The cardiovascular metabolic syndrome
Rana, J.S.

Citation for published version (APA):

General rights
It is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), other than for strictly personal, individual use, unless the work is under an open content license (like Creative Commons).

Disclaimer/Complaints regulations
If you believe that digital publication of certain material infringes any of your rights or (privacy) interests, please let the Library know, stating your reasons. In case of a legitimate complaint, the Library will make the material inaccessible and/or remove it from the website. Please Ask the Library: http://uba.uva.nl/en/contact, or a letter to: Library of the University of Amsterdam, Secretariat, Singel 425, 1012 WP Amsterdam, The Netherlands. You will be contacted as soon as possible.
Circadian Variation in the Onset of Myocardial Infarction: Effect of Duration of Diabetes Mellitus
Chapter 5

Abstract

There are conflicting reports regarding circadian variation in the onset of acute myocardial infarction (MI) among patients with diabetes mellitus. We therefore, studied the circadian pattern of the incidence of acute MI in patients (n= 3882) enrolled in the Onset Study stratified by the presence, type and duration of diabetes. The Onset Study was conducted at 64 US 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. Subgroups analysis was performed according to the presence, type and duration of diabetes by the $\chi^2$ test (dividing the day into four 6-hour 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 $\geq$ 5 years had a marked attenuation of the morning peak. Patients with 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 $\geq$ 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.
Background

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 differences 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. 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 (14). Zarich et al. 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 (15).

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 mellitus, among patients enrolled in the Determinants of Myocardial Infarction Onset Study (16).

Methods

The Onset Study was conducted in 64 medical centers in the United States. Between August 1989 and September 1996, 3882 patients (1258 women and 2624 men) were interviewed at a median of 4 days (range 0 to 30) after having a myocardial infarction. 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 (CK) 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 myocardial infarction, a method previously validated with the use of serial CK 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 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 into four 6-hour 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 chi-square 1-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 $\chi^2$ test.

**Results**

The characteristics of the study population have been previously reported (16-18) and are summarized in Table 1.

The Figure shows the hourly distribution of MI symptom onset, among patients with and without history of diabetes. A statistically significant circadian pattern of MI symptom onset with a single peak in the morning hours was observed in patients
Table 1 – Characteristics of Onset Study Patients According to Medical History of Diabetes.

<table>
<thead>
<tr>
<th>Variables*</th>
<th>Diabetes (n= 814)</th>
<th>No diabetes (n= 3068)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>64±11.5</td>
<td>60.6±12.9</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Female</td>
<td>356 (43.8%)</td>
<td>902 (29.4%)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>White race</td>
<td>656 (80.6%)</td>
<td>2734 (88.6%)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>BMI (kg/m^2)</td>
<td>26.9±5.6</td>
<td>28.5±5.0</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Current Smoker</td>
<td>173 (21.3%)</td>
<td>296 (36.4%)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Former smoker</td>
<td>353 (43.4%)</td>
<td>1200 (39.1%)</td>
<td>0.03</td>
</tr>
<tr>
<td>Obese (&gt; 29 kg/m^2)</td>
<td>358 (44.0%)</td>
<td>890 (29.0%)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>†No Exertion</td>
<td>698 (85.7%)</td>
<td>2292 (74.7%)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Education:</td>
<td></td>
<td></td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Less than high school</td>
<td>218 (26.8%)</td>
<td>641 (20.9%)</td>
<td></td>
</tr>
<tr>
<td>Complete High school</td>
<td>356 (43.8%)</td>
<td>1267 (41.3%)</td>
<td></td>
</tr>
<tr>
<td>Some College</td>
<td>240 (29.5%)</td>
<td>1163 (37.9%)</td>
<td></td>
</tr>
<tr>
<td>Past Cardiac History</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Previous MI</td>
<td>289 (35.5%)</td>
<td>758 (24.7%)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Angina</td>
<td>260 (32%)</td>
<td>687 (22.4%)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>476 (58.5%)</td>
<td>1221 (39.8%)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>CHF - Baseline</td>
<td>31 (3.8%)</td>
<td>540 (1.8%)</td>
<td>.001</td>
</tr>
<tr>
<td>Regular Use of Medication</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>321 (39.4%)</td>
<td>1135 (37.0%)</td>
<td>0.2</td>
</tr>
<tr>
<td>Ca Blockers</td>
<td>289 (35.5%)</td>
<td>638 (20.8%)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Digoxin</td>
<td>85 (10.4%)</td>
<td>172 (5.6%)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>B- Blockers</td>
<td>189 (23.2%)</td>
<td>644 (21%)</td>
<td>0.17</td>
</tr>
<tr>
<td>ACE Inhibitors</td>
<td>158 (22.7%)</td>
<td>328 (10.7%)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Characteristics of Index Hospitalization</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHF</td>
<td>173 (21.3%)</td>
<td>344 (11.2%)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Q-wave Infarction</td>
<td>412 (50.6%)</td>
<td>1795 (58.5%)</td>
<td>.001</td>
</tr>
<tr>
<td>Thrombolytic Therapy</td>
<td>258 (31.7%)</td>
<td>1292 (42.1%)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

* Missing data; 39 patients for race, 60 patients for BMI, 32 patients for smoking status, 73 patients for previous MI. † Physical exertion >6 METs less than once weekly. ACE = angiotensin-converting enzyme; BMI = body mass index; CHF = congestive heart failure; VT = ventricular tachycardia.

without diabetes (p-value< 0.001), whereas no such peak was observed among 814 patients with a history of diabetes (p-value = 0.16).

Table 2 shows the distribution of the time of MI onset in 6-hour 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 with type 2
Table 2: Circadian Variation of Acute Myocardial Infarction by Type and Duration of Diabetes Mellitus.

<table>
<thead>
<tr>
<th>No Diabetes, %</th>
<th>0:00 - 5:59</th>
<th>6:00 - 11:59</th>
<th>12:00 - 17:59</th>
<th>18:00 - 23:59</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>3068</td>
<td>21</td>
<td>30</td>
<td>26</td>
<td>23</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>814</td>
<td>22</td>
<td>28</td>
<td>24</td>
<td>26</td>
<td>0.06</td>
</tr>
</tbody>
</table>

Type of Diabetes

| Type 2 < 5yrs, % | 246 | 18 | 31 | 24 | 26 | 0.03 |
| Type 2 ≥ 5yrs, %| 258 | 23 | 23 | 28 | 26 | 0.65 |
| Type 1, %       | 137 | 25 | 28 | 21 | 26 | 0.73 |

* P-value for 1 degree of freedom $\chi^2$ goodness of fit test.

Hourly frequency distribution of time of symptom onset of myocardial infarction. Panel A shows the distribution in patients without a history of diabetes. Panel B shows the distribution in patients with diabetes. The line represents the fitted harmonic regression model. P-values from the 1-degree of freedom goodness of fit test for uniform distribution. MN – Midnight.

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 or more year duration.

Although not a previous hypothesis we noted that patients with diabetes appeared to have a higher proportion of infarcts in the late evening around 10 to 11 pm (figure). Despite this, the harmonic regression analysis did not demonstrate a statistically significant secondary peak in MI onset among patients with diabetes (p-value = 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 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 myocardial infarction. Hjalmarson et al. were the first to show, that the characteristic day-night pattern in the onset of myocardial infarction is altered in patients with diabetes (4). These findings have been confirmed by several studies (19-22). In conflicting reports, 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 causes 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, causing unstable angina and acute MI (30). Moreover it has been demonstrated that patients receiving Beta 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 recently diagnosed patients with type 1 diabetes (35). In patients with type 2 diabetes, Toyry et al. observed that the risk to develop parasympathetic neuropathy increased sharply after 5 years, and prevalence for combined autonomic neuropathy reached 65% after 10 years of follow up (36). In a recent study in patients with type 2 diabetes, cardiac sympathetic dysinnervation was observed even before ECG-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 and colleagues demonstrated, using spectral analysis of heart rate variability, that diabetic autonomic neuropathy is associated with a marked diminution of parasympathetic activation during sleep (38). In a similar study (39) Sayer et al. found that the rhythm of sympathovagal balance was significantly attenuated in patients with diabetes compared to those without diabetes. This indicates that neuropathic defects that characterize patients with type 2 diabetes have potentially important physiological consequences including loss of the normal 24-hour blood pressure profile (40) with the loss of its characteristic nocturnal dip.

These factors might predispose patients with long standing diabetes to trigger cardiovascular events at nighttime along with the absence of morning peak, accounting for attenuation of circadian variation of MI in these patients (41).

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 I 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.

Acknowledgements

This study was supported by Grant HL41016 for the Determinants of Myocardial Infarction Onset Study from the National Heart, Lung, and Blood Institute, Bethesda, Maryland, Grant T32-HL07374-22 from the National Institutes of Health, Bethesda, Maryland, and Grant 9630115N from the American Heart Association, Dallas, Texas.
Circadian variation and diabetes mellitus

References

30. Muller JE, Tofler GH, Verrier RL. Sympathetic activity as the cause of the morning increase in cardiac events. A likely culprit, but the evidence remains circumstantial. Circulation. 91: 2508-9, 1995

