Differing Circadian Patterns of Symptom Onset in Subgroups of Patients With Acute Myocardial Infarction*

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Circadian variation of the onset of acute myocardial infarction has been noted in many studies and may carry important pathophysiologic implications. However, only a few previous studies have attempted subgroup analyses. In 4,796 patients with documented acute myocardial infarction, the time of onset was recorded. As in other studies, the peak of onset occurred in the morning from 6:01 AM to 12:00 noon, and 28% of the population (1.16 times the average percentage for the other time periods) experienced symptom onset in that period (p<0.001). There was a second, lower peak (25%) in the evening between 6:01 PM and 12:00 midnight, which was also observed in some previous studies. We sought to determine whether or not the presence of subgroups with specific clinical characteristics would exhibit different patterns and thereby contribute to these peaks in the overall population. In patients with a history of congestive heart failure (n=606) or with non–Q wave infarction (n=832), a pronounced peak (29%) occurred only in the evening. Two nearly equal peaks were observed in patients older than 70 years of age (n=1,422), smokers (n=2,057), diabetics (n=767), women (n=1,213), and patients taking β-blocking drugs (n=847). Finally, in patients with a previous myocardial infarction (n=1,104), no peaks were observed. In a subgroup of patients (n=1,084) free of the most important modifying factors, there was a single very pronounced late morning peak (32%, 1.39 times the average percentage for the other time periods, p<0.001) without evidence of a second evening peak. It is concluded that marked differences in diurnal patterns of myocardial infarction onset occur in subgroups of patients with modifying factors, particularly non–Q wave infarction, smoking, β-blocker use, diabetes, prior congestive heart failure, and prior myocardial infarction. The circadian pattern observed in a given total population reflects the contributions of these subgroups. (Circulation 1989;80:267–275)

A circadian variation in the frequency of onset of acute myocardial infarction has been described in a number of studies during the past 25 years.1–8 Most show an increased onset in the morning with a peak incidence between 6:00 AM and 12:00 noon, although a secondary peak in the late evening has also been reported in some studies.1–3,5–7 A circadian variation in onset of other manifestations of cardiac ischemia, usually with a late morning peak, has also been reported for sudden death, stable and unstable angina pectoris, and ST segment changes of silent myocardial ischemia.9–14 The World Health Organization multicenter study showed only a morning peak in a large number of patients younger than 65 years of age.4 However, some of the populations from individual study centers did exhibit an evening peak, and others showed different patterns. These differences could be due in some instances to small

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population numbers, to different customs within the countries represented in the study, or to differences in the populations with respect to patients with various modifying factors. The latter possibility has not been considered previously.

Few studies of circadian rhythm have analyzed subsets of patients. In a recent study by Muller et al, gender, age, smoking or coffee drinking habits, and a history of angina pectoris or of myocardial infarction were reported not to alter the characteristic pattern of a morning peak of myocardial infarction onset; however, the characteristic morning pattern was not detected in patients receiving β-blockers before the onset of infarction. In preliminary reports, patients with non-Q wave infarction appear to exhibit a lack of the typical circadian pattern.\textsuperscript{15,16}

The purpose of the present study was to further analyze circadian patterns in the onset of symptoms of acute myocardial infarction in the above subgroups and in subgroups with other characteristics that are considered to reflect or influence the physiologic status of the patient, including a history of hypertension, diabetes, or congestive heart failure. Thus, our overall goal was to determine whether or not such subgroups exhibit different diurnal patterns and can thereby contribute to the overall pattern of onset in a given total population.

\textbf{Methods}

\textbf{Patients}

The date and time of symptom onset were recorded in 4,796 patients (25\% women; age, 63±12 [mean±SD] years) who were later determined to have had an acute myocardial infarction based on at least two of the following criteria: 1) characteristic chest pain, 2) electrocardiographic changes with evolution of Q waves (Q wave infarction) or typical ST segment and T wave changes without Q waves (non-Q wave infarction), and 3) typical elevation of creatine kinase (CK) (more than one value at least 2 standard deviations above the laboratory normal measured by 6-hour sampling). The third criterion was required for non-Q wave infarction. Q waves acceptable for diagnosis were as follows: 1) anterior, Q wave ≥0.03 second in any precordial lead, 2) inferior, Q wave in leads III, and aVF ≥0.03 second or > 25\% of R wave in depth, and 3) lateral, Q wave in leads I and aVL ≥0.03 second or > 25\% of R wave. Posterior infarctions were those resulting in an initial R wave in lead V\textsubscript{1} or V\textsubscript{2} of 0.04 second with R/S greater than 1. More than 98\% of patients had characteristic chest pain, and nearly all of the remaining 2\% exhibited other symptoms such as dyspnea, orthopnea, syncope, or nausea that brought them to the emergency room.

The patients were part of a multicenter study supported by the Specialized Center of Research (SCOR) on Ischemic Heart disease at the University of California, San Diego (UCSD SCOR Collaborative Database), in which data were collected prospectively to study the natural history of acute myocardial infarction. One criterion for inclusion in the study was admission to the coronary care unit within 24 hours of symptom onset. Therefore, to verify eligibility, the dates and times of onset of symptoms and coronary care unit admission were noted as precisely as possible. If the time of onset was not clear (5–10\% of cases), the research nurse who reviewed the time notations by emergency room personnel interviewed the patient further at the time informed consent was obtained (generally 24–48 hours after admission) and usually could establish a time of symptom onset. For patients experiencing no chest pain or repeated episodes of chest pain before admission, the time of symptom onset was considered to be 6 hours before the first elevation of CK.

Patients were admitted to the UCSD Medical Center (n=801) from 1969 to 1987, to the Veterans Administration Hospital of San Diego (n=438) from 1979 to 1987, to the Naval Hospital of San Diego (n=540) from 1979 to 1987, to the Vancouver General Hospital, British Columbia, Canada, (n=2,541) from 1976 to 1987, to the Sharp Memorial Hospital, San Diego, (n=170) from 1986 to 1987, and to the Hospital Cantonal, Geneva, Switzerland, (n=306) from 1985 to 1987. The research nurses at all these centers were trained to follow uniform protocols for patient entry and data gathering.

The only exclusion criteria were failure to sign an informed consent form or coronary artery bypass surgery within the first week. Patients were approached for informed consent in the second or third day after their condition had stabilized; only about 5\% refused. Before 1979, emergency coronary artery bypass surgery was not performed, but since then, it has been performed with increasing frequency. About 2\% of patients were excluded from 1979 to 1985 for early coronary artery bypass surgery; since 1985, early surgery has not been a criterion for exclusion.

\textbf{Variables}

As part of the study protocol, data concerning the patient’s history and clinical course were routinely noted on special data gathering forms by the research nurses and entered into a computer database as described elsewhere.\textsuperscript{17,18} In the present study, subgroups of the patients were examined based on age, gender, history of congestive heart failure, of myocardial infarction, of hypertension, of diabetes, smoking at the time of study admission, use of β-blockers before onset of symptoms, and infarction type (Q wave or non–Q wave). These variables were selected a priori for subgroup analysis to confirm the results of previous studies or because these variables were considered likely to affect the physiologic status of the patient and thereby potentially affect the circadian rhythm of onset of myocardial infarction. Wake-time activity data were not available.

Hospital records or electrocardiograms were examined to corroborate history of infarction. Documented previous systolic blood pressure 160
mm Hg or greater diastolic blood pressure 100 mm Hg or greater defined a history of hypertension. A history of congestive heart failure was defined as shortness of breath on exertion associated with either orthopnea or paroxysmal nocturnal dyspnea. Patients were classified as diabetics based on recorded history; insulin dependency was not required. Patients were considered smokers if they regularly used cigarettes; exsmokers were considered nonsmokers at the time of infarction. The medications but not the dose that each patient was receiving before myocardial infarction were routinely recorded. Table 2 shows the distribution of these factors in the study population.

Time of Symptom Onset

For the population as a whole and for various subgroups, the frequency of symptom onset was tabulated for each hour in the day beginning 1 minute after the previous hour (i.e., 12:01 AM–01:00 AM, 01:01 AM–02:00 AM, etc.). In addition, four 6-hour intervals were defined as follows: 12:01 AM–6:00 AM, 6:01 AM–12:00 noon, 12:01 PM–6:00 PM, and 6:01 PM–12:00 midnight.

Statistical Analysis

The distribution of symptom onset within the four time intervals was tested for uniformity in the overall population and in various patient subsets by the $\chi^2$ test for goodness of fit. A $\chi^2$ value large enough to reject the hypothesis implies nonuniformity. In addition, the independence of time of onset from various factors was examined first with a $\chi^2$ statistic computed from the 2 by 4 (with and without the factor by the four time intervals) contingency table. A $\chi^2$ value large enough to reject this hypothesis implies that there is some interaction between time of onset and the factor. Another test of such independence is the Mantel-Cox statistic from a "survival" analysis, in which the time of the event (onset of symptoms of myocardial infarction) occurs within a 24-hour time interval. At the beginning of the interval, no events have occurred, and by the end of the interval, each patient has had an event. Thus, the pattern of event times for patients with and without a given factor can be compared. With a similar approach, factors univariately significant at the $p<0.1$ level from the above analysis were analyzed in a multivariate Cox regression to determine which factors independently influence the pattern of events (time of onset).

For the entire population and certain subsets of patients, the ratios of the percentage for highest peak to the average of the percentages for remaining periods were computed.

Results

Entire Population

The frequency of symptom onset by hour of onset is shown in Figure 1, upper panel, for all 4,796 patients. The distribution is not uniform ($p<0.001$) and exhibits a peak (28%) between 6:01 AM and 12:00 noon. This peak was 1.16 times the average of the other three time periods. A secondary peak (25%) was discernible between 6:01 PM and 12:00 midnight (Figure 1, bottom panel). The three study centers with the largest patient enrollment showed the typical early morning peak and a smaller secondary evening peak. Two centers had fairly even distribution, and one had a high morning peak with no secondary peak.

Subgroups With Both Morning and Evening Peaks

Table 1 presents the percentage of patients with and without each factor examined having onset of symptoms in each of the four time intervals; the percentages for the peak periods are asterisked. In patients over 70 years of age, smokers, diabetics, those receiving $\beta$-blockers at the time of symptom onset, and women (not shown in Figure 2), the morning and the evening peaks were of the same size. In patients over 70 years of age (30% of the population), 26.7% had symptom onset in the morning and 25.9% in the evening. For smokers at the time of infarction (44% of the population), 26.5% had symptom onset in the morning and 26.2% in the evening; nearly the same peak values (26.4% and 26.9%, respectively) were exhibited by patients receiving $\beta$-blockers at the time of admission (18% of the population). In diabetic patients (16% of the population), the morning and evening periods contained 27.5% and 27.8% of patients. A similar pattern was observed in women (25% of the popu-
TABLE 1. Percentages of Patients With and Without Various Factors in the Four 6-Hour Intervals of Symptom Onset

<table>
<thead>
<tr>
<th>Time interval</th>
<th>12:01 AM–6:00 AM</th>
<th>6:01 AM–12:00 noon</th>
<th>12:01 PM–6:00 PM</th>
<th>6:01 PM–12:00 midnight</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Two peaks</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age&lt;70 yr</td>
<td>22.7</td>
<td>28.5*</td>
<td>23.9</td>
<td>24.9</td>
</tr>
<tr>
<td>Age&gt;70 yr</td>
<td>23.8</td>
<td>26.7*</td>
<td>23.6</td>
<td>25.9*</td>
</tr>
<tr>
<td>Men</td>
<td>23.0</td>
<td>28.0*</td>
<td>24.4</td>
<td>24.6</td>
</tr>
<tr>
<td>Women</td>
<td>23.1</td>
<td>28.0*</td>
<td>22.2</td>
<td>26.7*</td>
</tr>
<tr>
<td>Nonsmokers</td>
<td>23.4</td>
<td>29.1*</td>
<td>23.3</td>
<td>24.2</td>
</tr>
<tr>
<td>Smokers</td>
<td>22.6</td>
<td>26.5*</td>
<td>24.7</td>
<td>26.2*</td>
</tr>
<tr>
<td>Nondiabetics</td>
<td>22.9</td>
<td>28.0*</td>
<td>24.4</td>
<td>24.7</td>
</tr>
<tr>
<td>Diabetics</td>
<td>24.1</td>
<td>27.5*</td>
<td>20.6</td>
<td>27.8*</td>
</tr>
<tr>
<td>No β-blockers</td>
<td>23.2</td>
<td>28.4*</td>
<td>23.6</td>
<td>24.8</td>
</tr>
<tr>
<td>β-blockers</td>
<td>21.8</td>
<td>26.4*</td>
<td>24.9</td>
<td>26.9*</td>
</tr>
<tr>
<td><strong>One peak</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No history of CHF</td>
<td>23.0</td>
<td>28.5*</td>
<td>23.9</td>
<td>24.6</td>
</tr>
<tr>
<td>History of CHF</td>
<td>22.9</td>
<td>24.8</td>
<td>23.4</td>
<td>28.9*</td>
</tr>
<tr>
<td>Q-wave MI</td>
<td>23.3</td>
<td>28.6*</td>
<td>23.8</td>
<td>24.3</td>
</tr>
<tr>
<td>Non-Q wave MI</td>
<td>21.3</td>
<td>25.0</td>
<td>25.6</td>
<td>28.1*</td>
</tr>
<tr>
<td><strong>No peak</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No history of MI</td>
<td>22.2</td>
<td>28.7*</td>
<td>23.9</td>
<td>25.2</td>
</tr>
<tr>
<td>History of MI</td>
<td>25.5</td>
<td>25.6</td>
<td>23.6</td>
<td>25.3</td>
</tr>
<tr>
<td><strong>Typical pattern</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No history of hypertension</td>
<td>24.3</td>
<td>27.8*</td>
<td>23.2</td>
<td>24.7</td>
</tr>
<tr>
<td>History of hypertension</td>
<td>21.3</td>
<td>28.2*</td>
<td>24.7</td>
<td>25.8</td>
</tr>
</tbody>
</table>

*Percentages are peak periods of symptom onset.
CHF, congestive heart failure; MI, myocardial infarction.

Subgroups With Dominant Evening Peak

In patients with a history of congestive heart failure (13% of the population), the peak between 6:01 PM and 12:00 midnight was most pronounced, with 28.9% of the patients experiencing the onset of myocardial infarction (Figure 3), whereas the morning peak was attenuated (24.8%). Patients with a non-Q wave infarction (20% of the population) exhibited only an evening peak of onset (28.1%).

Subgroup With No Peak

Patients with a history of myocardial infarction (23% of the population) exhibited no discernible peak (Figure 4). However, the circadian pattern in these patients appeared to be dependent upon

**FIGURE 2. Bar and line graphs for subgroups with two peaks.** Distribution of hours of symptom onset of myocardial infarction by 6-hour intervals for subgroups with equal late morning and evening peaks (bar graphs). Line graphs show the distribution by hour.
whether they developed a Q wave or non-Q wave infarction. In patients with previous infarction and present Q wave infarction (Figure 4, middle panel), the incidence was highest from 12:01 AM to 6:00 AM and decreased throughout the day, whereas in patients with previous infarction and present non-Q wave infarction (Figure 4, bottom panel), the pattern tended to be reversed.

**Identification of Modifying Factors**

The overall percentage of patients with each clinical characteristic is shown in Table 2 with the results of the significance tests (see "Methods") that were used to examine the patterns of onset time for the various subgroups. The distribution of onset time within the four intervals was not uniform for women, smokers, diabetics, patients with non-Q wave infarction and hypertensives (test 1). Uniformity could not be rejected by this test for the remaining factors.

The hypothesis of independence (lack of interaction) between the four time intervals and the various factors (test 2) could be rejected (indicating an interaction) for diabetics, patients with a non-Q wave infarction, and for those with a history of myocardial infarction.

The pattern of actual infarct onset times (test 3) differed for smokers, patients with a history of congestive heart failure, those taking β-blockers at the time of infarction, and patients with a non-Q wave infarction compared with the subsets of patients without these factors. A multivariate Cox

**TABLE 2. Prevalence and Significance of Potential Modifying Factors**

<table>
<thead>
<tr>
<th>Factor</th>
<th>%</th>
<th>Test 1</th>
<th>Test 2</th>
<th>Test 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt; 70 yr</td>
<td>30</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>25</td>
<td>†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smokers</td>
<td>44</td>
<td>†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>History of diabetes</td>
<td>16</td>
<td>‡</td>
<td>*</td>
<td></td>
</tr>
<tr>
<td>β-Blockers</td>
<td>18</td>
<td></td>
<td></td>
<td>*</td>
</tr>
<tr>
<td>History of CHF</td>
<td>13</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Q wave MI</td>
<td>20</td>
<td>†</td>
<td>†</td>
<td>‡</td>
</tr>
<tr>
<td>History of MI</td>
<td>23</td>
<td></td>
<td></td>
<td>*</td>
</tr>
<tr>
<td>History of hypertension</td>
<td>42</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Test 1, χ² test of goodness-of-fit for uniformity; test 2, χ² test of independence for 2 by 4 contingency table; test 3, Mantel-Cox test of difference in onset pattern for patients with and without factor. CHF, congestive heart failure; MI, myocardial infarction. *p < 0.10, †p < 0.05, ‡p < 0.01
regression analysis of the factors identified by test 3 selected non–Q wave infarction ($p<0.01$) and smoking ($p<0.03$) as the most important determinants of the time of symptom onset, and $\beta$-blockade was only of marginal importance ($p<0.1$). These last two analyses were repeated using the interval of infarct onset rather than the exact time, and the same results were obtained.

Subgroups Without Various Modifying Factors

When the circadian pattern was examined for the subset of all patients without one of the factors (Table 1), only a single late morning peak (asterisked percentages in Table 1) was evident. The subgroup of patients 70 years of age or younger and not receiving $\beta$-blockers ($n=2,777$) showed one single, marked morning peak (29.4%) that was 1.25 times the average for the other three time periods (Figure 5, top panel, uniformity rejected $p<0.001$). This subgroup is fairly comparable to the WHO study that reported patients less than 65 years of age who were admitted before 1976, which was before the widespread use of $\beta$-blockers. In a selected subgroup ($n=1,084$) without the factors that showed either an interaction (test 2) or a different pattern than that for patients without the factor (test 3), that is, those with Q wave infarction without history of myocardial infarction, congestive heart failure, or diabetes, who were not smokers or taking $\beta$-blockers at the time of symptom onset, the morning period included 31.6% of all infarctions (Figure 5, bottom panel, uniformity rejected; $p<0.001$). This single peak was 1.39 times higher than the average of the other three time periods. This single pronounced peak was also observed for the 287 women (morning peak, 30.2%) and for the 412 patients over 70 years of age (morning peak, 31.8%) within this subgroup.

Discussion

This study confirms the finding of other studies\textsuperscript{1–8} that symptom onset is most frequent in the late morning from 6:01 AM to 12:00 noon. Also, in our population as a whole, a second, smaller peak occurred in the late evening between 6:01 PM and 12:00 PM, which is a finding in accord with other studies.\textsuperscript{1–3,5–8} Only recently has it been suggested that the characteristic circadian rhythm may not occur in some subsets of patients with acute myocardial infarction.\textsuperscript{7,15} Because of the relatively small number of patients in the subsets examined previously, these results seemed tentative. Also, the presence of patients with these or other modifying factors may account for the pattern observed in the population as a whole, which is a possibility that has not been considered previously and which was the subject of this analysis.

Circadian Patterns in Subgroups Previously Investigated

The present study in large subsets of patients strongly suggests that several patterns exist in the circadian variation of the onset of myocardial infarction. In our population, two peaks of similar size were found in some patient subsets (Table 1). These two peaks indicate that two periods of susceptibility may exist for some patients or that one set of patients in a subgroup has a morning and the other set an evening period of susceptibility.

Results confirm. Our finding of an evening peak in patients taking $\beta$-blockers at the time of myocardial infarction is in agreement with findings in the subgroup treated with $\beta$-blockers in the Multicenter Investigation of the Limitation of Infarct Size (MILIS) reported by Muller et al.\textsuperscript{7} Patients on $\beta$-blocker therapy in the present study showed a reduced late morning peak with an equal late evening peak; on the other hand, in the MILIS population, patients on $\beta$-blocker therapy ($n=135$) had the highest incidence of infarction onset in the late evening, whereas the adjacent early morning peak (between midnight and 6:00 AM) was nearly as high.\textsuperscript{7} Only seven of our patients taking $\beta$-blockers were over 70 years of age, which makes this subgroup fairly comparable with the total MILIS study population whose age limit was 75 years.
In a recent preliminary report from the Diltiazem Reinfarction Study,\textsuperscript{15} the onset of non-Q wave infarction did not exhibit diurnal variation with grouping by 2-hour intervals. However, in all 540 patients with non-Q wave infarction and in the subgroup of 397 patients not receiving a \( \beta \)-blocker, the incidence of infarction was higher during the second two quarters (each 27\%) of the day than in the first two quarters (21\% and 24\%). The Diltiazem Reinfarction Study excluded patients with more than mild heart failure. These results are consistent with our findings of an increased incidence of onset during the evening hours for patients with non-Q wave infarction.

\textbf{Results conflict.} The MILIS study (total \( n=847 \)) reported that the characteristic late morning circadian pattern of symptom onset was observed in patients younger and older than the median age, in men and women, in smokers and nonsmokers, in coffee drinkers and nondrinkers, and in patients with and without a history of angina pectoris or myocardial infarction.\textsuperscript{7} Subgroup sizes, other than for those taking \( \beta \)-blockers, were not stated. We found equal morning and evening peaks in older patients, in women, and in smokers, whereas patients with a history of myocardial infarction showed no characteristic peaks. The differences between these observations may be explained at least in part by the age limit and relatively small sample sizes in the MILIS study.

\textbf{Circadian Patterns in Subgroups Not Previously Investigated}

The finding of two peaks of symptom onset (morning and evening) for patients with diabetes, of only one evening peak for patients with a history of congestive heart failure, and of no altered circadian pattern in patients with a history of hypertension have not been reported previously and will require confirmation in further studies.

\textbf{Circadian Patterns in Selected Populations}

The restriction of patients included in various previous studies may explain some of the differences in the observed patterns of circadian variation of symptom onset. The two studies reporting a single peak were in highly selected patient populations.\textsuperscript{4,8} The World Health Organization reported on 8,900 patients from 19 European countries under 65 years of age admitted before 1976, which was before the widespread use of \( \beta \)-blockers.\textsuperscript{4} A similar subset of our population also exhibits only one morning peak (Figure 5). However, some of the individual centers within this study did have a second evening peak, and others had no peak at all in their patient populations. These differences could be due to small sample sizes, different customs in the countries regarding the evening meal or work habits, or a different distribution of patients with modifying factors. Interestingly, study centers with an older age distribution or with more diabetic patients tended to show the second evening peak. Also, among the centers in the present study, the hospital with the youngest and least-ill patient population showed only the late morning peak. In the Multicenter Chest Pain study,\textsuperscript{8} the mean age was 58 years (compared with 63 years in our population), and only a single late morning peak was found. The patients in the MILIS study\textsuperscript{7} were younger than 75 years of age, and among those with no prior \( \beta \)-blocker therapy (\( n=711 \)), there appeared to be only a single peak between 6:00 AM and 12:00 noon. Our results indicate that it is probably not age per se that is causing the alteration of the circadian pattern but rather the presence of other factors that are more prevalent among older patients, because in our subgroup that was free from important modifying factors (Figure 5, bottom panel), patients over 70 years of age (\( n=412 \)) exhibited only a single peak.

\textbf{Pathophysiologic Aspects}

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{7,8,13,22} One obvious explanation is the increase in physical and mental stress that occurs after waking. It is well known that an increase in sympathetic activity occurs after waking and that a rise occurs in plasma levels of catecholamine and of cortisol (morning peak approximately 6:00 AM, decreasing but still high until noon).\textsuperscript{22,23} Heart rate, blood pressure, coronary vascular tone,\textsuperscript{24–26} and platelet aggregability.\textsuperscript{22,27} Furthermore, a lower fibrinolytic activity has been reported during the early morning hours.\textsuperscript{28} These diurnal variations are reported from studies of healthy volunteers and reflect mechanisms that have been postulated to cause or trigger ischemic events and the development of acute myocardial infarction. Thus, the circadian variation of such physiologic variables may contribute to the increased incidence of myocardial infarction onset and other ischemic manifestations in the late morning.

The reasons for a second, late evening peak are less obvious. The evening peak may reflect altered circadian rhythms due to late working hours or reflect that some individuals are “night people” rather than “morning people.”\textsuperscript{27} Other investigators have postulated that the morning and evening peaks are related to sleep-mediated factors with changes in autonomic regulation.\textsuperscript{29} Because a bimodal rhythm for the tendency to fall asleep has been described,\textsuperscript{30} Schwab\textsuperscript{31} commented that because coronary artery spasm is seen more often in the very early morning hours (peak at 3:00 AM) in patients with variant angina,\textsuperscript{26} a sequence of events may be initiated that ends in infarction; on the other hand, he suggests\textsuperscript{31} that nocturnal ischemia associated with prior myocardial infarction and congestive heart failure in some patients may explain the evening peak,\textsuperscript{31} and both of these subgroups in the present study failed to exhibit the characteristic morning circadian pat-
tern. Also, the late-evening and early-morning onset could be linked to dilation of the left ventricle at lower heart rates in the supine position with elevation of filling pressure, which has been reported to be associated with nocturnal ischemia.32

It is now established that persistently increased sympathetic activity causes desensitization and receptor down-regulation.33 This has been described in patients with heart failure34 and appears to occur with increasing age.35 Such down-regulation also may be present in smokers because normal subjects consuming 24 cigarettes during a 12-hour period have been reported to have a 45% rise in urinary excretion of norepinephrine and a higher heart rate during the day and night.36 Modulation of receptor sensitivity occurs quite rapidly37 and may be one explanation for the blunted morning peak and increased late peak of onset observed in this study among smokers compared with nonsmokers and for the absent morning peak among patients with a history of congestive heart failure and for those with previous myocardial infarction.

**Limitations**

One potential weakness of this and several other studies is subjective reporting of the exact time of onset of symptoms, although we believe our data are as accurate as such retrospectively gathered information can be (see “Methods”). In the MILIS database,2 a good correlation (r=0.85, p<0.01) was found between enzyme-estimated (CK-MB) and pain-estimated onset of infarction. However, even with the CK method, a lag time of 4 hours from onset of pain to the first enzyme elevation is assumed; certainly, not all patients experience a precise 4-hour lag time, and inaccuracy related to frequency of sampling could also alter the time identified as the beginning of CK-MB elevation.

Information about the normal wake-time and daily activity period were not part of the present study protocol so that we were not able to adjust the time of onset of symptoms for this variable. Thus, if the onset of infarction is more closely related to activity cycle rather than the actual time of day, our results and those of a number of other studies are imprecise.

Multivariate analyses of our data indicate that development of a non-Q wave infarction is the most important independent factor determining the time of infarct onset. However, patients experiencing non-Q wave infarction were more often over 70 years of age, women, diabetics, with previous myocardial infarction or congestive failure, and on β-blocker therapy at the time of infarction. This subgroup also had fewer smokers, and this factor was second in importance in the multivariate analysis. Whether the importance of non-Q wave infarction is due to the cumulative effect of the above modifying factors or to a specific, different mechanism that precipitates non-Q wave infarction is unknown. We await the results of future studies to confirm the results of our subgroup analyses.

**Implications**

Certain factors appear to modify the characteristic circadian variation of infarction onset. Individuals with one or more such variables are more likely to experience onset of infarction later in the day than in the late morning, and the second peak seen in our total population and in other studies appears to reflect the presence of these individuals. Thus, populations or subgroups free from these modifying factors have only one distinct morning peak. Because different times of onset may reflect different pathophysiologic mechanisms, subgroup analysis seems important for establishing such patterns. Therefore, future analyses of diurnal rhythms concerned with physical and mental stress, hemodynamic variations, neuroendocrine responses, and thrombotic or fibrinolytic activities seem most likely to provide further information about the natural history of myocardial infarction onset when carried out in subgroups of patients that are well defined and of adequate size.

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