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Original Article

Circadian pattern of symptoms onset in patients ≤35 years presenting with ST-segment elevation acute myocardial infarction

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ABSTRACT

Background: There are scarce data regarding the circadian pattern of symptoms onset in young patients presenting with acute myocardial infarction (AMI). We explored whether young patients with ST-segment elevation AMI exhibit a circadian variation in symptoms onset.
Methods: We recruited prospectively 256 consecutive patients who had survived their first ST-segment elevation AMI ≤35 years of age. Patients were categorized into 4 groups by 6-h intervals over 24 h.
Results: In 49 patients (19.1%) the clinical presentation of AMI was atypical. The symptoms onset was as follows: 00:01 to 06:00, 19.1%, 06:01 to 12:00, 32.4%; 12:01 to 18:00, 28.1%; and 18:01 to 24:00, 20.3%. There was a significant association between the time of day and the likelihood of symptoms onset (Rayleigh test, $p < 0.001$). Between 00:01 and 06:00 the incidence of AMI onset was lower than expected and between 06:01 and 12:00 was higher ($p = 0.034$ and $p = 0.011$, respectively), whereas in the other 6-h period groups no difference was found between expected and observed AMI incidence ($p = 0.280$ and $p = 0.131$). No significant differences were found regarding clinical characteristics, i.e. traditional risk factors, reperfusion treatment of AMI, ejection fraction of left ventricle, time interval from pain onset to hospital arrival, dietary habits and physical activity, among the 6-h period groups.
Conclusions: ST-segment elevation AMI in individuals ≤35 years of age follows a circadian pattern with a morning peak. This information might be useful for the prompt diagnosis and treatment of AMI in very young patients which occurs rarely and frequently with atypical clinical presentation.

1. Introduction

Circadian rhythm influences cardiovascular physiology by inducing variations in blood pressure, heart rate, cardiac output and endothelial function [1,2]. It is well established that different cardiovascular events including acute myocardial infarction (AMI), exhibit a specific time-of-day relation with higher incidence during sleep to wake transition [3–9].

Circadian patterns of AMI were first described in 1976 by the World Health Organization Regional Office for Europe which reported a peak incidence in the onset of pain between 8:00 am and 10:00 am [10]. However, a secondary peak during the afternoon has also been noted while diabetics display a more uniform day distribution [5,6].

AMI is an uncommon entity in young adults and its incidence depends on the cut-off age used [11]. It has been reported that <1% of patients with acute coronary syndrome are ≤35 years [12]. Young patients with AMI differ from older patients in the risk factor profile and in the extent of atheromatic plaque coronary burden. In particular, young coronary patients are characterized by a higher proportion of heavy smoking, a lower proportion of hypertension and diabetes mellitus (DM) and a relatively high proportion (15-20%) of angiographically “normal” coronary arteries [13,14].

Data regarding the circadian pattern in young patients with AMI are sporadic. Chan et al. [15] reported a circadian variation with a peak from 00:01 to 06:00 in Chinese patients with AMI under the age of 45 years. Young patients with AMI compose an excellent model to examine the circadian variation since confounders such as DM and treatment with beta-blockers and antiplatelet agents are infrequent.

The aim of our study was to investigate the circadian pattern in patients who suffered an ST-segment elevation AMI before the age of

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36 years and therefore obtain useful information for the pathophysiology, diagnosis and treatment of AMI in very young patients.

2. Materials and methods

2.1. Study population

We enrolled prospectively 256 consecutive patients who had survived their first AMI occurring ≤35 years of age. They were recruited from the Coronary Care Unit of 2 large hospitals (University General Hospital Attikon in Athens and General Hospital of Nikea in Piraeus) between 1996 and 2014. Only patients with first ST-segment elevation AMI were enrolled. The diagnosis of ST-segment elevation AMI was based on the following criteria: history of typical chest pain lasting >30 min, electrocardiographic changes characterized by ST-segment elevation ≥1 mm in at least 2 adjacent leads and diagnostic evolutionary pattern of myocardial injury markers. If the clinical presentation was not typical (i.e. atypical chest pain) but the ECG changes and the evolutionary pattern of myocardial injury markers were present the diagnosis of ST-segment elevation AMI was also made.

All patients underwent cardiac catheterization prior to discharge. Coronary artery stenosis was defined as >50% reduction in lumen diameter of any of the three coronary arteries or their main branches. Coronary arteries with smooth contours and no focal diameter reduction or with non-hemodynamically significant atherosclerotic lesions (<50% stenosis) were defined as "normal or near normal".

All participants were interviewed during hospitalization and the risk factors were recorded. Special attention was paid on recording the accurate time of onset of chest pain of AMI. Patients were categorized into 4 groups by 6-h intervals over 24 h according to the onset of AMI symptoms (00:01–06:00, 06:01–12:00, 12:01–18:00 and 18:01–24:00).

Peripheral blood samples were collected from patients within 12 h from admission for assessing lipid and homocysteine levels. Hypercholesterolemia was defined as total cholesterol >200 mg/dL (>5.2 mmol/L) or a history of previous use of cholesterol lowering drugs; hypertension was defined as blood pressure ≥140/90 mmHg or a history of previous antihypertensive treatment; DM was defined as fasting plasma glucose >125 mg/dL (6.94 mmol/L) or the use of glucose lowering treatment. Smoking habits and body mass index [BMI] (weight in kg/height^2 in m^2) were also evaluated. Obesity was defined as BMI ≥30 kg/m^2 and metabolic syndrome (MS) was diagnosed using the criteria of the American Heart Association/The National Heart Lung and Blood Institute [16].

Dietary habits during the preceding year were evaluated by a validated diet score that assesses adherence to Mediterranean dietary pattern [17]. The score is derived by a questionnaire that includes the 11 main components of the Mediterranean diet (non-refined cereals, fruits, vegetables, potatoes, legumes, olive oil, fish, red meat, poultry, full fat dairy products and alcohol). Each question is scored on a scale of 0 through 5 according to the frequency of food consumption per week. In particular, the consumptions of items presumed to be close to this pattern (i.e. olive oil) were assigned scores 0, 1, 2, 3, 4 and 5 when a participant reported no consumption, rare, 1–2 times/week, 2–3 times/week, 3–5 times/week and daily, respectively. For the consumption of foods presumed to be away from this pattern (i.e. red meat) the scores were assigned on a reverse scale. Therefore, the diet score ranges between 0 and 55. Higher values of this diet score indicate greater while lower values worse adherence to the Mediterranean diet.

Physical activity during the preceding year was also assessed by a translated short version of the International Physical Activity Questionnaire (IPAQ), as index of weekly energy expenditure using frequency (times per week), duration (in minutes per time) and intensity of physical activity. The IPAQ measures are expressed as metabolic equivalents (MET) min week^{-1}. MET is defined as 3.5 mL $O_2 \times kg^{-1} \times min^{-1}$. We used the following MET estimates of IPAQ: vigorous physical activity = 8 METs, moderate = 4 METs, walking on average = 3.3 METs and sitting = 0 METs. For calculating the overall METs physical activity, each category was multiplied with its special MET estimate value. IPAQ has reasonable measurement properties for monitoring population levels of physical activity [18].

Finally, all patients before discharge underwent an echocardiographic study and the left ventricular ejection fraction (LVEF) was measured using the biplane method of discs (modified Simpson's rule) [19].

The study was approved by the ethics committee of our institution and all subjects gave their informed consent.

2.2. Statistical analysis

Continuous variables are expressed as mean ± SD and were compared between groups of patients using Student's t test or Mann–Whitney test. Categorical variables are presented as absolute and relative frequencies, and associations between categorical variables were tested using the chi-square test. The Rayleigh test was used to evaluate the hypothesis of a uniform distribution of time onset of AMI symptoms. A two-sided binomial test was performed to examine whether the frequency of AMI was higher than the expected rate. A p value <0.05 was considered significant. The SPSS version 22 (SPSS Inc., Chicago, Illinois, USA) and STATA version 9.1 (StataCorp LP, College Station, Texas, USA) were used.

3. Results

3.1. Baseline characteristics

We initially recruited 258 consecutive patients ≤35 years of age who were admitted with the diagnosis of first ST-segment elevation AMI. Two patients died during hospitalization and were excluded from analysis. The mean age at presentation was 32.2 ± 3.6 years for men and 32.4 ± 4.4 years for women ($p = 0.840$).

Table 1 presents the patients' characteristics at the time of incident AMI. Smoking was the most prevalent risk factor. Analysis of coronary angiograms revealed coronary artery stenosis in 207 (80.9%) patients. In particular, one hundred thirty-six patients (53.1%) had 1-vessel disease, 48 (18.8%) had 2-vessel disease and 23 (9.0%) had 3-vessel disease. None of the patients were on beta-blockers or antiplatelet agents prior admission while 7 were taking statins.

The onset of AMI was between 00:01 and 06:00 in 49 patients (19.1%), between 06:01 and 12:00 in 83 patients (32.4%), between 12:01 and 18:00 in 72 patients (28.1%), and between 18:01 and 24:00 in 52 patients (20.3%) (Fig. 1). There was a significant association between the time of day and the likelihood of the onset of symptoms (Rayleigh test, $p < 0.001$). Between 00:01 and 06:00 the incidence of AMI symptoms onset was lower than the expected and between 06:01 and 12:00 was higher ($p = 0.034$ and $p = 0.011$, respectively), whereas in the other time intervals no difference was found between expected and observed AMI incidence ($p = 0.280$ and $p = 0.131$, respectively).

In 49 patients (19.1%) the clinical presentation of AMI symptoms was atypical. In particular, the predominant complaint was atypical chest pain in 28 patients, gastrointestinal symptoms in 10 patients, profuse weakness in 6 patients, syncope in 2 patients, focal neurological deficits in 2 patients and palpitations in 1 patient. The proportion of young patients without significant CAD who presented with atypical symptoms did not differ from those who had significant CAD (22.4% vs. 18.4%, $p = 0.513$).

There were no differences in clinical characteristics i.e. traditional risk factors, reperfusion treatment of AMI, LVEF, time interval from pain onset to hospital arrival, dietary habits and physical activity, among the four 6-h interval groups (data not shown). We further compared the patients' characteristics whose symptoms onset of AMI was between 06:01 and 12:00 (group with the highest incidence of symptoms onset) with the other three groups together (those with