviewed at a median of 4 days (range 0–30) after having an MI.

Trained research interviewers identified eligible patients by reviewing coronary care unit admission logs and patient charts. For inclusion, patients were required to have a creatine kinase level above the upper limit of normal for each center, positive MB isoenzymes, an identifiable onset of symptoms typical of infarction, and the ability to complete a structured interview. The institutional review board of each center approved this protocol, and interviewers obtained informed consent from each patient.

Interviewers used a structured data abstraction and questionnaire form. Information collected from each interview and chart review included patient age, sex, medical history, and medication use (both prescription and nonprescription). We used the patient-reported time that the discomfort began as the onset time for acute MI, a method previously validated with the use of serial creatine kinase values (1).

We defined diabetes as a history of diabetes obtained during chart review or the current use of any hypoglycemic medication. The type of treatment for diabetes was considered as diabetes controlled by diet, use of oral hypoglycemics (first- and second-generation sulfonylureas, metformin), or insulin therapy. Duration since diagnosis of diabetes was established from the medical records if available; otherwise, interviewers asked the patients to report the duration.

The hourly frequency of the onset of MI symptoms was graphically displayed. We used harmonic regression models to evaluate the circadian

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MI, myocardial infarction.

TABLE 1
Characteristics of Onset Study patients according to medical history of diabetes

Variables*	Diabetes (n = 814)	No diabetes (n = 3,068)	P value
Age (years)	64 ± 11.5	60.6 ± 12.9	<0.001
Female	356 (43.8%)	902 (29.4%)	<0.001
White race	649 (80.6%)	2,694 (88.6%)	<0.001
BMI (kg/m^2)	28.5 ± 5.6	26.9 ± 5.0	<0.001
Current smoker	171 (21.3%)	1,109 (36.4%)	<0.001
Former smoker	353 (43.4%)	1,200 (39.1%)	0.03
Obese (>29 kg/m^2)	355 (44.0%)	882 (29.0%)	<0.001
†No exertion	698 (85.7%)	2,292 (74.7%)	<0.001
Education			<0.001
Less than high school	214 (26.8%)	626 (20.9%)	
Complete high school	350 (43.8%)	1,238 (41.3%)	
Some college	236 (29.5%)	1,136 (37.9%)	
Past cardiac history			
Previous MI	284 (35.5%)	743 (24.7%)	<0.001
Angina	261 (32%)	689 (22.4%)	<0.001
Hypertension	476 (58.5%)	1,220 (39.8%)	<0.001
CHF, baseline	31 (3.8%)	540 (1.8%)	0.001
Regular use of medication			
Aspirin	321 (39.4%)	1,136 (37.0%)	0.2
Ca blockers	289 (35.5%)	638 (20.8%)	<0.001
Digoxin	85 (10.4%)	171 (5.6%)	<0.001
β-blockers	189 (23.2%)	644 (21%)	0.17
ACE inhibitors	158 (22.7%)	330 (10.7%)	<0.001
Characteristics of index hospitalization			
CHF	173 (21.3%)	344 (11.2%)	<0.001
Q-wave infarction	252 (50.6%)	1,126 (58.5%)	0.001
Thrombolytic therapy	258 (31.7%)	1,291 (42.1%)	<0.001

*Missing data; 39 patients for race, 40 patients for BMI, 32 patients for smoking status, 73 patients for previous MI, 82 patients for education, and 1,460 for Q-wave infarction. †Physical exertion ≥6 METs less than once weekly. CHF, congestive heart failure.

variation of onset of MI symptoms in patients with diabetes and patients without diabetes as previously reported (17). For further analysis we divided the day in into four 6-h intervals from 0:00 to 5:59, 6:00 to 11:59, 12:00 to 17:59, and 18:00 to 23:59. The presence of circadian variation was tested using the χ^2 one degree of freedom goodness-of-fit test for uniform distribution. Difference in the circadian variation in the onset of MI was assessed using a Pearson χ^2 test.

RESULTS

The characteristics of the study population have been previously reported (16–18) and are summarized in Table 1. Figure 1 shows the hourly distribution of MI symptom onset among patients with and without a history of diabetes. A statistically significant circadian pattern of MI symptom onset with a single peak in the morning hours was observed in patients without diabetes ($P < 0.001$), whereas no such peak was observed among 814 patients with a history of diabetes ($P = 0.16$).

Table 2 shows the distribution of the time of MI onset in 6-h intervals, according to the type and duration of diabetes. A significant morning peak in MI symptom onset was seen among patients without diabetes and was somewhat blunted in the entire group of patients with diabetes. Further analysis revealed that the expected morning peak in the MI symptom onset was preserved among patients who had type 2 diabetes diagnosed within the past 5 years. However, there was no apparent circadian variation in MI onset among patients with type 1 diabetes or those with type 2 diabetes of 5 years or more duration.

In a sensitivity analysis, we found that the circadian variation in MI onset was absent in all patients with diabetes for 5 or more years, regardless of treatment type. Among patients with diabetes for <5 years, the morning peak was maintained only among those who were treated with diet or oral hypoglycemic agents but was lost among insulin-treated patients. This may reflect a more severe disease or perhaps a longer preclinical phase among patients who are treated with insulin soon after receiving the diagnosis.

Although not a previous hypothesis, we noted that patients with diabetes seemed to have a higher proportion of infarcts in the late evening at approximately 22:00 to 23:00 (Fig. 1). Despite this, the harmonic regression analysis did not demonstrate a statistically significant secondary peak in MI onset among patients with diabetes ($P = 0.13$).

DISCUSSION

In this multicenter study of early survivors of acute MI, we observed a circadian pattern of acute MI symptom onset in patients with and without a history of diabetes. However, patients with type 1 diabetes and those with type 2 diabetes for 5 or more years had a marked attenuation of the morning peak in acute MI.

Hjalmarson et al. (4) were the first to show that the characteristic day–night pattern in the onset of MI is altered in patients with diabetes. These findings have been confirmed by several studies (19–22). In conflicting re-

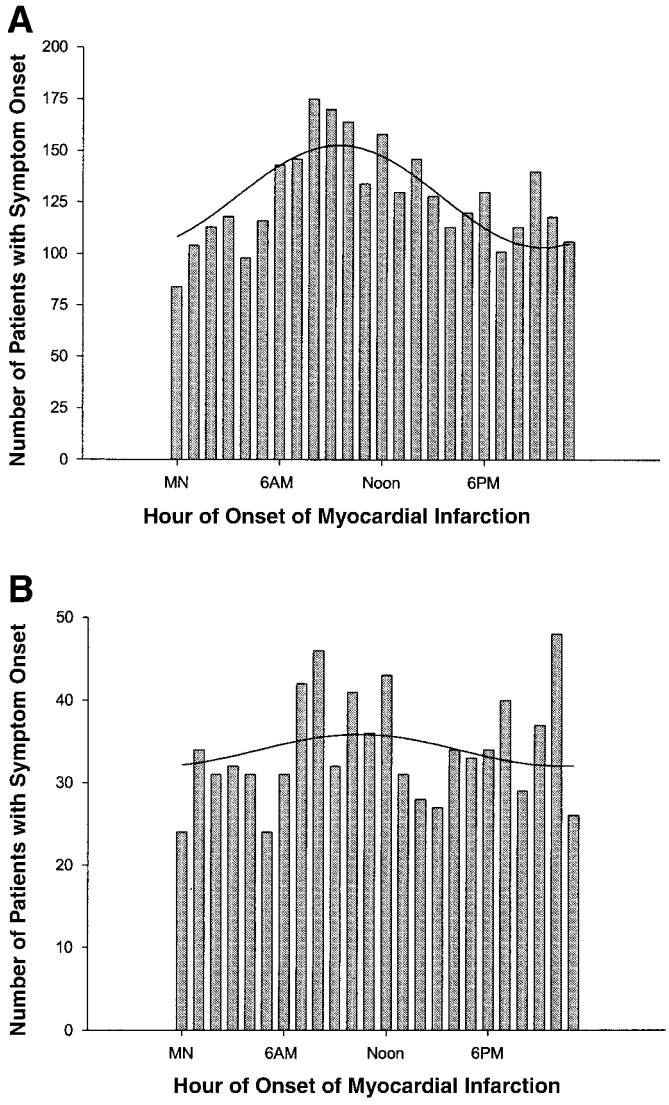

FIG. 1. Hourly frequency distribution of time of symptom onset of MI. *A*: Distribution in patients without a history of diabetes ($n = 3,068$, $P < 0.001$). *B*: Distribution in patients with diabetes. The line represents the fitted harmonic regression model ($n = 814$, $P = 0.16$). *P* values from the one degree of freedom goodness-of-fit test for uniform distribution. MN, midnight.

ports, other studies failed to show such a variation in the circadian pattern in the onset of MI (5,6,23,24) among patients with a history of diabetes.

A surge in sympathetic activity and vagal withdrawal in the morning hours alters homodynamic forces and may cause atherosclerotic plaques to rupture in the morning (25). Morning elevation in plasma catecholamines and renin levels, heart rate and blood pressure, and coronary blood flow (26–29) may increase shear forces in the coronary arterial bed, thus promoting plaque disruption and causing unstable angina and acute MI (30). Also, a morning increase in platelet reactivity may make a thrombus more likely to grow and cause symptoms (27). It has been demonstrated that patients who receive β-blockers fail to exhibit the morning increase in the incidence of MI (31,32).

This concept that the autonomic nervous system plays an important role in determining the circadian pattern of cardiovascular events suggests that in patients with diabetes, abnormalities in the circadian rhythm of autonomic tone may be responsible for the altered temporal onset of cardiovascular events (33,34).

Autonomic neuropathy is common in diabetes, affecting 8% of patients with recently diagnosed type 1 diabetes (35). In patients with type 2 diabetes, Toyry et al. (36) observed that the risk of developing parasympathetic neuropathy increased sharply after 5 years, and prevalence for combined autonomic neuropathy reached 65% after 10 years of follow-up. In a recent study in patients with type 2 diabetes, cardiac sympathetic dysinnervation was observed even before electrocardiogram-based cardiac autonomic neuropathy was diagnosed (37).

As previously mentioned, in the general population, the circadian rhythm of sympathovagal balance consists of a daytime prevalence sympathetic activity with a prominent increase in parasympathetic activity during the night (24). Bernardi et al. (38) demonstrated that diabetic autonomic neuropathy is associated with a marked diminution of parasympathetic activation during sleep. Sayer et al. (39) found that the rhythm of sympathovagal balance was significantly attenuated in patients with diabetes compared with those without diabetes. Similarly, patients with diabetes and symptomatic autonomic neuropathy have been shown to have markedly impaired heart rate variability (40,41). Lower heart rate variability in turn has been shown to be associated with an increased risk of development of coronary heart disease in individuals with diabetes (42). Another indicator of autonomic dysfunction in patients with diabetes is increased QT dispersion (43), which is associated with an increased risk of cardiovascular events in this patient population (44,45). Furthermore, increased QT dispersion has been associated with blunted circadian variation in blood pressure and altered sympathovagal balance in patients with type 1 diabetes (46).

Other important physiological correlates of cardiac autonomic dysfunction associated with more prolonged diabetes include loss of normal nocturnal dip in blood pressure during the night (47), blunted circadian variation

TABLE 2
Circadian variation of acute MI by type and duration of diabetes

	n	0:00–5:59	6:00–11:59	12:00–17:59	18:00–23:59	*P* value*
No diabetes (%)	3068	21	30	26	23	<0.001
All diabetes (%)	814	22	28	24	26	0.06
Type of diabetes						
Type 2 <5 years (%)	246	18	31	24	26	0.03
Type 2 ≥5 years (%)	258	23	23	28	26	0.65
Type 1 (%)	137	25	28	21	26	0.73

*P value for 1 degree of freedom χ^2 goodness-of-fit test. Duration of diabetes was missing for some patients.

of fibrinolytic activity and plasminogen activator inhibitor-1 antigen levels (48), persistent elevation of factor VII antigen and von Willebrand factor antigen (48), and increased platelet activation (49). 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.

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.

Our study demonstrates that the circadian morning peak of MI symptom onset is attenuated in patients with type 1 diabetes or type 2 diabetes for 5 or more years, 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 and thus the variable extent of underlying autonomic dysfunction. Variation in the mechanism producing MI may have implications for prevention in patients with diabetes.

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