ORIGINAL

Influence of diurnal variation in the size of acute myocardial infarction

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Abstract
Objective: To evaluate whether the size of acute myocardial infarction (AMI) shows circadian variability.
Design: An observational, prospective study.
Setting: A 12-bed coronary care unit.
Patients: Consecutive patients diagnosed with ST-elevation myocardial infarction (STEMI) undergoing primary percutaneous coronary intervention.
Interventions: The patients were divided into two groups according to the time of onset of AMI symptoms (group A: 0–12 h, group B: 12–24 h).
Main variables of interest: Age, sex, cardiovascular risk factors, coronary anatomy, left ventricular ejection fraction, infarct location, time from onset of symptoms to reperfusion, presence of heart failure upon admission, and peak troponin I value.
Results: A total of 108 patients with a diagnosis of STEMI were included. Patients in group A showed a higher troponin I concentration compared to group B (troponin I: 70.85 ± 16.38 ng/ml vs 60.90 ± 22.92 ng/ml, p = 0.003). In the multivariate analysis the onset of AMI between 0 and 12 h was identified as an independent predictor of infarct size (OR: 1.133, 95%CI 1.012–1.267, p = 0.01).
Conclusions: An onset of AMI between 0 and 12 h results in a significantly larger final size of necrosis compared with any other time of presentation.
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PALABRAS CLAVE
Infarto agudo de miocardio; Ritmo circadiano; Tamaño de infarto

Influencia de la variabilidad diurna en el tamaño del infarto agudo de miocardio

Resumen
Objetivo: Evaluar si el tamaño del infarto agudo de miocardio (IAM) presenta variabilidad circadiana.
Diseno: Estudio prospectivo observacional.

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**Introduction**

The circadian rhythm is the biological clock that regulates most of the mechanisms in our body. In recent years, different clinical studies have shown acute myocardial infarction (AMI) to be more frequent in the first hours of the morning.\(^1\) No single underlying physiopathological mechanism is involved in this phenomenon; rather, a number of contributing factors have been identified: increased blood pressure and heart rate, increased vasomotor tone, increased platelet aggregability accompanied by diminished fibrinolytic activity, and variations in circulating hormone levels.\(^2\) The present study was designed to determine whether AMI size also shows circadian variability.

**Patients and methods**

A prospective study was made of the patients admitted to the Coronary Unit of a third-level hospital, diagnosed with AMI with ST-segment elevation and subjected to primary angioplasty. AMI was diagnosed based on the criteria published in the medical literature,\(^3\) and all patients were revascularized according to the established time periods. The patients were divided into two groups according to the time of onset of AMI (group A: 0:00–12:00 h; group B: 12:00–24:00 h). Clinical, angiographic and laboratory test variables were analyzed.

AMI size was quantified based on the peak troponin I concentration. The blood samples for this evaluation were collected every 8 h on the first day, and every 24 h over the next three days, in accordance with the hospital protocol. Troponin I was determined by means of immunoenzymatic techniques using an ELISA test. The within- and between-test coefficients of variability were 2.2% and 5.9%, respectively. The limit of detection was established as 0.12 ng/ml.

The study was approved by the Clinical Research Ethics Committee of the hospital, and all patients gave informed consent to participation in the trial.

**Results**

The results were analyzed using the SPSS version 15.0 statistical package (SPSS Inc., Chicago, IL, USA). Qualitative variables were expressed as percentages, while quantitative variables were presented as the mean ± standard deviation (SD). The Kolmogorov–Smirnov test was used to assess normal distribution of the study variables. The chi-squared test was used for the comparison of two qualitative variables. The differences in means between two quantitative variables exhibiting a normal distribution were analyzed with the Student t-test for non-paired samples. Multivariate analysis was carried out using a binary logistic regression model to demonstrate whether infarction onset is an independent predictor of infarct size. The model included variables such as cardiovascular risk factors, age, sex, anterior location of the infarct, multivessel coronary arterial disease, left ventricular ejection fraction, time of start of the symptoms and troponin I levels. Statistical significance was considered for \(p < 0.05\).

A total of 108 patients diagnosed with AMI with ST-segment elevation were included in the study. The subjects in group A presented a higher troponin I concentration than those in group B (70.85 ± 16.38 ng/ml vs 60.90 ± 22.92 ng/ml, \(p = 0.003\)) (Fig. 1). The rest of the clinical variables, including ischemia time, infarct location, age, sex, cardiovascular risk factors and hemodynamic variables showed no statistically significant differences (Table 1). In the multivariate analysis, a time of onset of AMI between 0:00 and 12:00 h was found to be an independent predictor of infarct size (OR: 1.133, 95%CI 1.012–1.267; \(p = 0.01\)).

**Discussion**

Circadian rhythms are known to influence many cardiovascular physiopathological processes. Studies in rodents have shown that infarct size can be influenced by the time of day.\(^4\) In humans, the fact that AMI is more frequent in the first
Influence and between necrosis. Figure (AMI two infarction) values myocardial Age Table 1 Demographic, laboratory test and hemodynamic data of the study population.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group A (AMI 0:00–12:00 h) (n = 21)</th>
<th>Group B (AMI 12:00–24:00 h) (n = 87)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>60 ± 12</td>
<td>65 ± 11</td>
<td>0.09</td>
</tr>
<tr>
<td>Sex (males), n (%)</td>
<td>18 (86)</td>
<td>67 (77)</td>
<td>0.38</td>
</tr>
<tr>
<td>Arterial hypertension, n (%)</td>
<td>12 (57)</td>
<td>45 (52)</td>
<td>0.40</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>10 (48)</td>
<td>25 (29)</td>
<td>0.09</td>
</tr>
<tr>
<td>Hypercholesterolemia, n (%)</td>
<td>7 (33)</td>
<td>46 (53)</td>
<td>0.10</td>
</tr>
<tr>
<td>Smoker, n (%)</td>
<td>9 (43)</td>
<td>35 (40)</td>
<td>0.82</td>
</tr>
<tr>
<td>CD, n (%)</td>
<td>11 (52)</td>
<td>38 (44)</td>
<td>0.92</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>56 ± 10</td>
<td>56 ± 12</td>
<td>0.86</td>
</tr>
<tr>
<td>Anterior AMI, n (%)</td>
<td>10 (48)</td>
<td>39 (45)</td>
<td>0.81</td>
</tr>
<tr>
<td>Killip class &gt; I, n (%)</td>
<td>3 (14)</td>
<td>8 (9)</td>
<td>0.65</td>
</tr>
<tr>
<td>Pain-reperfusion time (min)</td>
<td>244 ± 67</td>
<td>240 ± 70</td>
<td>0.80</td>
</tr>
<tr>
<td>Final post-PTCA TIMI flow</td>
<td></td>
<td></td>
<td>0.72</td>
</tr>
<tr>
<td>0–1</td>
<td>1 (5)</td>
<td>4 (5)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>3 (14)</td>
<td>15 (17)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>17 (81)</td>
<td>68 (78)</td>
<td></td>
</tr>
<tr>
<td>Creatinine, mg/dl</td>
<td>0.95 ± 0.21</td>
<td>1.10 ± 0.34</td>
<td>0.67</td>
</tr>
<tr>
<td>Total cholesterol, mg/dl</td>
<td>182 ± 40</td>
<td>185 ± 51</td>
<td>0.81</td>
</tr>
</tbody>
</table>

Values expressed as n (%) or mean ± standard deviation.

PTCA: percutaneous transluminal coronary angioplasty; CD: coronary arterial disease; LVEF: left ventricle ejection fraction; AMI: acute myocardial infarction; TIMI: thrombolysis in myocardial infarction.
relationship between serum melatonin levels and coronary arterial disease.\textsuperscript{12}

Several years ago, we showed that AMI patients have lower nocturnal melatonin concentrations than the controls.\textsuperscript{13} We therefore postulate that AMI occurring between 0:00 and 12:00 h involves a larger infarct size due at least in part to the presence of lower serum melatonin levels, and therefore to lesser antioxidant and ischemia/reperfusion damage protective action.\textsuperscript{14} In this context, we consider that further studies of these cardioprotective mechanisms are needed, as they may have future diagnostic, protective and therapeutic implications for patients with AMI.

Our study has a number of limitations, such as the small sample size and the indirect calculation of infarct size based on the elevation of myocardial necrosis markers. Although this measurement approach has been extensively validated, the current technique of choice is cardiac MRI.\textsuperscript{15} The high cost and limited availability of this technique has not allowed us to include it in our study protocol, however.

In conclusion, this prospective study shows the time of day to exert an important influence upon the presentation of AMI and on infarct size – the latter being larger when infarction occurs between 0:00 and 12:00 h in the morning.

Conflict of interest

The authors declare no conflicts of interest.

References