Lack of Diurnal Variation in the Onset of Non-Q Wave Infarction

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Data concerning the time of onset of myocardial infarction were obtained for 540 of the 544 patients with creatinine kinase (CK)-MB-confirmed non-Q wave myocardial infarction enrolled in the multicenter Diltiazem Reinfarction Study. Data were also collected for 627 patients who were screened but excluded. Among the 1,167 patients, no diurnal pattern of onset could be found at either 2- or 6-hour intervals. Among the 540 patients enrolled in the trial, no pattern could be found at these intervals either, although at 8-hour intervals, 27% of infarctions occurred between midnight and 8:00 AM, compared with 37% between 8:00 AM and 4:00 PM and 36% between 4:00 PM and 12:00 AM (p=0.02). In contrast to the patterns previously noted for Q wave myocardial infarction, there was no preponderance of non–Q wave infarction in the late morning. Circadian rhythm was also absent among patients not treated with β-blockers as well as among patients presenting with ST segment elevation on their enrollment electrocardiograms. Diabetics, women, and patients with first infarction were more likely to present during the afternoon hours. We conclude that the late morning preponderance seen for Q-wave myocardial infarction is not discernable in patients with non–Q wave myocardial infarction. This observation suggests that the pathogenesis of these two infarct subtypes is different or that the process of thrombotic coronary occlusion in Q wave infarction (sustained) differs from that in non–Q wave infarction (nonsustained). (Circulation 1990;81:548–555)

Several recent studies1–3 have demonstrated significant diurnal variation in the onset of acute myocardial infarction. These findings confirm those of epidemiologic studies published in the 1960s and 1970s4–7 that showed that infarction is more likely to occur in the morning hours and less so during the night. The time course of these fluctuations parallels recently observed increases in platelet aggregability and increased plasma activity of various components of the clotting system,8–11 surges in adrenergic activity,10–12 as well as troughs in the activity of the intrinsic fibrinolytic system.13,14 These observations were made principally in patients with Q wave infarction. In these patients, coronary angiography has shown the underlying pathology to be a thrombus superimposed on an atherosclerotic plaque that completely obstructs antegrade coronary blood flow.15,16 However, approximately 30–40% of patients presenting with acute myocardial infarction do not evolve Q waves17 and unlike patients with Q wave myocardial infarction, complete coronary occlusion is observed in only 20–30% during the early stages of infarction.18,19

We recently performed a large multicenter prospective study in patients with non–Q wave infarction and sought to determine whether a circadian rhythm (similar to that observed for Q wave infarctions) exists in these patients, since similarities or differences in the pattern of onset should have significant pathogenetic implications. The purpose of this trial, performed between 1982 and 1985, was to determine whether reinfarction in patients with non–Q wave myocardial infarction could be prevented by prophylactic treatment with a calcium channel blocker. The design and results of this study have been published elsewhere.20 We thus analyzed data concerning the time of onset of symptoms reported by patients in this trial to determine whether or not a diurnal pattern was present in patients with non–Q wave myocardial infarction.
Methods

Study Enrollment

Since enrollment in the Diltiazem Reinfarction Study required that treatment be implemented between 24 and 72 hours after the onset of non-Q wave infarction, the time of onset of pain felt, representing the acute infarction, was recorded systematically on the case report form of all participants and patients screened. The criteria for the diagnosis of non-Q wave infarction in brief consisted of 1) ischemic chest pain of at least 30 minutes in duration; or 2) new ST segment elevation or depression of at least 0.1 mV or new T wave inversions in two or more contiguous leads; and 3) consecutive elevated plasma CK-MB activity in two samples separated by at least 4 hours.

Exclusion criteria were as follows: 1) new or presumably new Q waves of 30 msec or more in duration, an R/S ratio of 1 or greater in V1, along with a 40 msec R wave in V1, a 50% loss of R wave in two or more contiguous leads, or ST-T changes limited to leads with preexisting Q waves; 2) conduction disturbances that would mask the development of new Q waves; 3) bradycardia <50 beats/min; 4) second- or third-degree atrioventricular block; 5) cardiogenic shock; 6) therapy with a calcium blocker, oral anticoagulant, or a full dose of heparin that could not be discontinued; 7) coronary artery bypass surgery within 3 months; 8) serious noncardiac diseases; 9) pregnancy; 10) refusal of the patient or physician to participate; or 11) age greater than 75 years.

Assessment of Diurnal Variation

The time of onset of infarction was defined as the time of onset of ischemic symptoms. A close correlation has been demonstrated previously between onset of infarction (determined using plasma CK) and the onset of symptoms in a population consisting primarily of patients with Q wave infarction. To determine whether a particular time period during the day was associated with a more frequent onset of non-Q wave infarction, the 24-hour period was divided into either 2-, 6-, or 8-hour intervals and the number of patients with onset of infarction during each interval compared with the number of patients with onset of infarction during the other intervals.

The excess risk of infarction occurring during any particular interval was defined as the ratio of the number of patients assigned to each specified interval to the mean of the number of patients assigned to each of the other intervals. This was devised as a measure of the prevalence of infarction during any given period of the day. Fourteen baseline clinical characteristics obtained from the case report form were also analyzed in relation to the time of onset of infarction (Table 1).

Statistical Analysis

The hypothesis that the number of patients with infarction during each time interval was equal to an expected frequency for each interval was tested using a χ² goodness of fit analysis. Event rates by time

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<th>Table 1. Baseline Characteristics Examined</th>
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<td>Previous treatment with β-blockers</td>
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<td>Diabetes</td>
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<td>Previous myocardial infarction</td>
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CK, creatinine kinase.

![Figure 1. Symptom-determined time of onset for 1,167 screened patients (dark bars) and 540 patients with non-Q wave myocardial infarction enrolled in (light bars) the Diltiazem Research Study. Subdivision is by 2-hour intervals. Time of day is represented on a continuous 24-hour scale. Incidence of infarction is slightly lower in the very early morning, but otherwise no level of significance is present.](http://circ.ahajournals.org/)

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intervals for patients with each baseline characteristic were compared with event rates for patients without the characteristics in the 6- or 8-hour time intervals. When baseline characteristics were analyzed, a standard $\chi^2$ analysis was used. Baseline characteristics expressed as continuous variables were plotted using a 24-hour time scale and the plots were inspected visually. Virtually no variation was noted for these additional characteristics and formal statistical analysis was not pursued. Continuous variables were not analyzed using predetermined breakpoints.

Results

One thousand six hundred three patients meeting inclusion criteria were screened for the trial and 576 (36%) were randomized. Thirty-two of the randomized patients had Q waves and are excluded from further analysis. Pertinent data is available on 540 of the remaining 544 randomized patients (99%), as well as on 627 of 1,059 patients (59%) excluded. The time of onset of symptoms could therefore be assessed in 1,167 of 1,571 patients (74%).

The plot in Figure 1, based on two hourly intervals shows that the only diurnal trend among either the 540 enrolled patients or all 1,167 screened patients was a tendency toward a lower incidence of infarction in the early morning. Although small peaks in the frequency of infarction among the 1,167 screened patients appeared between 6:00 AM and noon and 6:00 PM and midnight (excess risk of infarction=1.05 and 1.06, respectively), analysis using 6- and 8-hour intervals did not reveal statistical significance for these patterns.

Because the enrolled patients were best characterized and form a more homogeneous group, further analyses are restricted to this group. When the timing of infarct onset was subdivided into 8-hour intervals (Figure 2a), the diminished early morning frequency became significant ($p=0.02$), while the difference between the number of infarctions in the other two groups was not significant. When the day was divided into 6-hour intervals (Figure 2b), no diurnal pattern was detected. This was also true when 6-hour intervals were deliberately chosen (Figure 2c) so that one group (8:00 AM–2:00 PM) contained the largest number infarctions possible (excess risk of infarction=1.17).

One hundred eighty-six (34%) of the patients in the trial had ST segment elevation on their presenting 12-lead ECG. Because this particular population resembles one that might be expected to present with Q wave infarction, these patients were analyzed separately (Figure 3). The pattern seen was identical to that of the group as a whole; there was a tendency for a lower rate of infarction in the very early morning (excess risk of infarction midnight to 6:00 AM=0.67), but the rates during the other three intervals were similar and for this subgroup of patients statistical significance was not achieved (excess risk of infarction=1.04, 1.36, and 0.98, respectively, $p<0.1$). The same was true for 8-hour intervals.

A previous report$^2$ had indicated that the circadian rhythm of onset of infarction was attenuated in
patients already receiving β-blockers. One hundred forty-three patients in the trial were on a β-blocker at the time of their infarction. As shown in Figure 4a, the group not receiving β-blockers had virtually the same diurnal pattern as that seen in the patients receiving β-blockers. When these two groups were divided into 6- and 8-hour intervals and compared using χ² analysis, there was no difference between them. When the 397 patients not receiving β-blockers were examined at 8-hour intervals (Figure 4b), there was a significant decrease in the incidence of infarction between midnight and 8:00 AM (excess risk of infarction = 0.75, p < 0.05). When this subgroup was examined at 6-hour intervals, there was no late morning preponderance of infarction (Figure 4c).

When the other 13 baseline characteristics listed in Table 1 were examined using 6- and 8-hour intervals, three factors (female gender, diabetes, and patients with first infarction) showed a preponderance to presentation in the afternoon.

Among the 109 diabetics enrolled in the trial, 37 infarctions (34%) occurred between noon and 6:00 PM (excess risk of infarction = 1.54, p < 0.05). Peaks in the frequency of infarction actually occurred between noon and 4:00 PM (18 expected, 29 observed) and 8:00 PM and midnight (18 expected, 26 observed). Among the 118 women, 41 infarctions (34%) occurred between noon and 6:00 PM and 39 (33%) between 6:00 PM and midnight (excess risk of infarction = 1.51 and 1.54, respectively, vs. 1.03 and 1.05 for men; p < 0.01). Among the 282 patients with a first infarction, 118 infarctions (42%) occurred between 8:00 AM and 4:00 PM compared with 64 events among the 200 patients with prior myocardial infarction (32%), while 93 (33%) first infarctions occurred between 4:00 PM and midnight compared with 77 infarctions (39%) among the latter group (p < 0.03).

The mean values during each 2-hour period for admission heart rate, blood pressure, and enzymatically determined infarct size did not manifest a diurnal variation.

Discussion

Since this study describes a pattern in the timing of non-Q wave infarction that is quite different than that reported for Q wave infarction, potential limitations in its design require analysis. First, information was not available on the sleep and wake cycles of the patients. A sample of patients with wide dispersion in their time of arising could conceivably have a blunted pattern of onset of infarction. However, patients enrolled in this trial should be a general sampling of the North American population and would not be expected to lead different patterns of living than patients enrolled in other studies of myocardial infarction, which did show circadian patterns. The second limitation concerns the timing of onset of
symptoms. Since patients were enrolled in the trial only after infarction was confirmed by elevated plasma CK-MB, they were formally interviewed only after hospitalization. It is conceivable that during the 1–3 days before enrollment, patients’ memories of the precise timing of symptoms could have become clouded. However, during the duration of the trial, coronary care units were alerted to the trial’s requirements in relation to the time of enrollment and were instructed to record the reported time of symptom onset as precisely as possible at admission. At the time of study enrollment, every effort was made to corroborate this record by interviewing the patient and completing the case report form. Finally, in order to assure that all patients enrolled in the trial actually had non–Q wave infarction, increased CK-MB activity was required in two samples rather than the one sample customarily required. However, from 1982 to 1984, patients presented, on the average, 6–8 hours after the onset of infarction, so in almost all cases if the first sample exhibited increased CK-MB, the second sample would as well. It is therefore unlikely that this criterion resulted in a biased sample of non–Q wave infarctions.

Since enrollment required only that CK-MB elevation be determined by each individual center’s laboratory (sampling frequency before enrollment was not regulated), sufficient data are not available to allow estimation of the onset of infarction using cardiac enzymes. Although the outcome of such an analysis cannot be predicted, the study by Muller et al2 did find that the pattern of diurnal variation was more pronounced when enzymatically determined onset rather than symptom-determined onset was used. Nonetheless, a close correlation between the two was observed. In that study, the subpopulation of patients with non–Q wave infarction had a diurnal trend demonstrable using CK analysis but not using onset of symptoms. However, our data included an even larger number of non–Q wave infarctions and still did not detect a significant deviation from the mean incidence of infarction in the late morning. Thus, this finding is probably not due to an inadequate sample size or to the absence of enzymatically determined infarct onset. It could be argued that the correlation between methods of estimating onset was demonstrable only for Q wave myocardial infarction and may not be valid for non–Q wave myocardial infarction, since the latter is characterized by earlier peak plasma CK activity peak probably due to more rapid washout.21,22 However, the effect on the initial

**FIGURE 4a.** Symptom onset in patients receiving and not receiving β-blockers.

**FIGURE 4b.** Symptom onset among patients not receiving β-blockers subdivided by 8-hour intervals. Uniformity cannot be rejected, indicating no detectable diurnal pattern.
onset of CK release would probably be minimal, and the above noted correlation would remain valid.

The documentation of diurnal variation of ischemic events not characterized by complete coronary occlusion has not been as definitive as for that of Q wave infarction. More frequent ambulatory ECG evidence of ischemia has been reported in the early morning hours and reports of lower exercise threshold for ischemia in the morning are conflicting, but these events have been reported in ambulatory patients in whom higher heart rates and blood pressure previously observed in the morning may play a role. Sudden cardiac death occurs more frequently during the morning, but this is a much more complex event than infarction, and early morning increases in catecholamine levels and rate pressure product may play as important a role as coronary occlusion.

Our study examined a representative sample of patients presenting with non-Q wave infarction. The only similarity between the pattern of onset seen in these patients and that previously reported in patients with Q wave infarction is a lower incidence in the very early morning hours. Although this was not the case among our screened patients, it was so among the patients actually enrolled in the trial. These hours correspond to the time when most individuals would be expected to be asleep (there may be more variation in the numbers of patients asleep before midnight) and would therefore have lower heart rates and blood pressures. Thus, the hemodynamic shear forces that may contribute to rupture or ulceration of the atherosclerotic plaque, and ultimately to development of the unstable coronary syndrome, might be reduced in patients with both Q wave and non-Q wave infarction.

Unlike the pattern previously reported among patients with Q wave infarction, circadian tendency toward late morning onset is not present in those with non-Q wave infarction. A nadir in the frequency of both forms of infarction occurs in the early morning hours, but non-Q wave infarction does not have the subsequent rise in frequency that has been observed for Q wave infarction. (Very slight peaks did occur in the late morning and late evening hours among the screened patients, but these did not approach statistical significance.) This difference in timing of the onset of Q wave and non-Q wave infarction may have significant pathogenetic implications. It has been well-documented that Q wave infarction is associated with an occlusive intracoronary thrombus in the majority of cases. Though indirect, current evidence suggests that non-Q wave myocardial infarction is precipitated by total occlusion but that the occlusion is aborted by early spontaneous reperfusion. The role of coronary spasm in the onset of infarction has not been elucidated and, thus, remains a consideration at least in patients undergoing non-Q wave infarction. Angiographic studies have demonstrated that the extent, severity, and location of coronary artery atherosclerosis are virtually identical in patients with Q wave and non-Q wave myocardial infarction. More recently, coronary morphological studies have demonstrated that the coronary lesions seen in patients with non-Q wave infarction are more frequently roughened and irregular and show the same features suggestive of plaque rupture or hemorrhage that are seen in patients with Q wave infarction following thrombolysis. Thus, it appears that despite sharing a similar anatomic substrate with patients who have Q wave infarction, patients with non-Q wave infarction have nonsustained coronary arterial occlusion.

Three subgroups in our study did show different circadian patterns. Diabetics had more infarctions occurring in the afternoon with relatively sharp peaks between noon and 4:00 PM and 8:00 PM and midnight. These periods may correspond to peak insulin effects. Similarly, the increased afternoon frequency of infarctions among women may represent endocrinologic variation in the regulation of coagulation and vascular tone or may reflect differences in the extent of coronary arterial atherosclerosis present. The increased frequency of morning and evening infarctions among patients with prior infarction may be a reflection of our selection process. That is, we excluded patients with new Q waves, however, reinfarction in patients with prior infarction may in some cases represent a different disease process, recoclusion of a vessel that had undergone late spontaneous reperfusion at a remote point in time, rather than de novo occlusion and early spontaneous reperfusion.
However, interpretation of findings in these subgroups should be performed very cautiously because of the small number of patients involved and because of the large number of variables considered in the subset analyses, which could result in chance significance. The failure of patients with non-Q wave infarction to follow the same diurnal pattern seen for Q wave infarction as well as for activity of the clotting system adds another piece of evidence to the occlusion-reperfusion hypothesis. The propensity for incomplete occlusion may be due to a variety of factors including increased intrinsic fibrinolytic activity, lack of vascular tone necessary to sustain the clot, or perhaps less severe endothelial dysfunction. Detailed investigation and comparison of the vasomotor and clotting responses in patients with Q wave and non-Q wave infarction should be rewarding in shedding light on why the non-Q wave infarction undergoes what appears to be spontaneous reperfusion. Results of such investigations should have pathogenetic and therapeutic implications for Q wave and non-Q wave infarctions.

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