

## Cardiovascular Risk Factors in the Circadian Rhythm of Acute Myocardial Infarction

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**Introduction and objectives.** The aim of this study was to analyze the influence of modifiable cardiovascular risk factors on the circadian rhythm of acute myocardial infarction.

**Patients and method.** We analyzed a retrospective cohort of 54 249 patients from a multicenter study of acute myocardial infarction (the Spanish ARIAM study). The variables were time of onset of symptoms, age, sex, previous ischemic heart disease, coronary unit discharge status, previous stroke, familial antecedents of ischemic heart disease, hypertension, diabetes, dyslipidemia, smoking, and reinfarction. To verify the presence of circadian rhythm, we developed a simple test of equality of time series based on cosinor analysis of multiple sinusoid curves. Three sinusoids (24, 12, and 8 hour periods) were used.

**Results.** The time of onset of pain showed a circadian rhythm ( $P < .01$ ), with a peak at 10:07 am and a trough at 4:46 am. All subgroups categorized according to the presence of the variables analyzed here showed a circadian rhythm, with a sinusoid curve after adjustment. In patients with diabetes or reinfarction or who were smokers, the sinusoid curve was bimodal.

**Conclusions.** Time of onset of symptoms in patients with acute myocardial infarction follows a circadian rhythm. Diabetes, smoking and reinfarction can modify the standard circadian rhythm of onset of myocardial infarction.

**Key words:** *Circadian rhythm. Acute myocardial infarction. Cardiovascular risk factors.*

### Factores de riesgo cardiovascular en el ritmo circadiano del infarto agudo de miocardio

**Introducción y objetivos.** El objetivo de este trabajo es analizar la influencia de los factores de riesgo cardiovascular modificables en el ritmo circadiano del infarto agudo de miocardio.

**Pacientes y método.** Análisis retrospectivo de 54.249 pacientes incluidos en la base de datos del proyecto ARIAM con diagnóstico de infarto agudo de miocardio. Se analizan las variables hora de inicio, edad, sexo, cardiopatía isquémica previa, estado en el momento del alta de la unidad coronaria, antecedentes familiares de cardiopatía isquémica, accidente cerebrovascular previo, hipertensión arterial, dislipemia, diabetes, tabaquismo y reinfarto. El análisis de ritmo se ha efectuado utilizando un test simple de igualdad de series basado en el análisis cosinor de múltiples sinusoides, eligiendo 3 armónicos (24, 12 y 8 h) para su ajuste.

**Resultados.** La hora de inicio del infarto muestra ritmo circadiano ( $p < 0,01$ ) con pico a las 10,07 y valle a las 4,46 h. Todos los subgrupos categorizados por la presencia de las variables analizadas presentaron ritmo circadiano, con una curva ajustada de aspecto sinusoidal. Los pacientes con diabetes, reinfarto y tabaquismo muestran una curva sinusoidal de aspecto bimodal.

**Conclusiones.** El infarto agudo de miocardio presenta ritmo circadiano. La diabetes, el tabaquismo y el reinfarto pueden modificar el ritmo habitual de aparición del infarto.

**Palabras clave:** *Ritmo circadiano. Infarto agudo de miocardio. Factores de riesgo cardiovascular.*

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### INTRODUCTION

Cardiovascular risk factors have long been studied in order to gain insight into the physiopathology, epidemiology and therapy of acute myocardial infarction (AMI). In this respect, recent advances in chronobiological methods have provided new knowledge regar-

## ABBREVIATIONS

AMI: acute myocardial infarction.

ding the behavior of rhythmical phenomena and their effects on cardiovascular risk.<sup>1-14</sup>

The majority of cardiovascular risk factors (which are well known) predispose the individual to developing acute coronary syndrome (in any of its different guises). Many of these factors can be used as prognostic indicators in patients who have suffered an AMI.<sup>15-17</sup> The present paper pays particular attention to those that might influence the circadian variability of AMI.

A number of recent studies have suggested that cardiovascular events show temporal variability, and that episodes of myocardial ischemia are irregularly distributed over time, with an increased incidence during certain hours of the day, days of the week or even months of the year.<sup>4,18-28</sup>

Although myocardial ischemia can occur at any time of day, a circadian rhythm has been confirmed for the appearance of acute ischemic heart disease in the general population. Further, the MILIS<sup>18</sup> study showed there to be a circadian pattern in the appearance of AMI. Other studies<sup>25,28-34</sup> have confirmed these findings, although they show slight variations with respect to the beginning and end of peak incidence.

Some factors appear to modify the circadian rhythm of infarction in the general population, causing clinical AMI to be recognized over different time ranges.<sup>22,35,36</sup> In patients with ischemic heart disease (understood here as any of its manifestations, e.g., angina, AMI, casual angiographic findings or findings appreciated from the results of functional tests, asymptomatic disease, etc), the rhythm of AMI symptom onset is similar to that of the general population, with a morning peak incidence. Patients who have suffered a previous AMI show a significantly increased number of episodes of ischemia during the evening (18:00 h-24:00 h); these also last significantly longer than usual.<sup>20</sup>

The ISIS-2 study reported the absence of a circadian rhythm in AMI symptom onset in diabetic patients,<sup>37</sup> while others indicate circadian variations in the same type of patient with a peak incidence between 6:00 h and 12:00 h.<sup>9</sup> In some studies, patients older than 70, smokers and women have shown a bimodal distribution of ischemic episodes with morning and evening peaks for AMI symptom onset.<sup>20,22</sup>

The present work attempts to determine the hours in which AMI symptoms begin in the general population and on the possible influence that different cardiovascular risk factors may have on the rhythm de-

tected.

## PATIENTS AND METHODS

The data examined in this work were those recorded by the ARIAM (*Análisis del Retraso en el Infarto Agudo de Miocardio*) project. Symptom onset times for AMI were recorded and an analysis performed to detect which variables might modify their periodicity.

The ARIAM project is a Spanish, multicenter study involving 119 centers around the country.<sup>38</sup> Its database is an open registry and the information it contains is updated continuously. Among the data recorded is information on the main cardiovascular risk factors.<sup>39</sup> Patients are "enrolled" consecutively from the moment that centers join the project. Currently, data are held on 86 000 patients; some 10 000 new patients are enrolled every year.

The study population consisted of 54 249 patients registered in the database between May 1994 and 2003. To study the influence of cardiovascular risk factors on the circadian rhythm of AMI onset, a subpopulation of 18 665 patients was selected whose files recorded the presence of these variables (information for these patients was obtained from the DATARIAM-CAR database; this is associated with the general database containing the information for the above 54 249 patients).

All patients had a firm diagnosis of AMI. The diagnostic criteria for AMI initially used were those defined by the WHO and validated by the American College of Cardiology. After the Committee for the Redefinition of Acute Myocardial Infarction published its findings (consensus document of the Joint European Society of Cardiology/American College of Cardiology) in September 2000, the new criteria developed were gradually introduced at the participating centers; currently these are used for diagnosing every potential case of AMI.<sup>40,41</sup>

The influence of the following variables on the time of AMI symptom onset were recorded: sex, age ( $\geq 70$  years and  $< 70$  years, in agreement with the majority of the literature), prior ischemic heart disease (in any of its clinical forms, diagnosed by anamnesis or electrocardiogram), condition at discharge (dead or alive), family background of ischemic heart disease (angina or AMI in men  $< 55$  years old and in women  $< 60$  years old), prior cerebrovascular accident (hemorrhagic or ischemic), arterial hypertension, diabetes mellitus, dyslipidemia, use of tobacco, and reinfarction.

### Type of Study

This was a retrospective study in which the data recorded in the ARIAM database were analyzed. These data were processed in successive stages. Patient re-

cords were ordered chronologically. Data were recorded for the period 1 May 1994 until 31 October 2003.

### Statistical Analysis

The study population was characterized using basic, descriptive statistical values (means for continuous variables and percentages or distribution of frequencies for discrete variables).

To analyze the influence of each variable on the circadian rhythm of AMI symptom onset, the study population was divided into different subgroups.

The goodness of fit of the different variables was examined by the  $\chi^2$  test: since each of the subgroups was defined by a single qualitative variable, attempts were made to determine whether the distribution of the AMI episode frequencies for each followed any rule, i.e., whether they fitted expected frequencies. The aim was to determine whether, for each variable, the frequencies were distributed according to a set pattern.

Circadian rhythms and their harmonics can be demonstrated using the cosinor method.<sup>42</sup> This allows an adapted cosine curve to be constructed, in which several variables can be identified. The terms employed in chronobiological analysis when using the cosinor method are: *a) rhythm*: the periodicity of a pattern that oscillates in time: if the variation pattern is not periodic there is no rhythm; *b) period*: the time necessary to complete one cycle of a rhythmical phenomenon (the inverse of frequency); *c) circadian*: a rhythm with a period of approximately 24 h; *d) frequency*: the number of cycles completed in a given time; *e) MESOR* (midline estimating statistic of rhythm): the mean value between the maximum and minimum values of the sinusoidal curve; *f) amplitude*: the peak measurement of a rhythm above the mean threshold estimated by a mathematical function that measures the difference between the highest and lowest values on the cosine curve; *g) acrophase*: the time at which the maximum value established from the variable in the adapted cosine curve is measured; *h) batiphase*: the time at which the minimum value of the variable is established from the adapted cosine curve; and *i) cosine analysis*: the adaptation of a cosine curve to a rhythm by least squares regression.

Via the null amplitude test, the simple cosinor method can confirm the existence of a rhythm; via the amplitude-acrophase test it can be used to compare different rhythms.

In addition, the multiple and populational cosinor methods can be used to compare the rhythms of individuals from different subgroups.<sup>42</sup> The limitations of this method are well known. Among the most serious is its low efficacy when used with data series that do not follow a reasonably sinusoidal distribution (such a

distribution can be confirmed by the sinusoidality test). When this is the case, a fit is obtained in which the acrophase and batiphase are out of phase with the true maxima and minima respectively.<sup>9,43,44</sup>

To address the problems of the cosinor method, the system developed by Alberola et al<sup>45</sup> was used. This was developed using the Matlab® platform and involves the use of the most important harmonics of the variables under study. In this way, the curves adjusted by the basic period and other harmonics better reproduce the effects of the different variables on the temporal distribution of AMI.<sup>43</sup>

Significance was set at  $\alpha=5\%$  for the existence of rhythmicity and for the comparison of rhythms.

### RESULTS

Data for the study were all recorded between 1994 and 2003. The study population was composed of 54 249 patients registered between May 1994 and October 2003 in the ARIAM database. The analysis of modifiable cardiovascular risks was performed on a subpopulation of 18 665 patients.

Table 1 shows the distribution of the total population, its general characteristics and the distribution of the different cardiovascular risk factors. Tables 2 and 3 show the results of the rhythmometric study. As a whole, the study population showed a circadian rhythm with respect to AMI symptom onset. Peak incidence, or acrophase, was detected at 10:07 h; the nadir or batiphase occurred at 4:46 h. The circadian pattern—the standard pattern—was sinusoidal (Figure 1).

The subgroups resulting from the division of the population by sex and age also showed a circadian rhythm for AMI symptom onset, with the acrophase at around 10:00 h and the batiphase between 4:30 and 5:00 h. The patterns for these subgroups were similar to that seen in Figure 1 (Table 2).

Some of the subgroups analyzed showed bimodal patterns in their AMI symptom onset curves. Patients with diabetes mellitus (Figure 2) and those who had suffered reinfarction (Figure 3) showed a circadian rhythm with a 12 h period; the reinfarction patients showed a nocturnal batiphase (0:22 h). This same pattern was observed in patients with prior ischemic heart disease.

The smoker subgroup showed a lower evening than morning peak; this produced a plateau of AMI symptom onset incidence during the day. During the night, the incidence of AMI symptom onset in smokers and non-smokers was the same (Figure 4).

Having suffered a previous cerebrovascular accident, or having high blood pressure, dyslipidemia or family history of heart disease was found to have an influence on the circadian rhythm of AMI symptom onset, although the patterns produced were similar to the standard curve of Figure 1.

**TABLE 1. General Characteristics of the Population and the Distribution of Cardiovascular Risk Factors**

Variable	n	%
Overall	54 429	100
Sex		
Male	40 988	75.6
Female	13 261	24.4
Age		
<70 years	32 346	59.6
≥70 years	21 903	40.4
Prior ischemic heart disease	17 790	32.8
Condition at discharge		
Alive	49 226	90.7
Dead	5023	9.3
Cardiovascular risk factors	18 665	100
Prior cerebrovascular accident	1132	6.1
Family history of ischemic heart disease	1572	7.8
High blood pressure	9166	49.1
Diabetes mellitus	5378	28.8
Dyslipidemia	6582	35.3
Smokers	6428	34.4
Reinfarction	3085	16.5

**TABLE 2. Variables Affecting Circadian Rhythm (Risk Factor Markers and Non-Modifiable Cardiovascular Risk Factors)**

Variables	Circadian Rhythm		
	Yes/No	Acrophase	Batiphase
Overall	Yes	10:07 h	4:46 h
Sex			
Male	Yes	10:13 h	4:51 h
Female	Yes	9:49 h	4:29 h
Age			
<70 years	Yes	10:01 h	4:46 h
≥70 years	Yes	10:13 h	4:47 h
Prior ischemic heart disease			
Yes	Yes	9:22 h	4:45 h
No	Yes	10:09 h	4:50 h
Condition at discharge			
Alive	Yes	10:08 h	4:48 h
Dead	Yes	9:38 h	4:31 h
Prior cerebrovascular accident			
Yes	Yes	10:23 h	5:06 h
No	Yes	9:53 h	4:47 h
Family history of ischemic heart disease			
Yes	Yes	11:07 h	4:46 h
No	Yes	10:05 h	4:45 h

**DISCUSSION**

The periodicity of myocardial infarctions has been

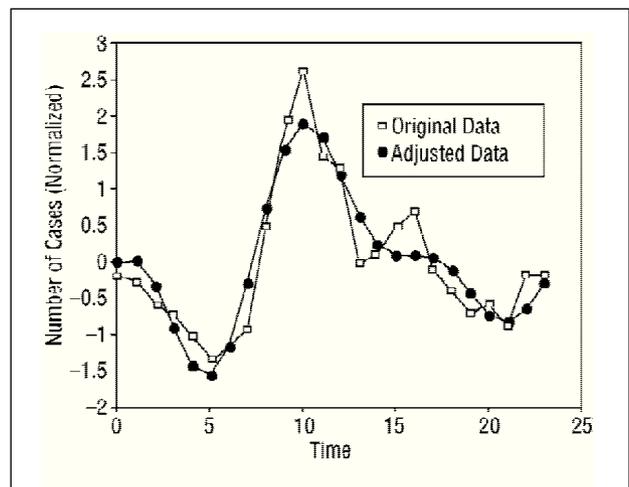
**TABLE 3. Comparative Analysis of Circadian Rhythm According to Different Cardiovascular Risk Factors**

Variables	Circadian Rhythm			
	Yes/No	Acrophase	Batiphase	P
High blood pressure				
Yes	Yes	9:48 h	4:45 h	.81
No	Yes	10:03 h	4:52 h	
Diabetes mellitus				
Yes	Yes	9:40 h	4:49 h	<.05
No	Yes	10:01 h	4:48 h	
Dyslipidemia				
Yes	Yes	9:43 h	4:46 h	.84
No	Yes	9:59 h	4:49 h	
Smoking				
Yes	Yes	10:22 h	5:02 h	<.05
No	Yes	9:47 h	4:43 h	
Reinfarction				
Yes	Yes	0:22 h	4:59 h	<.05
No	Yes	10:00 h	4:46 h	

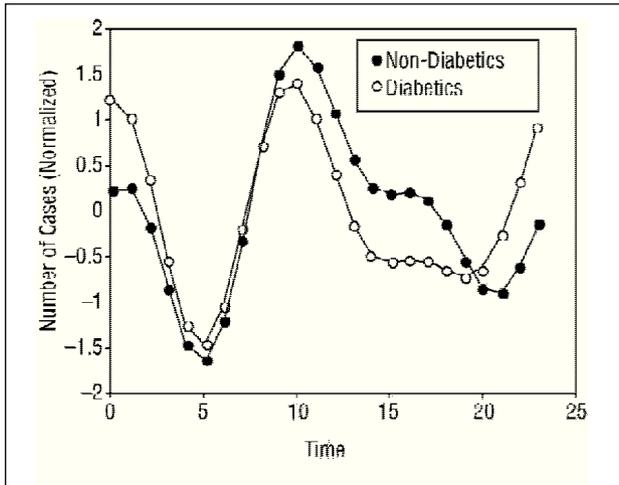
reported in numerous studies over the last twenty years.<sup>18-20,22,27,29,31,33,37,46-49</sup>

In the present patients (taken as a whole), a circadian rhythm was found for the onset of AMI symptoms. All the risk factor subgroups (previous cerebrovascular accident, family background of ischemic heart disease, diabetes, use of tobacco, dyslipidemia, hypertension, and reinfarction) showed a statistically significant clinical circadian rhythm for AMI symptom onset.

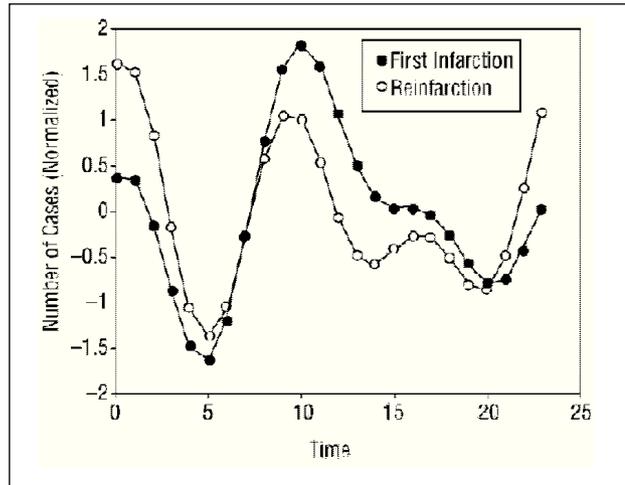
Some of the results obtained disagree with those of previous studies which report a lack of a circadian rhythm in certain populations. The methodology used to analyze rhythmicity in these previous studies, and the small size of their sample populations, may be the



**Fig. 1.** Circadian rhythm in the general population showing a standard pattern with a single incidence peak in the morning and a progressive decline over the rest of the day and night.



**Fig. 2.** Circadian rhythm of the subgroup with diabetes, showing a bimodal pattern with two incidence peaks (morning and night-time) of different amplitude.



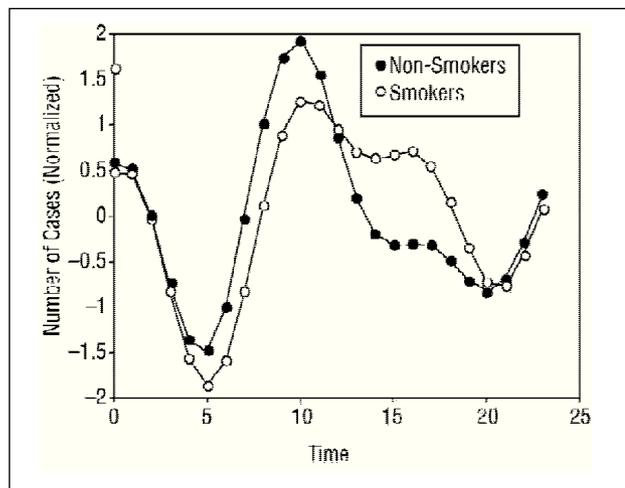
**Fig. 3.** Circadian rhythm of the subgroup suffering reinfarction, showing a bimodal pattern with two incidence peaks (morning and night-time) of different amplitude.

reason for this. For example, these earlier studies report no influence of high blood pressure on the circadian rhythm of AMI symptom onset. In the present study, high blood pressure did affect AMI symptom onset although the final curve was similar to the standard curve, with a morning peak.

Dyslipidemia affected AMI symptom onset in a manner very similar to high blood pressure. Again, the curve was similar to the standard curve for the entire population, with a morning peak.

The subgroup of patients who had suffered a previous cerebrovascular accident showed a circadian rhythm for AMI symptom onset. The curve was similar to the standard curve for the total population, although there was a more marked nocturnal incidence. As well as the possible influence of the drugs used in the treatment of these patients on the circadian rhythm of AMI symptom onset, an ischemic accident may, in some cases, affect the cerebral connections of the hypothalamic nucleus. The circadian rhythm of AMI symptom onset might therefore be modified, though this hypothesis has not been corroborated by electrophysiological or chronobiopathological studies.

The diabetic subgroup showed a circadian rhythm with a bimodal pattern involving one morning and one nocturnal peak (Figure 2). This might be explained by the autonomic dysregulation that diabetic patients suffer. The factors intimately associated with the pathogenesis of thrombotic episodes of AMI could be modified, both in terms of their circadian variability and intensity. The circadian rhythm of the heart rate and the nocturnal reduction in blood pressure could become attenuated, the morning threshold for platelet aggregation raised, fibrinolytic activity reduced, and daytime vascular thrombogenicity in-



**Fig. 4.** Circadian rhythm of the smoker subgroup, showing an evening incidence plateau.

creased, etc.<sup>1,5,50</sup>

Behar et al<sup>29</sup> and Zarich et al<sup>51</sup> indicate that AMI symptoms in diabetic patients show a circadian rhythm with a single morning peak. In the work of Zarich et al,<sup>51</sup> this circadian rhythm is no longer seen in patients with serious dysregulation of the autonomous nervous system. Hjalmarson et al<sup>22</sup> and Gilpin et al<sup>20</sup> found a circadian rhythm with two peaks (morning and night-time) of similar intensity. The ISIS-2 (Second International Study of Infarct Survival) group also reported that diabetic patients had a circadian rhythm different to that of non-diabetics (although not significantly so).<sup>37</sup> Finally, other authors have reported the absence of a circadian rhythm with respect to the onset time of AMI symptoms in pa-

tients with diabetes.<sup>37,52,53</sup>

The changes in the regulation of the autonomic nervous system experienced by diabetic patients may be one of the main reasons for the loss of a standard circadian rhythm for AMI symptom onset. The 2 incidence peaks might reflect this alteration, along with the greater sensitivity of the adrenergic receptors outside the morning maximum described in other subgroups. The frequent association between diabetes and other cardiovascular risk factors should also be remembered; frequent interactions may occur between diabetic phenomena and the pharmacological treatment of cardiovascular risks associated with the disease.

In patients with reinfarction, a significantly different circadian rhythm was found, with a bimodal incidence pattern in which the morning peak was attenuated and the evening peak as large as the morning peak (Figure 3). Since the patients with reinfarction met the inclusion requirement for prior ischemic heart disease, it is logical to think that their pharmacological treatments might be the cause of the changes seen in the presentation of the reinfarction. The results reported in this respect in the literature are contradictory. Hansen et al<sup>47</sup> found a circadian rhythm for AMI symptom onset in a sample of 1872 reinfarction patients. The pattern found was similar to that reported in the present work, with both morning and night-time incidence peaks. Hjalmarson et al<sup>22</sup> and Gilpin et al,<sup>20</sup> however, found no such circadian rhythm in patients who had suffered a previous AMI (n=104); these patients showed a daily cycle that differed depending on whether a Q wave was present or not for the current AMI. Behar et al<sup>29</sup> found a circadian rhythm in a sample of 477 patients, with a very notable morning peak of incidence. In all these papers, the methodology used was the comparison of incidence of AMI onset over 6 h intervals using the  $\chi^2$  test.

Figueras et al<sup>54</sup> affirm that the onset of symptoms of a new infarction are subject to a circadian rhythm with an earlier incidence peak (between 0:00 h and 6:00 h) than that seen for first AMI, probably due to the anti-angina medication the patients received.

A comparison of the rhythms detected for first AMI and reinfarction shows them to have significant differences. The circadian rhythm of first AMI patients shows a standard pattern with a single morning peak followed by a progressive decline. Reinfarction patients, however, show a bimodal pattern, with circadian and a 12 h cycle, involving a larger nocturnal than morning peak (Figure 3). It may be that this difference in patterns is due to the pharmacological treatments used by patients who have already suffered an AMI.

The subgroup of smokers showed a circadian rhythm of AMI symptom onset different to that of non-smokers. The adjusted curve for the smokers shows a circadian rhythm of reduced amplitudes and a double peak inci-

dence during the day, one in the morning and the other (less prominent) at around 16:00 h. The non-smokers showed a classic curve with a 24 h period and a single incidence peak followed by a progressive decline towards a nocturnal low point (Figure 4).

The results of Hjalmarson et al<sup>22</sup> are in agreement with the present data with respect to the double peak of incidence shown by smokers. Kinjo et al,<sup>35</sup> however, report a single nocturnal peak in young male smokers. In the present work, this subgroup of smokers showed the same double daily peak incidence and nocturnal low point as mentioned above (Figure 4). According to Toftler et al,<sup>13</sup> tobacco might increase platelet aggregability. Certainly there is a relationship between smoking a cigarette and the activation of the sympathetic mechanisms of the autonomic nervous system. Spacing out smoking over the day might favor the attenuation of the morning peak and the appearance of an evening incidence plateau.

## CONCLUSIONS

The onset time of AMI symptoms follows a sinusoidal curve with a morning peak and an early morning trough, conferring the appearance of these symptoms a circadian rhythm. This sinusoidal pattern and morning peak is maintained irrespective of sex or age in patients who have suffered prior ischemic heart disease or a prior cerebrovascular accident, and among those with family histories of ischemic heart disease (risk markers). Those with high blood pressure and dyslipidemia (modifiable factors) also show this pattern. However, patients with diabetes, who smoke, or who suffer reinfarction, show a double incidence peak in their curves.

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