Increased Morning Incidence of Myocardial Infarction in the ISAM Study: Absence With Prior β-Adrenergic Blockade

Stefan N. Willich, MD, Thomas Linderer, MD, Karl Wegscheider, PhD, Alain Leizorovicz, MD, Ives Alamercery, Rolf Schröder, MD, and the ISAM Study Group

The time of acute myocardial infarction was determined in all 1,741 patients of the ISAM (Intravenous Streptokinase in Acute Myocardial Infarction) Study, based on onset of clinical symptoms and evaluation of plasma CK-MB enzyme time-activity curves. The incidence of myocardial infarction was markedly increased between 6:00 AM and 12:00 noon compared with other times of day (p<0.001). Myocardial infarction occurred 3.8 times more frequently between 8:00 and 9:00 AM (hour of maximum incidence) than between 12:00 midnight and 1:00 AM (hour of minimum incidence). Time of myocardial infarction based on clinical and enzymatic methods correlated well (r=0.95). Patients with higher or lower left ventricular ejection fraction, higher or lower degree of wall motion abnormalities and residual stenosis of the coronary arteries, and one-, two-, or three-vessel disease exhibited a similar circadian pattern, suggesting that the morning is a risk period for patients with mild as well as severe coronary artery disease. Only the group of patients receiving β-adrenergic blocking therapy before the event did not show an increased morning incidence of myocardial infarction. This observation may contribute to an understanding of the mechanisms by which β-blockers reduce the incidence of myocardial infarction. Further investigation of physiologic changes occurring during the morning period of increased risk of myocardial infarction may lead to better understanding of the disorder. Design and timing of cardioprotective medication may play a crucial role in improving prevention of acute myocardial infarction. (Circulation 1989;80:853–858)

The incidence of myocardial infarction has been reported to exhibit a circadian variation.1 This finding was revealed in the data base evaluation of a major myocardial infarction study, and its significance is not yet clear. However, the potential importance of the observation is underlined by the emerging knowledge of a circadian variation in the incidence of other cardiovascular diseases, such as sudden cardiac death, symptomatic and asymptomatic myocardial ischemia, and stroke, all of which have been shown to occur more frequently during the morning than at other times of day.2-6

In the case of myocardial infarction and sudden cardiac death, a minor secondary peak period in the evening has been suggested.1,2 Cardiac medication administered before myocardial infarction may influence the circadian pattern in the incidence of myocardial infarction.1 The well-characterized population of the ISAM (Intravenous Streptokinase in Acute Myocardial Infarction) Study provided an ideal tool for prospectively testing some of the hypotheses from earlier studies.7,8 If, in fact, there is an increased incidence of myocardial infarction during certain periods of the day, such knowledge may contribute to a better understanding of the mechanisms of the disease and to improved design and timing of cardioprotective medication.

Methods

Study Population

The present investigation is based on the data base generated by the ISAM Study from 1982 to 1985, which was conducted primarily to determine the effect of intravenous streptokinase on early and late mortality, size of myocardial infarction, and ven-
tricular performance. Details of the study and results of the primary endpoints have been published.\textsuperscript{7,8} Briefly, the study included 1,741 patients from 83 hospitals in the Federal Republic of Germany, Switzerland, and Canada. Eligibility criteria included an age of 75 years or less, clinical symptoms of evolving myocardial infarction, ST segment elevation of 1 mm or more in the extremity leads and of 2 mm or more in the chest leads, initiation of study medication within 6 hours of onset of symptoms, and absence of contraindications to thrombolytic therapy. Time of admission to the coronary care unit was recorded in all 7,715 patients screened for ISAM participation. All randomized patients underwent a standardized interview, including specific questions on the precise time of onset of clinical symptoms. Serial serum CK-MB samples (2-hour intervals) were analyzed in a central enzyme laboratory. Electrocardiographic recordings obtained at sequential time points including the time of admission and 24 hours thereafter were analyzed in a central laboratory.

The time of myocardial infarction was assessed 1) by the information derived from the patient interviews and 2) by subtracting 4 hours from time of initial CK-MB elevation above normal plasma concentration (10 IU/l).\textsuperscript{9} Coronary angiography was performed in 924 patients 3–4 weeks after myocardial infarction, and the results were analyzed in the angiography core laboratory.\textsuperscript{7} Degree and extent of coronary artery disease were determined, and left ventricular ejection fraction and a dyssnergy index were calculated. The circadian pattern in the incidence of myocardial infarction was determined in older and younger patients, men and women, patients with higher and lower left ventricular ejection fraction and dyssnergy index, in those with one-, two-, or three-vessel disease, and in groups of patients with different degrees of residual stenosis of the infarct-related coronary artery. Time of myocardial infarction was also determined in the subgroups of patients who received \(\beta\)-adrenergic blocking agents or calcium antagonists before their myocardial infarction.

Statistical Analysis

To determine whether or not the incidence of myocardial infarction exhibited a systematic circadian variation, the following statistical approach was prospectively chosen. The uniformity of infarct onset among all 24 1-hour intervals was tested using the \(\chi^2\) goodness-of-fit test. Based on a previous report\textsuperscript{1} of an increased incidence of myocardial infarction during the second quarter of day, that is, 6:00 AM to 12 noon, \(\chi^2\) goodness-of-fit test was performed to determine differences among four 6-hour intervals (12:00 midnight–6:00 AM, 6:00 AM–12:00 noon, 12:00 noon–6:00 PM, 6:00 PM–12:00 midnight). A one-sided binomial test was used to provide additional confirmation of whether or not the frequency of myocardial infarction during the second quarter of the day was significantly higher than the 25% rate expected with random distribution. The Pearson’s correlation coefficient was used to compare time of myocardial infarction based on clinical and enzymatic methods. Spectral analysis was performed to determine more specifically the circadian pattern in the incidence of myocardial infarction. Only \(p\) values less than 0.05 were considered significant.

Results

The incidence of myocardial infarction assessed by onset of clinical symptoms exhibited a marked

![Figure 1](http://circ.ahajournals.org/)

**Figure 1.** Bar graph of incidence of myocardial infarction of 1,741 patients of the ISAM (Intravenous Streptokinase in Acute Myocardial Infarction) Study. There is a marked circadian variation (\(p<0.001\)) with a peak during the morning hours. Myocardial infarction occurred 1.8 times more frequently between 6:00 and 12:00 AM compared with the average of other quarters of day. The risk of myocardial infarction in the afternoon and evening was approximately equally distributed, whereas during the night, a trough period occurred in the incidence of myocardial infarction.
circadian variation with a peak period during the morning (Figure 1). The number of infarcts during the second quarter of day (6:00 AM to 12:00 noon) was increased compared with the number of infarcts during the other quarters of day (Table 1, \(p<0.001\)). Myocardial infarction occurred 3.8 times more frequently between 8:00 AM and 9:00 AM (hour of maximum incidence) than between 12:00 midnight and 1:00 AM (hour of minimum incidence). When spectral analysis was performed, the only significant peak in the frequency domain corresponded to a wavelength of 24 hours, indicating that there was only one significant peak in the incidence of myocardial infarction during the 24-hour circadian variation.

In 911 patients, complete CK-MB sampling was available, and time-activity curves were evaluated assessing time of onset of myocardial infarction. In this group of patients, the time of myocardial infarction based on clinical and enzymatic methods correlated well \((r=0.95, p<0.001)\).

The circadian pattern in the incidence of myocardial infarction was similar among those with lower or higher ejection fraction, with lower or higher dyssynergy index, among older or young patients, and in male or female patients (Table 2). The circadian pattern in the incidence of myocardial infarction was also similar in patients with one-, two-, or three-vessel disease, in groups of patients with residual stenosis less than 75%, 75–95%, and greater than 95% of the infarct-related artery, in patients with anterior or inferior myocardial infarction, and in those treated with streptokinase or placebo (Table 2).

The only subgroup examined in which there was not a significantly increased morning incidence of myocardial infarction was the group of 206 patients receiving \(\beta\)-adrenergic receptor blocking therapy before their myocardial infarction (Figure 2A). In contrast, in the group of 147 patients treated with calcium antagonists before their myocardial infarction, there was a circadian variation with a peak incidence of myocardial infarction during the morning (Figure 2B) similar to the pattern observed for the group of 1,473 patients not receiving \(\beta\)-blockers before their myocardial infarction (Figure 2C). (In 62 patients information on possible previous \(\beta\)-blockade was not obtained.) The statistical power to detect an increased morning incidence of myocardial infarction in the group of patients on prior \(\beta\)-blockade, which would exhibit the same magnitude as the group of patients without prior \(\beta\)-blockade, was 99.5%.

Among all patients enrolled in the ISAM Study, 84% developed new Q waves on the 24-hour electrocardiogram compared with the recording obtained at admission (excluding patients with left bundle branch block).

### Discussion

The present results show a markedly increased risk of myocardial infarction from 6:00 AM to 12:00 noon (Figure 1). This morning peak was shown consistently in different subgroups, which indicated that it is a phenomenon not attributable to risk variables. During the afternoon and evening hours, the incidence of myocardial infarction was approximately evenly distributed. In a recent report\(^1\), the morning peak in the incidence of myocardial infarction was less pronounced compared with the present results, and there was a minor secondary peak in the early evening that did not appear in the present study. Spectral analysis applied in the present study corroborated the monophasic 24-hour variation. There was no indication of further perio-

### Table 2. Morning Peak in the Incidence of Myocardial Infarction in Subgroups (Percentage per Hour)

<table>
<thead>
<tr>
<th>Variable</th>
<th>6:00–12:00 AM</th>
<th>Other times</th>
<th>Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ejection fraction</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(\leq 50%)</td>
<td>296</td>
<td>5.7</td>
<td>3.6</td>
</tr>
<tr>
<td>&gt;50%</td>
<td>552</td>
<td>6.1</td>
<td>3.5</td>
</tr>
<tr>
<td><strong>Dyssynergy index</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(\leq 225)</td>
<td>427</td>
<td>6.1</td>
<td>3.5</td>
</tr>
<tr>
<td>&gt;225</td>
<td>422</td>
<td>5.8</td>
<td>3.6</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;60 yr</td>
<td>905</td>
<td>5.9</td>
<td>3.6</td>
</tr>
<tr>
<td>(\geq 60) yr</td>
<td>836</td>
<td>6.5</td>
<td>3.4</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>1,421</td>
<td>6.3</td>
<td>3.5</td>
</tr>
<tr>
<td>Female</td>
<td>320</td>
<td>5.9</td>
<td>3.6</td>
</tr>
<tr>
<td><strong>Myocardial infarction</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anterior</td>
<td>828</td>
<td>6.5</td>
<td>3.4</td>
</tr>
<tr>
<td>Inferior</td>
<td>877</td>
<td>6.0</td>
<td>3.5</td>
</tr>
<tr>
<td><strong>Therapy</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Streptokinase</td>
<td>859</td>
<td>6.2</td>
<td>3.5</td>
</tr>
<tr>
<td>Placebo</td>
<td>882</td>
<td>6.3</td>
<td>3.5</td>
</tr>
<tr>
<td><strong>Coronary artery disease</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>One-vessel</td>
<td>370</td>
<td>5.8</td>
<td>3.6</td>
</tr>
<tr>
<td>Two-vessel</td>
<td>302</td>
<td>5.8</td>
<td>3.6</td>
</tr>
<tr>
<td>Three-vessel</td>
<td>175</td>
<td>6.7</td>
<td>3.3</td>
</tr>
<tr>
<td><strong>Stenosis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(&lt;75%)</td>
<td>254</td>
<td>6.3</td>
<td>3.4</td>
</tr>
<tr>
<td>75–95%</td>
<td>323</td>
<td>5.8</td>
<td>3.6</td>
</tr>
<tr>
<td>&gt;95%</td>
<td>289</td>
<td>5.8</td>
<td>3.6</td>
</tr>
<tr>
<td><strong>Prior (\beta)-adrenergic blockade</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>206</td>
<td>4.9</td>
<td>3.9</td>
</tr>
<tr>
<td>Prior calcium antagonist therapy</td>
<td>147</td>
<td>6.8</td>
<td>3.3</td>
</tr>
<tr>
<td>No prior (\beta)-adrenergic blockade</td>
<td>1,473</td>
<td>6.5</td>
<td>3.4</td>
</tr>
<tr>
<td>Total</td>
<td>1,741</td>
<td>6.2</td>
<td>3.5</td>
</tr>
</tbody>
</table>

\(\dagger\)Residual stenosis of the infarct-related coronary artery.

\(\dagger\)Ratio of the hourly frequency of myocardial infarction during the second quarter of the day (6:00–12:00 AM) compared with hourly frequency of myocardial infarction during other times of the day (expected \(p<0.01\) but not significantly higher \(p>0.05\) than 1.}

Downloaded from http://circ.ahajournals.org/ by guest on July 14, 2017
myocardial infarction because this subtype appears not to exhibit a circadian variation.11

Although a circadian variation in the incidence of myocardial infarction was indicated in several previous studies, the validity of the timing of myocardial infarction based on clinical symptoms had not been clearly established.12–16 In the present study, the correlation between clinical methods and laboratory measurements in timing the onset of myocardial infarction was remarkably good (r=0.95), indicating the specific clinical characteristics of infarct symptoms and its reliability in determining time of myocardial infarction.

The mechanisms that lead to the increased incidence of myocardial infarction in the morning require further investigation. However, there are several clues to the factors responsible for this phenomenon. Blood platelets have been reported to be more responsive during the morning in healthy subjects and in patients with coronary artery disease.17,18 Conceivably, the increased morning platelet aggregability could enhance the risk of intracoronary thrombosis and thereby the risk of myocardial infarction and possibly sudden cardiac death.19–22 The increase in platelet aggregability appears to be related to physiologic changes occurring during the time of awakening and getting up.23 The importance of platelet characteristics is underlined by large clinical trials that have shown that24–27 antiplatelet therapy reduces myocardial infarction.

Another important factor in the pathogenesis of the increased morning incidence of myocardial infarction may be the morning increase in arterial blood pressure.28,29 First, the increase in myocardial oxygen demand related to blood pressure change may lead to increased vulnerability of the myocardium in case of transient reductions in blood supply. Second, the increase in arterial blood pressure could conceivably enhance the risk of plaque fissure that has been shown to occur rapidly before myocardial infarction.30 Other factors like hormonal changes31 or increase in the coronary artery tone32 may also play a role in the pathogenesis of morning increase in the incidence of myocardial infarction.

Patients receiving β-adrenergic blockers before their infarction did not have an increased morning incidence of myocardial infarction (Figure 2A), a finding that has been suggested recently.1 Visual analysis of this subgroup suggests an elevated incidence during the daytime until 6:00 PM, that is, a delay and prolongation of the peak period compared with the pattern in the total study population. However, clarification of this issue requires prospective future investigation. Patients on prior β-adrenergic blocking therapy may be protected by limitation of myocardial oxygen demand, prevention of the blood pressure surge in the morning, or other mechanisms. A recent report33 showed that β-adrenergic blockers suppressed the morning increase in episodes of myocardial ischemia, whereas calcium antagonists did not blunt this morning surge.
Furthermore, propranolol has been linked to a reduction of sudden cardiac deaths occurring during the morning.\textsuperscript{34} The significance of previous cardioprotective medication, therefore, seems to parallel the findings of the present study (Figure 2), suggesting a similar mechanism of the beneficial effect of $\beta$-adrenergic blockade in myocardial ischemia, acute myocardial infarction, and sudden cardiac death.

The incidence of sudden cardiac death, symptomatic and asymptomatic myocardial ischemia, and stroke shows a circadian pattern similar to that observed for myocardial infarction.\textsuperscript{2–6} Whether or not this is based on at least partially common pathophysioligic mechanisms remains to be determined. In one of those studies, the possible relation between the increased risk of myocardial ischemia and wake time has been emphasized,\textsuperscript{7} indicating that physical activity occurring after getting up may trigger myocardial ischemia. Studies that investigate the relation between time of getting up and risk of myocardial infarction may lead to further insight into trigger mechanisms of the disease.

The reasons for the increased morning risk of myocardial infarction are not yet known. It is necessary to further investigate the physiologic changes involved to eventually design more effective preventive therapy and to reduce the incidence of the disorder. Not only design and dosage but also optimal timing of cardioprotective medication may be of importance. The morning period should probably be more effectively covered by cardioprotective medication considering the effect achieved by conventional design and timing of medication. The observation that $\beta$-adrenergic blockade prevents an increased morning incidence of myocardial infarction may contribute to an understanding of the mechanisms by which $\beta$-blockers reduce incidence of myocardial infarction.\textsuperscript{13,16}

### References

10. Willich SN, Stone PM, Muller JE, Tofler GH, Crowder J, Parker C, Rutherford JD, Turi ZG, Robertson T, Passamani E, Braunwald E, the MILIS Study Group: High-risk subgroups of patients with non-Q-wave myocardial infarction based on direction and severity of ST segment deviation. \textit{Am J Cardiol} 1985;56:1110–1119

**KEY WORDS** • myocardial infarction • β-adrenergic receptors • circadian rhythm, morning • ISAM
Increased morning incidence of myocardial infarction in the ISAM Study: absence with prior beta-adrenergic blockade. ISAM Study Group.
S N Willich, T Linderer, K Wegscheider, A Leizorovitz, I Alamercery and R Schröder

_Circulation._ 1989;80:853-858
doi: 10.1161/01.CIR.80.4.853

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1989 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/80/4/853